Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for infantile haemangiomas of the skin (Review)

Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Pardo-Hernandez H, Arevalo-Rodriguez I

Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Pardo-Hernandez H, Arevalo-Rodriguez I.
Interventions for infantile haemangiomas of the skin.
Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD006545.
DOI: 10.1002/14651858.CD006545.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for infantile haemangiomas of the skin

Monica Novoa[1], Eulalia Baselga[2], Sandra Beltran[1], Lucia Giraldo[1], Ali Shahbaz[3], Hector Pardo-Hernandez[4], Ingrid Arevalo-Rodriguez[5,6]

[1]Paediatric Dermatology Department, Hospital San Jose-Fundacion Universitaria de Ciencias de la Salud, Bogota, Colombia. [2]Paediatric Dermatology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. [3]Department of Dermatology, University of Alberta, Edmonton, Canada. [4]Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau) - CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. [5]Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador. [6]Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS), Madrid, Spain

Contact address: Ingrid Arevalo-Rodriguez, Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Av. Mariscal Sucre s/n y Av. Mariana de Jesús, Quito, Ecuador. inarev7@yahoo.com.

Editorial group: Cochrane Skin Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 4, 2018.

Citation: Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Pardo-Hernandez H, Arevalo-Rodriguez I. Interventions for infantile haemangiomas of the skin. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD006545. DOI: 10.1002/14651858.CD006545.pub3.

ABSTRACT

Background

Infantile haemangiomas (previously known as strawberry birthmarks) are soft, raised swellings of the skin that occur in 3% to 10% of infants. These benign vascular tumours are usually uncomplicated and tend to regress spontaneously. However, when haemangiomas occur in high-risk areas, such as near the eyes, throat, or nose, impairing their function, or when complications develop, intervention may be necessary. This is an update of a Cochrane Review first published in 2011.

Objectives

To assess the effects of interventions for the management of infantile haemangiomas in children.

Search methods

We updated our searches of the following databases to February 2017: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, AMED, LILACS, and CINAHL. We also searched five trials registries and checked the reference lists of included studies for further references to relevant trials.

Selection criteria

Randomised controlled trials (RCTs) of all types of interventions, versus placebo, active monitoring, or other interventions, in any child with single or multiple infantile haemangiomas (IHs) located on the skin.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary outcome measures were clearance, a subjective measure of improvement, and adverse events. Secondary outcomes were other measures of resolution; proportion of parents or children who consider there is still a problem; aesthetic appearance; and requirement for surgical correction. We used GRADE to assess the quality of the evidence for each outcome; this is indicated in *italics*.

Main results

We included 28 RCTs, with a total of 1728 participants, assessing 12 different interventions, including lasers, beta blockers (e.g. propranolol, timolol maleate), radiation therapy, and steroids. Comparators included placebo, an active monitoring approach, sham radiation, and interventions given alone or in combination.

Studies were conducted in a number of countries, including China, Egypt, France, and Australia. Participant age ranged from 12 weeks to 13.4 years. Most studies (23/28) included a majority of females and different types of IHs. Duration of follow-up ranged from 7 days to 72 months.

We considered most of the trials as at low risk of random sequence generation, attrition bias, and selective reporting bias. Domains such as allocation concealment and blinding were not clearly reported in general. We downgraded evidence for issues related to risk of bias and imprecision.

We report results for the three most important comparisons, which we chose on the basis of current use. Outcome measurement of these comparisons was at 24 weeks' follow-up.

Oral propranolol versus placebo

Compared with placebo, oral propranolol 3 mg/kg/day probably improves clinician-assessed clearance (risk ratio (RR) 16.61, 95% confidence interval (CI) 4.22 to 65.34; 1 study; 156 children; *moderate-quality evidence*) and probably leads to a clinician-assessed reduction in mean haemangioma volume of 45.9% (95% CI 11.60 to 80.20; 1 study; 40 children; *moderate-quality evidence*). We found no evidence of a difference in terms of short- or long-term serious adverse events (RR 1.05, 95% CI 0.33 to 3.39; 3 studies; 509 children; *low-quality evidence*), nor in terms of bronchospasm, hypoglycaemia, or serious cardiovascular adverse events. The results relating to clearance and resolution for this comparison were based on one industry-sponsored study.

Topical timolol maleate versus placebo

The chance of reduction of redness, as a measure of clinician-assessed resolution, may be improved with topical timolol maleate 0.5% gel applied twice daily when compared with placebo (RR 8.11, 95% CI 1.09 to 60.09; 1 study; 41 children;*low-quality evidence*). Regarding short- or long-term serious cardiovascular events, we found no instances of bradycardia (slower than normal heart rate) or hypotension in either group (1 study; 41 children; *low-quality evidence*). No other safety data were assessed, and clearance was not measured.

Oral propranolol versus topical timolol maleate

When topical timolol maleate (0.5% eye drops applied twice daily) was compared with oral propranolol (via a tablet taken once per day, at a 1.0 mg/kg dose), there was no evidence of a difference in haemangioma size (as a measure of resolution) when measured by the proportion of patients with a clinician-assessed reduction of 50% or greater (RR 1.13, 95% CI 0.64 to 1.97; 1 study; 26 participants; *low-quality evidence*). Although there were more short- or long-term general adverse effects (such as severe diarrhoea, lethargy, and loss of appetite) in the oral propranolol group, there was no evidence of a difference between groups (RR 7.00, 95% CI 0.40 to 123.35; 1 study; 26 participants; *very low-quality evidence*). This comparison did not measure clearance.

None of our key comparisons evaluated, at any follow-up, a subjective measure of improvement assessed by the parent or child; proportion of parents or children who consider there is still a problem; or physician-, child-, or parent-assessed aesthetic appearance.

Authors' conclusions

We found there to be a limited evidence base for the treatment of infantile haemangiomas: a large number of interventions and outcomes have not been assessed in RCTs.

Our key results indicate that in the management of IH in children, oral propranolol and topical timolol maleate are more beneficial than placebo in terms of clearance or other measures of resolution, or both, without an increase in harms. We found no evidence of a difference between oral propranolol and topical timolol maleate with regard to reducing haemangioma size, but we are uncertain if there is a difference in safety. Oral propranolol is currently the standard treatment for this condition, and our review has not found evidence to challenge this. However, these results are based on *moderate-* to *very low-quality evidence*.

The included studies were limited by small sample sizes and risk of bias in some domains. Future trials should blind personnel and participants; describe trials thoroughly in publications; and recruit a sufficient number of children to deduce meaningful results. Future trials should assess patient-reported outcomes, as well as objective outcomes of benefit, and should report adverse events comprehensively. Propranolol and timolol maleate require further assessment in RCTs of all types of IH, including those considered problematic, as do other lesser-used interventions and new interventions. All treatments should be compared against propranolol and timolol maleate, as beta blockers are approved as standard care.

PLAIN LANGUAGE SUMMARY

Treatments for haemangiomas (a cluster of small blood vessels that form a lump) of the skin in children

What is the aim of this review?

This Cochrane Review aimed to assess the benefits and harms of treatments for haemangiomas of the skin in infants and children (known as 'infantile haemangiomas'). We collected and analysed 28 relevant clinical trials to answer this question.

Key messages

Only one of our key comparisons (propranolol versus placebo) measured clearance of the haemangioma, with *moderate-quality evidence* supporting this result. We found *low-* or *moderate-quality evidence* for the following specific measures of resolution: reduction in volume, redness, and size. We found *very low-* and *low-quality evidence* for results concerning side effects, meaning we were unable to draw definitive conclusions about safety.

Oral propranolol is currently the standard treatment for this condition, and we did not find evidence to contest this treatment in terms of efficacy and safety. However, potential biases in the design of many of the included trials affect our confidence in the results of the review. High-quality future research should assess the effects of propranolol and timolol maleate, as well as other new and older medications, on outcomes that are important to patients.

What was studied in the review?

Infantile haemangiomas are soft, raised swellings on the skin, often with a bright-red surface caused by a non-cancerous overgrowth of blood vessels in the skin. The majority of lesions are uncomplicated and will shrink on their own by age seven; however, some require treatment if they occur in high-risk areas (e.g. near the eyes) or cause psychological distress.

We included all types of treatment for infantile haemangiomas, which could have been given alone or in combination, or compared to each other, to a 'placebo' (i.e. a treatment with no active agent), or against children whose haemangiomas were untreated but observed.

What are the main results of the review?

We included 28 studies, with a total of 1728 participants, which assessed lasers, beta blockers (e.g. propranolol), steroids, radiation therapy, and other treatments. Treatments were compared against an active monitoring approach (observation), placebo, sham radiation, or other interventions (given alone or in combination with another treatment). Studies were conducted in multiple countries; participant age ranged from 12 weeks to 13.4 years; and most studies included more girls than boys (23/28). Children had different types of haemangioma. Duration of follow-up ranged from 7 days to 72 months.

The following results were measured 24 weeks after the beginning of treatment. All non-safety outcomes presented here were clinician assessed (i.e. assessed by the physician in charge of a patient).

When compared with placebo treatment, propranolol taken by mouth at a dose of 3 mg/kg/day is probably more beneficial in terms of complete or almost-complete clearance of swelling and reduction in volume of the haemangioma (*moderate-quality evidence*). We found no evidence of a difference between the two treatments in terms of short- or long-term serious or other side effects (*low-quality evidence*). Most of the evidence for this comparison was based on an industry-sponsored study.

Timolol maleate 0.5% gel applied topically twice daily may reduce redness as a measure of resolution when assessed against placebo (*low-quality evidence*). Short- or long-term serious cardiovascular events were not reported in either group. There were no other safety data for timolol maleate compared with placebo (*low-quality evidence*). This comparison did not assess clearance of the swelling.

There was no evidence of a difference between propranolol taken by mouth (via a tablet once per day, at a 1.0 mg/kg dose) and topical timolol maleate (0.5% eye drops applied twice daily) in terms of their effect on reducing haemangioma size by 50% or more (*low-quality evidence*). There were more general short- or long-term side effects (such as severe diarrhoea, tiredness, and decreased appetite) with propranolol, but due to very *low-quality evidence*, these results are uncertain. This comparison did not assess clearance of the swelling.

Most of the comparisons assessed, including those described above, did not report on the following outcomes: parent or child's opinion of improvement; the proportion of parents or children who consider there is still a problem; and cosmetic appearance.

How up-to-date is this review?

We searched for studies up to February 2017.

Summary of findings for the main comparison. Oral propranolol compared to placebo for infantile haemangiomas of the skin

Oral propranolol compared to placebo for infantile haemangiomas (strawberry birthmarks) of the skin

Patient or population: infantile haemangiomas (strawberry birthmarks) of the skin
Setting: all settings (outpatient care)
Intervention: oral propranolol
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral propranolol				
Clearance, as assessed by a clinician at any follow-up - 3 mg/kg/day 24 weeks' follow-up	36 per 1000	604 per 1000 (153 to 1000)	**RR 16.61** (4.22 to 65.34)	156 (1 RCT)	⊕⊕⊖⊖ **MODERATE** [1]	
A subjective measure of improvement, as assessed by the parent or child, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Adverse events experienced at short or long term - Serious adverse events 24 weeks' follow-up	37 per 1000	38 per 1000 (12 to 124)	**RR 1.05** (0.33 to 3.39)	509 (3 RCTs)	⊕⊖⊖⊖ **LOW** [2]	
Other measures of resolution, as assessed by a clinician, at any follow-up - percentage change in mean haemangioma volume at 24 weeks	Mean: -14.1% (SD not reported)	Mean: -60% (SD not reported)	MD **45.9% lower** (80.2% lower to 11.6% lower)	40 (1 RCT)	⊕⊕⊕⊖ **MODERATE** [3]	Mean difference was reported by the study authors, but no SDs were reported for group means.
Proportion of parents who consider their child still has a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Proportion of children who consider they still have a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

Aesthetic appearance as assessed by physician, child, or parent, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group (the event rate in the single study or the mean event rate in the meta-analysis) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by one level for imprecision (wide confidence interval around the estimate of the effect).
[2]Downgraded by two levels for imprecision (wide confidence interval around the estimate of the effect and low number of events).
[3]Downgraded by one level for risk of bias.

Summary of findings 2. Topical timolol compared to placebo for infantile haemangiomas of the skin

Topical timolol maleate compared to placebo for infantile haemangiomas (strawberry birthmarks) of the skin

Patient or population: infantile haemangiomas (strawberry birthmarks) of the skin
Setting: all settings (outpatient care)
Intervention: topical timolol maleate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with topical timolol maleate				
Clearance, as assessed by a clinician at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

A subjective measure of improvement, as assessed by the parent or child, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Adverse events experienced at short or long term - Serious cardiovascular adverse events - bradycardia 24 weeks' follow-up	See comment	See comment	Not estimable	41 (1 RCT)	⊕⊕⊖⊖ **LOW** [1]	No events of bradycardia reported in Chan 2013.
Other measures of resolution, as assessed by a clinician, at any follow-up - no redness	45 per 1000	369 per 1000 (50 to 1000)	**RR 8.11** (1.09 to 60.09)	41 (1 RCT)	⊕⊕⊖⊖ **LOW** [2]	
Proportion of parents who consider their child still has a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Proportion of children who consider they still have a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Aesthetic appearance as assessed by physician, child, or parent, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group (the event rate in the single study) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by two levels for imprecision (low number of participants and events).
[2]Downgraded by two levels for imprecision (wide confidence interval around the estimate of the effect and low number of participants and events).

Summary of findings 3. Oral propranolol compared to topical timolol for infantile haemangiomas of the skin

Oral propranolol compared to topical timolol maleate for infantile haemangiomas (strawberry birthmarks) of the skin

Patient or population: infantile haemangiomas (strawberry birthmarks) of the skin
Setting: all settings (outpatient care)
Intervention: oral propranolol
Comparison: topical timolol maleate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with topical timolol maleate	Risk with oral propranolol				
Clearance, as assessed by a clinician at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
A subjective measure of improvement, as assessed by the parent or child, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Adverse events experienced at short or long term - general adverse events 24 weeks' follow-up	See comment	See comment	**RR 7.00** (0.40 to 123.35)	26 (1 RCT)	⊕⊝⊝⊝ **VERY LOW** [1]	There were 3 events in the oral propranolol group and no events in the topical timolol maleate group. Due to no events in the control group, absolute events could not be calculated.
Other measures of resolution, as assessed by a clinician, at any follow-up - size reduction ≥ 50% 24 weeks' follow up	615 per 1000	695 per 1000 (394 to 1000)	**RR 1.13** (0.64 to 1.97)	26 (1 RCT)	⊕⊕⊝⊝ **LOW** [2]	
Proportion of parents who consider their child still has a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.
Proportion of children who consider they still have a problem, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

Aesthetic appearance as assessed by physician, child, or parent, at any follow-up - not reported	See comment	See comment	Not estimable	-	See comment	We did not identify any studies reporting this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group (the event rate in the single study) and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by three levels: one level due to unclear risk of selection and performance bias and two levels for imprecision (wide confidence interval around the estimate of the effect and low number of participants and events).
[2]Downgraded by two levels: one level due to unclear risk of selection and performance bias and one level for imprecision (small sample size).

BACKGROUND

Please refer to the following website for definitions of technical terms: www.ncbi.nlm.nih.gov/mesh.

Description of the condition

Infantile haemangiomas (IH) are the most common vascular tumours among children, occurring in 3% to 10% of infants (Léauté-Labrèze 2015). They were previously known as 'strawberry birthmarks' or 'strawberry naevi', or 'capillary haemangiomas', terms currently withdrawn by current classifications about vascular tumours (www.issva.org/classification). They are benign and of endothelial cellular origin, characterised by a rapid pattern of propagation in the first months of life, then followed by a period of involution that can take several years (Bruckner 2006). Sometimes the IH is characterised by a precursor lesion at birth. Infantile haemangiomas undergo a phase of rapid growth within the first few months of the first year (Baselga 2016; Wang 2017). Regression is completed in 60% of patients by their fourth birthday, 76% by their seventh birthday, and approximately 90% by their ninth birthday (Zimmermann 2010). However, it has been observed in some retrospective studies that the complete regression has been achieved at 3.5 years (Baselga 2016), and also at four years of follow-up (Darrow 2015). While most lesions develop in a straightforward way, about 12% of cases result in clinically significant complications requiring referral (Leaute-Labreze 2015). In addition, IH can result in lifelong sequelae, which can cause psychological distress (Léauté-Labrèze 2015). More than 50% of untreated IH leave permanent sequelae that may cause disfigurement (Baselga 2016). Bauland and colleagues found residual lesions in 69% of 137 IH studied (Bauland 2011), and Baselga and colleagues in 54.9% out of 184 IH studied (Baselga 2016).

Infantile haemangiomas appear more commonly among Caucasians (understood to be white individuals), being evident in up to 12% of all children (Zimmermann 2010). Infantile haemangiomas affect females in a ratio of 3:1 (Zimmermann 2010). Sixty per cent of IH are located in the head and neck area, whereas 25% occur on the trunk and 15% on the extremities (Zimmermann 2010). Infantile haemangiomas can be divided by their morphology into superficial haemangiomas, subcutaneous (deep) haemangiomas, and mixed haemangiomas (www.issva.org/classification) (Sethuraman 2014). Superficial haemangiomas appear as a bright-red vascular plaque with an irregular surface. Subcutaneous or deep haemangiomas present as protruding vascular swelling under normal or bluish skin. Mixed or combined haemangiomas show a combination of both superficial and deep characteristics. Infantile haemangiomas usually present as single lesions, although 20% of affected infants develop multiple tumours (van de Kerkhof 1998; Zimmermann 2010). The skin covering haemangiomas may become ulcerated, exposing the underlying blood vessels and making them more liable to bleed from minor trauma and become infected,

Infantile haemangiomas are not normally present at birth, or they are present only as a precursive mark, in the form of a pink macule, telangiectatic patches, or areas that appear bruised (Vega 2017). Infantile haemangiomas generally proliferate during the first year of life, with most growth being completed by age six to nine months. Eighty per cent of haemangioma growth is completed by age three months, and 80% of haemangiomas have completed growth by age five months (Tollefson 2012). Despite the self limiting nature of most IH, several complications have been observed, including bleeding, ulceration and infection, deformation and disfigurement, impairment of vision, and airway obstruction (Achauer 1997; Syed 1999). Children under the age of three are seldom aware of their haemangiomas. Most IH resolve spontaneously; however, when they cause complications, they can be dangerous or present a risk to a person's life.

The diagnosis of an IH is typically made clinically, based on its appearance and characteristic behaviour. When there is doubt in the diagnosis, additional studies such as Doppler ultrasound or skin biopsy may be performed (Holland 2013).

Studies have shown that blood vessel cells (positive for glucose transporter 1 (GLUT1)) in IH are similar to those found in the placenta (Ma 2017); this has raised the possibility that placental cells may become dislodged during pregnancy, travel into the foetus, and grow postnatally to form a haemangioma (Ma 2017). Some mechanisms have been studied in the pathogenesis of infantile haemangiomas such as tissue hypoxia and pathologic vasculogenesis leading to endothelial cell proliferation (Ma 2017). Predisposing factors have also been described in some studies, including low birth weight, advanced maternal age, multiple gestations, pre-eclampsia, and gestational diabetes mellitus (Castren 2016). Infantile haemangiomas have also been more frequently noted in children whose mothers had chorionic villus sampling (CVS) compared with the general population (Kaplan 1990).

Management of IH can be challenging. Each option involves significant drawbacks or side effects, or both. Although most haemangiomas are self limited and do not need treatment, some indications for treatment include the following: high-output cardiac failure, bleeding, ulceration, risk of permanent disfigurement, or airway or visual obstruction. Location, age of the patient, risk of complications, and growth rate are all factors that physicians must consider in managing patients with IH (Holland 2013).

Recently, Léauté-Labrèze 2015 described their chance observation of an antiproliferative effect of propranolol (PR) on IH. Since the introduction of propranolol in 2008, this drug has showed a highly effective profile with tolerable adverse events, in comparison with previous recommended interventions used for IH (e.g. steroids, interferon, chemotherapy) (Zou 2013). Minimal or no side effects have been reported with propranolol, and the response rate has approached 100% (Léauté-Labrèze 2015). Propranolol is now the first-line treatment for IH and has been approved for this indication (Baselga 2016; Chinnadurai 2016a).

Description of the intervention

The diagnosis of an IH is typically made clinically, based on appearance and characteristic behaviour. When the diagnosis is uncertain, additional tests such as a Doppler ultrasound or skin biopsy may be performed (Holland 2013). The vast majority of infantile haemangiomas will regress on their own and require no further treatment; therefore, an active monitoring approach is usually implemented (Darrow 2015). However, IH can occur in high-risk areas, such as near the eyes, throat, and nose, impairing their function. If vision is obscured at a critical stage in brain development, complications such as failure to develop binocular

vision can result (Darrow 2015). A large variety of treatments have been used historically, and many are still in use.

Beta blockers, for example oral propranolol, are the current standard care, approved both by the US Food and Drug Administration and the European Medicines Agency, with complete regression without sequelae after six months of treatment in 60% of cases (Darrow 2015). Propranolol has also been assessed for intralesional and topical administration (Zaher 2013). The recommended dose of propranolol in oral administration is 3 mg/kg/day divided into two doses, for at least six months (Leaute-Labreze 2015). Reported adverse effects include hypoglycaemia, bradycardia, hypotension, bronchospasm, sleep disturbance, and gastrointestinal disorders (Ji 2015). Propranolol interacts with other medications such as insulin, non-steroidal anti-inflammatories, antiarrhythmics, and calcium channel blockers (Holland 2013). In practice, when medication is warranted for infantile haemangioma, propranolol is the first-choice drug. Parents and healthcare professionals must monitor infants closely for adverse effects (Leaute-Labreze 2015).

In addition, topical timolol maleate, a non-selective beta blocker, is available in a 0.25% and 0.5% solution, as well as an extended release 0.5% (5 mg/mL) gel-forming solution. Frequency and method of application have varied from once daily under occlusion to twice daily without occlusion; 1 to 2 drops have typically been used and are usually given for 2 to 6 months (Zheng 2018). Adverse effects of timolol maleate in the paediatric population, especially in high-risk premature infants, include bradycardia and bronchospasm (Holland 2013).

The following other treatments besides oral propranolol and topical timolol maleate have been assessed and might still be in use (Glassberg 1989).

- **Atenolol** is a cardioselective beta blocker; it is a large, lipophobic molecule and has limited ability to cross the blood–brain barrier (Bayart 2017). Its use may sometimes be preferred if patients experience side effects with propranolol. Treatment with atenolol is recommended in an oral dose of 1 mg/kg/day for three to six months, depending on the positive response or the presence of adverse events such as bradycardia, hypotension, dizziness, and lethargy (Abarzua-Araya 2014; Raphael 2011). Some interactions with other medicaments have been suggested, including verapamil, clonidine, and ibuprofen (Doshan 1986; Hansson 1975).
- **Bleomycin**, a well-known anticancer and sclerosing agent, has been used to treat haemangiomas (Luo 2011). Recommended dosage and duration of treatment depends on the age of the patient and the size of the lesion. Some clinicians have used a standard injection of bleomycin of 0.3 to 0.6 mg/kg per injection, and others have used a mixture of 5 mL 2% lidocaine, 5 mg dexamethasone, and 8 mg bleomycin A5 (Pienaar 2006). Some documented adverse events for this agent include oedema and ulceration (Luo 2011). No interactions with other drugs have been reported.
- **Captopril**, an angiotensin-converting enzyme inhibitor, has been suggested for potential use in the treatment of IH, due to its effects in inhibition of angiogenesis and vasculogenesis (Christou 2012). Dosage and duration of administration have not yet been standardised; Zaher and colleagues used oral captopril at 0.5 to 1 mg/kg/day, in a titrating dose, while Tan and colleagues used a dose of 0.1 to 0.5 mg/kg under response (Tan 2012; Zaher 2016). Cardiac side effects requiring dose reduction or suspension have been documented for its use in IH (Zaher 2016). Treatments known to have interactions with captopril include aliskiren, everolimus, sirolimus, and lithium (Medicines.ie 2018).
- **High-intensity focused ultrasound (HIFU)** is a non-invasive surgical option with rapid evolvement in recent years that is mainly used in the management of solid tumours (Fu 2012). Documented side effects include damage in the focal point, endothelial cell loss, necrosis, and vascular discontinuity (Fu 2012). Different levels of energy have been used for different purposes, ranging from 2.6 to 4.5 W (Fu 2012). Lesions in the Fu 2012 studies were small- to medium-sized (from 0.8 cm x 0.6 cm to 6.0 cm x 5.0 cm). No interactions have been reported.
- **Interferon,** an inhibitor of angiogenesis, developed as an antiviral agent, has been suggested as a potential intervention for IH (Ezekowitz 1992; Greinwald 1999), especially for infants with life-threatening haemangiomas unresponsive to corticosteroids. Some studies have suggested a dosage of interferon alpha-2b of 3 million units/m^2 subcutaneously, from daily to 5 times per week for 6 to 24 months (Ezekowitz 1992; Greinwald 1999). Reported side effects include fever, malaise, transient neutropenia, and liver disease (Holland 2013). Known interactions of interferon alpha-2 include use of theophylline, acalabrutinib, and lamivudine, among others (EMC 2018).
- **Methylene blue** is an inhibitor of nitric oxide synthase and guanylate cyclase and is used in the management of vasoplegia syndrome, septic shock, hepato-pulmonary syndrome, and malaria, among others (Ginimuge 2010). This intervention has not been widely evaluated in the management of IH. The mechanism of action of methylene blue in photodynamic therapy has shown effects in the elimination of bacterial agents in superficial and deep excisional wounds, as well as the treatment of resistant plaque psoriasis. Reported adverse effects in high doses include cardiac arrhythmias, coronary vasoconstriction, decreased cardiac output, renal blood flow, and mesenteric blood flow (Ginimuge 2010). As methylene is a monoamine oxidase (MAO) inhibitor, it could interplay with MAO inhibitors as well as selective serotonin reuptake inhibitor (SSRI) to produce serious serotonin toxicity (Ginimuge 2010).
- **Imiquimod** is an immune-response modifier (a substance that changes the way the immune system works), which has been used in the management of condyloma, actinic keratoses, and basal cell carcinoma (McCuaig 2009). It has been suggested that imiquimod 5% cream, applied once daily for up to 16 weeks, can induce involution of superficial IH (McCuaig 2009). Reported side effects of imiquimod include local erythema, crusting, and contact dermatitis (McCuaig 2009).
- **Laser treatments** (including pulsed dye, argon, carbon dioxide, neodymium-doped yttrium aluminum garnet (Nd:YAG), sequential/concurrent dual-wavelength laser and erbium) should be considered if there is a contraindication for systemic treatment, such as a history of sensitivity to beta blockers, asthma, renal disease, heart disease, or hypoglycaemia (Chinnadurai 2016a; Chinnadurai 2016b). Some reported side effects of laser treatment include purpura, swelling, blisters, hypopigmentation, bleeding, infection, and atrophic or hypertrophic scarring (Chinnadurai 2016a; Chinnadurai 2016b). Protocols of administrations are multiple and depend on the laser pulse width, age of the patient, IH anatomical location,

cooling materials, and size of the tumour (Chinnadurai 2016a; Chinnadurai 2016b). A study recently assessed the concurrent or sequential administration of laser with other potential interventions (Lu 2016). Infants require a general anaesthetic for treatment because laser treatment can be painful. Early childhood anaesthesia carries the usual risks of complications associated with anaesthesia and as well as with neurocognitive impairment.

- **Oral ibuprofen plus oral paracetamol**, as a combination of non-steroidal anti-inflammatory and analgesic drugs (NSAIDs), has a role in the management of ulcerated IH located in the head and neck region (Tiwari 2016). Recently, Tawfik 2015 assessed a combination of oral ibuprofen and paracetamol in doses of 10 and 16.2 mg/kg 8-hourly versus oral propranolol for up to 6 months.
- **Radiation therapy** has been conventionally used for treating life- or function-threatening haemangiomas that have been unresponsive to treatment with corticosteroids. Side effects of using ionising radiation include blisters, infection, and ulcers, while possible lasting complications include pigmentation restricted to certain areas or hypopigmentation, the creation of scars, soft tissue dysplasia, and the retardation of bone growth (Fragu 1991; Probert 1975). Radiation therapy for haemangiomas includes ^{90}SR-^{90}Y radiation and soft X-ray radiation. Adverse effects include radionecrosis (acute) and scarring and skin cancer (long term).
- **Rapamycin** is a macrolide compound with immunosuppression and antiangiogenic activity (Li 2017). Oral and local administration have been assessed. Reported side effects include hyperlipidaemia, impaired glucose tolerance, anaemia, and acute renal toxicity (Li 2017).
- **Steroids** (administered topically, intralesionally, or systemically). Intralesional corticosteroids may be used for the treatment of small haemangiomas, usually involving the facial area. However, many dermatologists prefer systemic corticosteroids for periocular lesions, since intralesional administration has resulted in serious side effects including retinal artery occlusion and eyelid necrosis (Shorr 1986). Prednisolone is the most frequent steroid assessed for management of IH (Aly 2015), at a dosage of 2 mg/kg/day for six months. There is an interaction of steroids with concomitant administration of phenytoin, phenobarbital, ephedrine, estrogens, and diuretics (Bauman 2014). Steroid side effects include growth retardation, increased susceptibility to infectious disease, and hypertension (George 2004). Other minor, reversible complications associated with the administration of steroids include haematomas, periocular calcification, and eyelid pigmentation.
- **Surgery** is indicated for lesions that interfere with function if pharmacologic therapy fails or is contraindicated, as well as where ulceration or bleeding has occurred (Liang 2014). Surgical excision might also be used to improve the final cosmetic appearance if loose skin is left after IH regression (Smolinski 2005). In addition, cryotherapy can be used for small and flat haemangiomas, in order to accelerate haemangioma involution (shrinkage) (Grantzow 2001). Surgical intervention is commonly used for the correction of scarring as well as removal of residual tissue, but it can be used also for excision of life-threatening haemangiomas (Holland 2013).
- **Vincristine** is a vinca alkaloid that has been assessed in the treatment of IH, especially those IH unaffected by corticosteroids or in patients who cannot bear corticosteroids (Glade 2010). Single weekly doses of 1 to 1.5 mg/m^2 have been assessed (median of three cycles). Potential serious adverse events included constipation, neuromyopathy,(Glade 2010), and risk associated with placement of the central line (Holland 2013).
- **Active monitoring**. This approach has been shown to produce the best cosmetic outcomes for uncomplicated infantile haemangiomas (Dinehart 2001). In general, most haemangiomas resolve spontaneously without significant sequelae and follow-up can be the clinician's choice (Liang 2014).

How the intervention might work

Propranolol

Propranolol has been to shown to restrict the haemangioma's capillaries, causing a subsequent decrease in blood flow within the tumour. In addition, it has been suggested that propranolol can hinder angiogenesis and encourage apoptosis in IH cells (Wnek 2017). Potential mechanisms of action of propranolol include the stimulation of apoptosis in haemangioma endothelial cells through GLUT1 receptor antagonism; the prevention of catecholamine-induced angiogenesis; the constraint of the renin-angiotensin axis; and the interruption of signalling pathways that regulate progenitor cells (Wnek 2017). In contrast with corticosteroids, propranolol is effective during the proliferative phase of growth. Studies have recently suggested that propranolol administration in IH therapy generates a biological response involving changes in the expression of chosen apoptosis-regulating factors (Wnek 2017).

Timolol maleate

Topical timolol hinders IH growth and encourages the regression of superficial IH, although some studies have raised concerns about the effect of systemic absorption, as well side effects such as sleep disturbance (Danarti 2016).

Atenolol

The main effects of atenolol involve the beta-1 receptors with minor beta-2 effects (Abarzua-Araya 2014). Because atenolol does not act on pulmonary beta-2 receptors, it can be used in infants with pulmonary conditions, including reactive airway disease. Likewise, atenolol does not act on pancreatic beta-2 receptors and thus does not interfere with regulation of gluconeogenesis, glycogenolysis, and lipolysis (Bayart 2017).

Bleomycin

The action of bleomycin involves a decrease in the production of vascular endothelial cells, as well as the tempering of angiogenesis of the infantile haemangiomas (Luo 2011; Qiu 2015). In addition, its administration has an effect in the G2 and S phases of endothelial cells by inducing DNA deterioration and preventing its reconstruction, resulting in collapse, shrinkage, and fibrosis (Luo 2011; Qiu 2015).

Captopril

Because some components of the renin-angiotensin system (RAS) are expressed in proliferating IH, modulation of downstream products of RAS, including angiotensin-converting enzymes, could have a role in the treatment of IH (Zaher 2016). Similar to

propranolol, captopril leads to a decrease in vascular endothelial growth factor production via downregulation of angiotensin II (Itinteang 2011). In addition, captopril can inhibit the effect of kininase II and increase the plasma bradykinin levels (Waeber 1980).

High-intensity focused ultrasound (HIFU)

It has been suggested that the effectiveness of HIFU in the treatment of IH, as well as superficial skin lesions, could be similar to that shown in treating body parts and tumour (Fu 2012; Orsi 2010). High-intensity focused ultrasound produces coagulative necrosis in a focal point without effects in adjacent structures by means of ultrasonic tissue penetration. Biological effects of HIFU include coagulative necrosis, nuclei damage, membrane disruption, and apoptosis (Kennedy 2005).

Interferon

Interferon therapy works by inhibiting locomotion of capillary endothelium in vitro (Ezekowitz 1992). Although research from case series reports indicate similar results for interferon alpha-2a and interferon alpha-2b (Chang 1997), other research has indicated that the body may produce neutralising antibodies that reduce the efficacy of interferon alpha-2a as compared to interferon alpha-2b (Antonelli 1991). Earlier research on interferon showed it to have an effect on vascular tumours such as Kaposi's sarcoma (Ezekowitz 1992).

Intralesional methylene blue

Feng and colleagues have suggested that methylene has a role in the management of IH due to its endothelial effects by induced thrombosis of the lesion, blocking the vascular supply and accelerating the necrosis of the haemangioma (Feng 2000).

Imiquimod

Imiquimod has a pro-apoptotic and antiangiogenic activity. It activates the immune response system via the Toll-like receptor-7 on dendritic cells (Hu 2015; McCuaig 2009), resulting in induction of cytokines and interferon-gamma, as well as matrix metalloproteinase (McCuaig 2009).

Laser

Lasers generally work by destroying blood vessels in the IH, with the equivalent wavelength of light absorbed by IH haemoglobin (Anderson 1981). The light from the laser is transformed into heat, and it is transmitted to the vessel wall, producing coagulation and vessel closure (Tawfik 2015). Oxyhaemoglobin has been the classic target chromophore for vascular lesions, due to its absorption peaks at 418, 542, and 577 nm. Oxyhaemoglobin contained within vascular lumina absorb the light energy emitted from pulsed dye laser (PDL) devices, minimising collateral damage (Rothfleisch 2002).

In order to increase the tissue penetration of PDL, the original wavelength of 577 nm, which corresponds to the third absorption peak of oxyhaemoglobin, has been increased over the past decade to 585 nm, and the pulse duration has also been increased from 450 microseconds to 1.5 milliseconds. Cryogen-cooling devices have been added in order to reduce pain and related adverse events (Rothfleisch 2002).

Argon laser devices radiate blue-green light, with emissions between 488 to 514 nanometers on the electromagnetic spectrum (Rothfleisch 2002). Argon laser energy is emitted by a continuous beam, which penetrates tissue at a depth of 1 mm to 2 mm. Emissions are absorbed mainly by oxyhaemoglobin, although epidermal and dermal melanin also have a degree of absorption (Rothfleisch 2002). The popularity of the argon laser has markedly declined over the past decade because of its associated limitations and the development of the pulse dye laser (Rothfleisch 2002).

Carbon dioxide laser emits light in the infrared spectrum (10,600 nm), which is primarily absorbed by water molecules. Its action involves the excision or debulking of vascular tissue or actinically damaged facial skin (Al 2003; Krupa 2009).

Neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has been reported to have a weaker melanin absorption and a deeper effect on lesions (Rothfleisch 2002). In addition, Nd:YAG has a high absorption coefficient of methaemoglobin and deoxyhaemoglobin, both of which are major parts of blue veins. Due to the long pulsed duration feature, Nd:YAG has a slower and more uniformed heat effect in the IH vessels, which generates coagulation without rupturing the vessel or causing purpura or hyperpigmentation (Rothfleisch 2002).

Dual-wavelength laser combines PDL laser with YAG laser, allowing oxygenated haemoglobin to be transformed into methaemoglobin, and significantly increasing the Nd:YAG laser absorption rate. Local heat is reduced by a cooling system of -4 °C at the lesion site (Lu 2016).

The erbium laser (Er:YAG laser) produces a smaller zone of thermal injury, removing the epidermis in two or three passes, compared with the conventional CO_2 resurfacing lasers (McDaniel 1997). The 2940-nanometre wavelength of erbium produces a collagen absorption peak at 3030 nm (McDaniel 1997).

Oral ibuprofen plus oral paracetamol

In general, the mechanism of action of NSAIDs involves the inhibition of prostanoid biosynthesis (Abramson 1989). NSAIDs in combination with analgesics can have a role in the management of ulcerated IH, especially for pain relief (Tiwari 2016).

Radiation

Ionising radiation could be preferred due to its low chance of causing local scarring (Zhu 2015). In general, the pathophysiology of radiation-induced changes in the skin involves: 1) a transient early erythema, which remits after 24 to 48 hours; 2) a main erythematous reaction related to the severe loss of epidermal basal cells; 3) a subsequent phase of erythema combined with dermal ischaemia and possible necrosis; and 4) the appearance of dermal atrophy, telangiectasia, and necrosis (Hopewell 1990).

Rapamycin

Rapamycin has been reported to have a superior antihaemangioma activity due to its inhibition of the proliferation of haemangioma endothelial cells and vascular endothelial growth factor production (Li 2017).

Steroids

High-dose intralesional (injected directly into the lesion) or systemic (whole body) steroid therapies work by stopping the growth of the haemangioma through the promotion of stabilisation or regression, and possibly by softening the lesion (Bennett 2001).

Surgery

Surgical management involves removing the haemangioma in order to restore normal facial features (Liang 2014). Several techniques have been proposed including circular excision with purse-string closure (Mulliken 2002), as well as single-stage resection (Daramola 2012).

Vincristine

Vincristine is thought to act as an antiangiogenic through its effect on vascular endothelial growth factor (Azzopardi 2012). In addition, vincristine works by reducing the creation of microtubules, triggering mitotic arrest during metaphase, which produces apoptosis of tumour cells in vitro (Glade 2010).

Active monitoring

Despite the fact that it is hypothesised that several growth factors (e.g. hormonal, mechanical) are involved in the abnormal proliferation of endothelial cells in IH, the mechanism of action behind haemangiogenesis remains unknown (Marchuk 2001). In addition, most infantile haemangiomas are reported to involute completely by four years of age (Couto 2012).

Why it is important to do this review

A significant minority of babies (up to 1 in 10) develop infantile haemangiomas (Léauté-Labrèze 2015). While the majority of IH are non-problematic and will regress and disappear in five to seven years, a few will become problematic or cause mental distress to children and their parents (Csoma 2017). Some IH may also result in complications, including congestive heart failure, lifelong disfigurement, bleeding, ulceration, and visual and airway-related obstruction (Csoma 2017). In such cases, medical intervention with a variety of medical treatments may be necessary. Propranolol therapy has been recommended as the most effective way of treating IH, as it inhibits proliferation and incites regression of IH during the proliferative phase (Zhang 2017). However, other methods may still be in use. It was therefore necessary to review the efficacy and potential adverse events of these interventions for the management of IH.

A first assessment of these interventions was published by Leonardi-Bee in 2011 (Leonardi-Bee 2011), reporting information from four trials with limited evidence.

OBJECTIVES

To assess the effects of interventions for the management of infantile haemangiomas in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Any child (usually under 24 months) with single or multiple infantile haemangiomas located on the skin. We excluded participants above the age of 18 years. We excluded studies with a mixture of populations (including children and adults) that did not provide separate information for children. In addition, we excluded children with cases of very rare types of haemangiomas (including congenital haemangioma, haemangiomas associated with Kasabach-Merritt syndrome, and eruptive neonatal haemangiomatosis) and internal haemangiomas.

Types of interventions

We considered all types of interventions used in the treatment of infantile haemangiomas. Interventions could be given alone or in combination. The most commonly used interventions include the following.

- Beta blockers: propranolol, timolol maleate, and atenolol
- Lasers: pulsed dye, argon, carbon dioxide, Nd:YAG, and erbium
- Steroids: administered topically, intralesionally, or systemically
- Surgery: excision or cryotherapy
- Other treatments: imiquimod, interferon alpha-2a, bleomycin, vincristine, and rapamycin (administered topically, intralesionally, orally, or systemically)

Comparators included placebo, active monitoring (i.e. wait-and-see), or other interventions (e.g. systemic steroids versus laser therapy). Comparator interventions could be given alone or in combination.

Types of outcome measures

Primary outcomes

- Clearance, as assessed by a clinician at any follow-up: proportion of children with lesions completely cleared or with minimal residual signs (defined as faint macular erythema with no palpable component).
- A subjective measure of improvement, as assessed by the parent or child, at any follow-up.
- Adverse events experienced at short (immediately after treatment until 48 hours after) or long term (more than 48 hours after treatment) related to each intervention. These included skin atrophy (scarring where the skin is thinned, with or without depression at the skin surface), skin hypopigmentation (loss of skin pigmentation), and complications (including bleeding, ulceration, infection, deformation, disfigurement, vision impairment, airway obstruction, pain associated with treatment or ulceration, and/or side effects of treatments). We also considered reports of number of adverse events in general, as well as serious/severe adverse events (as defined by trial authors).

Secondary outcomes

- Other measures of resolution, as assessed by a clinician, at any follow-up. These included surface area, height or volume of lesion, and redness of lesion, preferably using an objective measure of assessment, such as photographs.
- Proportion of parents who consider their child still has a problem, at any follow-up.

- Proportion of children who consider they still have a problem, at any follow-up.
- Aesthetic appearance as assessed by physician, child, or parent, at any follow-up.
- Requirement for surgical correction, as assessed by a physician, at any follow-up.

Timing

We considered data recorded for six months or less from baseline to reflect short-term benefit, and we analysed these data separately from data recorded after six months' follow-up, apart from adverse events data, where we considered up to 48 hours from baseline short term.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials regardless of language or publication status (published, unpublished, in press, or ongoing).

Electronic searches

For this update, we revised our search strategies in line with current Cochrane Skin Group practices. Details of the previous search strategies are available in Leonardi-Bee 2011.

We searched the following databases up to 22 February 2017:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 1 in the Cochrane Library using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3;
- Embase via Ovid (from 1974) using the strategy in Appendix 4;
- AMED via Ovid (Allied and Complementary Medicine, from 1985) using the strategy in Appendix 5;
- PsycINFO via Ovid (from 1806) using the strategy in Appendix 6;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 7; and
- CINAHL via EBSCO (Cumulative Index of Nursing and Allied Health Literature, from 1981) using the strategy in Appendix 8.

Searching other resources

Trials registers

On 22 February 2017 we searched the following ongoing trials databases using the terms 'haemangioma', 'hemangioma', 'strawberry', 'naevi', or 'naevus':

- ISRCTN register (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/); and
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching reference lists

We checked the bibliographies of included studies for additional references to relevant trials.

Adverse effects

We did not perform a separate search for adverse effects of interventions used for the treatment of infantile haemangiomas. We considered adverse and side effects described in included studies only.

Data collection and analysis

Selection of studies

Two review authors (LG and SB) independently selected eligible studies. Authors reviewed titles and abstracts of all articles identified by the search to assess whether they met the inclusion criteria. The full texts of selected studies were further assessed to confirm their relevance for inclusion in the review. An additional third review author was consulted when disagreements arose (IAR). At any stage of the review, review authors were not blinded to the authors' names and institutions, journal of publication, or study results. All excluded studies and reasons for their exclusion are listed in the Characteristics of excluded studies tables.

Data extraction and management

Two review authors (LG and SB) independently performed data extraction using predesigned data collection spreadsheets. We extracted participant characteristics, methods of randomisation, blinding, comparisons of interest, number of children originally randomised by arm, and follow-up losses and outcomes. A third review author was consulted when disagreements arose (MN or IAR). We entered extracted data into Review Manager 5 for further analysis (Review Manager 5.3).

Assessment of risk of bias in included studies

As outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), two review authors (LG and SB) independently assessed risk of bias in included trials. We took six domains into consideration: random sequence generation, blinding of participants and personnel, blinding of outcome assessment, allocation concealment, selective reporting, and other biases. We assessed blinding of participants and blinding of personnel separately, as in most cases this information was partially reported (i.e. study authors reported blinding for participants or for personnel, but not both). We judged each domain to be at low, high, or unclear risk of bias. Disagreements were solved in consultation with a third review author (IAR). We assessed the direction and magnitude of bias, as well as its correlational impact on any findings (Higgins 2011). We summarised information in 'Risk of bias' tables in the Characteristics of included studies.

Measures of treatment effect

We expressed results as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes, and difference in means (MD) with 95% CI for continuous outcomes. Transformation of data was not required.

Unit of analysis issues

Where there were multiple intervention groups within a trial, we made pair-wise comparisons of similar active interventions versus no treatment, placebo, or other active intervention. Although we did not find any randomised controlled trials that used cross-over or internally controlled designs, we would have analysed the former using data only from the first phase pooled, where possible, with parallel-design studies. For the latter, we would have used appropriate techniques for paired designs without pooling with studies of other designs.

Dealing with missing data

In cases where participant dropout led to missing data, we conducted an intention-to-treat analysis. For dichotomous outcomes, we regarded children with missing outcome data as treatment failures and included them in the analysis. For continuous outcomes, we would have considered using the last recorded value carried forward for children with missing outcome data; however, these circumstances did not occur. If high levels of missing data were seen within the analyses, we planned to conduct sensitivity analyses to assess the robustness of the results from the approaches described above, by comparing the results with those excluding the missing data from the analyses. However, these circumstances did not occur.

Assessment of heterogeneity

We investigated heterogeneity with close visual examination of the forest plots. Additionally, we assessed statistical heterogeneity of effect sizes by means of the I^2 statistic. The I^2 statistic is employed to describe the per cent of total variation across all contributing trials due to heterogeneity rather than sampling error (Higgins 2011). If we identified signs of heterogeneity ($I^2 > 30\%$), we performed further exploration by prespecified subgroup analysis; furthermore, if we identified considerable per cent of heterogeneity ($I^2 > 80\%$), we did not present pooled results.

Assessment of reporting biases

We planned to use funnel plots, with respect to primary outcomes, to illustrate whether treatment estimates were related to study size or to determine variability among trials in an attempt to detect publication bias. If 10 or more trials are available, extrapolation based on asymmetry is plausible. However, due to scarcity of data in all comparisons, we were unable to perform a full analysis of reporting bias.

Data synthesis

For studies with a similar type of active intervention, we performed a meta-analysis to calculate a weighted treatment effect across trials using a random-effects (DerSimonian and Laird) model. We planned and carried out statistical analyses using Review Manager 5 (Review Manager 5.3). When it was not possible to perform a meta-analysis, we presented data narratively.

Subgroup analysis and investigation of heterogeneity

We planned to perform a subgroup analysis and to determine interaction tests to check for subgroup differences where meaningful. For the primary outcomes, we considered subgroup analyses for the following factors:

- dosage;
- duration of treatment;
- types of infantile haemangioma (superficial, deep, mixed, others);
- location of birthmark (low-risk or high-risk areas).

Due to scarcity of data in all comparisons, we were unable to perform a full investigation of heterogeneity.

Sensitivity analysis

We planned to conduct sensitivity analyses using trials classified as having low risk of bias in three core domains: allocation concealment, incomplete outcome data, and blinding of outcome assessment, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, due to scarcity of data in all comparisons, we were unable to perform a full sensitivity analysis.

'Summary of findings' tables

We assessed quality of the body of evidence (also known as certainty in the evidence) pertaining to primary and secondary outcomes using the principles of the GRADE system (Guyatt 2008). We also constructed 'Summary of findings' tables. Factors taken into consideration in the evaluation of quality of the evidence are study risk of bias, heterogeneity of data, directness of the evidence, precision of effect estimates, and potential publication bias (Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h). We developed the 'Summary of findings' table using a web-based version of the GRADEpro software (GRADEpro GDT), according to the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We selected information about currently used treatments for these 'Summary of findings' tables.

We developed 'Summary of findings' tables for the following comparisons:

- oral propranolol versus placebo;
- topical timolol maleate versus placebo;
- oral propranolol versus topical timolol maleate.

We assessed the quality of the evidence for the following outcomes in these comparisons:

- clearance (as assessed by a clinician);
- subjective measurements of improvement;
- adverse events;
- other measures of resolution;
- proportion of parents who consider their child still has a problem;
- proportion of children who consider they still have a problem; and
- aesthetic appearance.

For the outcome 'adverse events', we presented in the corresponding table the most frequent or the most important adverse event, or both, related to each intervention. When information about adverse events in general (including serious/severe adverse events) was available, we presented these results instead of individual findings.

RESULTS

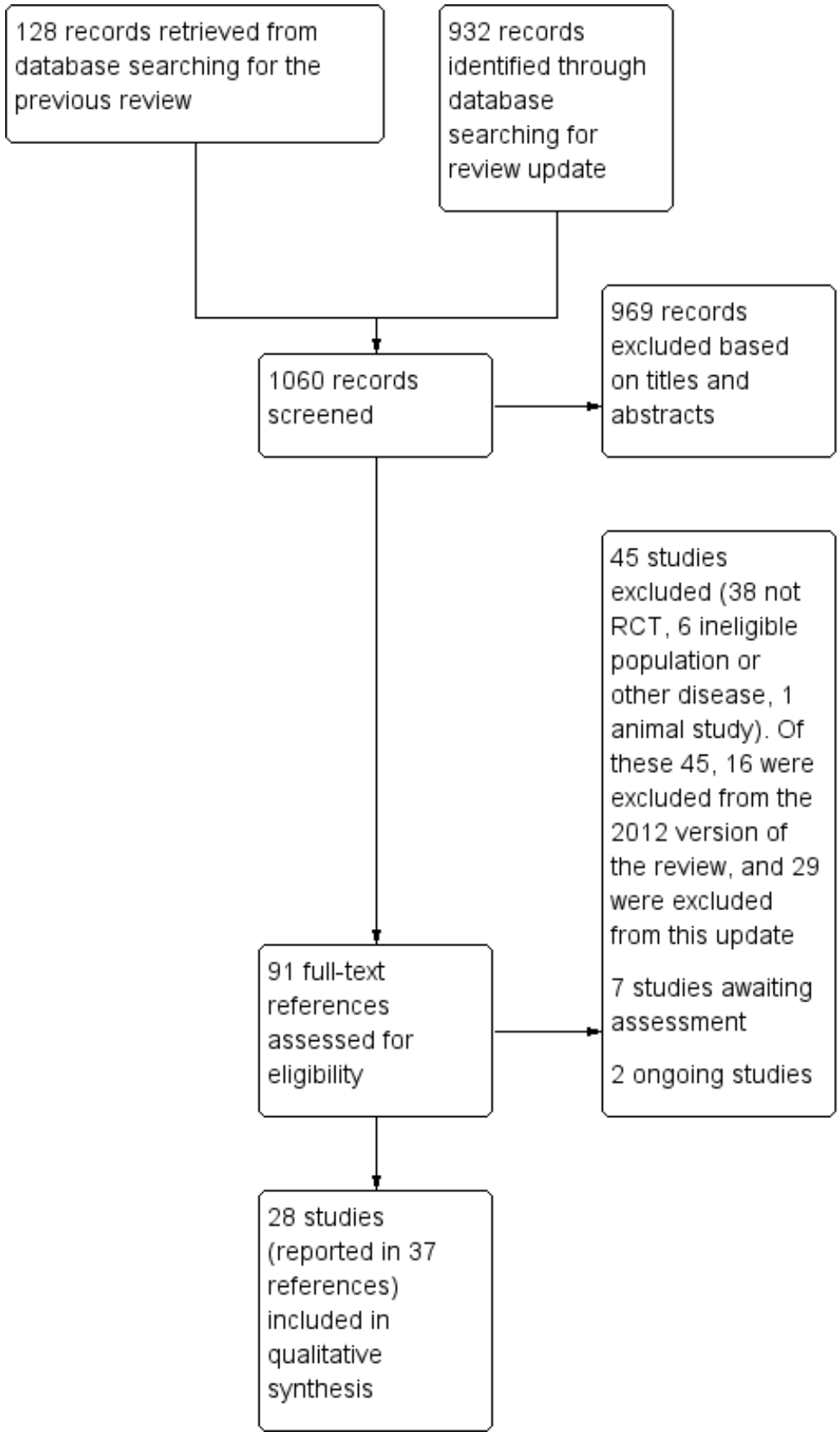
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Our updated searches identified 932 new records in addition to the 128 identified in the first version of this review. From the combined total of 1060 records, we screened out 969 records based on titles and abstracts. We examined the remaining 91 records in full text. From these, we excluded 45 studies (16 identified in the previous version of this review and 29 from this update, see Characteristics of excluded studies). We included 28 studies reported in 37 references (see Characteristics of included studies). We classified seven studies as awaiting assessment (see Characteristics of studies awaiting classification) and two further studies as ongoing (see Characteristics of ongoing studies). For a further description of the screening process, see the study flow diagram (Figure 1),

Figure 1. Study flow diagram.



Included studies

Twenty-eight studies (reported in 37 references) were eligible for inclusion in this updated review. All studies were published. The 28 studies enrolled and randomised a total of 1728 participants. Details of the included studies are provided in the Characteristics of included studies tables. Four of the 28 studies were included in the previous version of this review, with 24 new studies included in this update.

Design

A total of 21 studies used a two-arm design; six used a three-arm design; and one used a four-arm, parallel-group design.

Sample sizes

Numbers of children in the studies ranged from 12 in Zhang 2013 to 460 in Leaute-Labreze 2015. Only five studies reported a calculation of sample sizes prior to the beginning of the trial (Bauman 2014; Hogeling 2011; Kessels 2013; Leaute-Labreze 2015; Pope 2007).

Setting

Studies were conducted in Canada (Pope 2007), China (Feng 2000; Fu 2012; Gong 2015; Li 2016; Lu 2016; Tan 2012; Xu 2006; Zhang 2013; Zhong 2015; Zhu 2015), Germany (Jung 1977), Chile (Abarzua-Araya 2014), the UK (Batta 2002), the USA (Bauman 2014), Australia (Chan 2013; Hogeling 2011), Iran (Asilian 2015; Ehsani 2014), the Netherlands (Kessels 2013), France (Leaute-Labreze 2013; Leaute-Labreze 2015), India (Malik 2013; Tiwari 2016), and Egypt (Aly 2015; Tawfik 2015; Zaher 2013; Zaher 2016).

Participants

Baseline data were reported in 17 trials (Abarzua-Araya 2014; Asilian 2015; Batta 2002; Bauman 2014; Chan 2013; Ehsani 2014; Gong 2015; Hogeling 2011; Jung 1977; Kessels 2013; Leaute-Labreze 2013; Leaute-Labreze 2015; Li 2016; Lu 2016; Pope 2007; Zaher 2013; Zaher 2016). Four trials did not report the number of males and females included (Aly 2015; Malik 2013; Tiwari 2016; Xu 2006). One trial had equal numbers of males and females (Zhang 2013). The remaining 23 trials had a greater number of females than males, ranging from 58% in Li 2016 to 86% in Zaher 2013. The maximum age of enrolment at the beginning of the trial, as an inclusion criterion, ranged from 14 weeks in Batta 2002 to five years in Hogeling 2011; four studies did not clearly state this information (Lu 2016; Tawfik 2015; Zaher 2013; Zaher 2016). Age was heterogeneously reported in the included studies (mean, medians, ranges for total, or subgroups were reported). In 19 studies reporting mean age, this ranged from 12 weeks in Pope 2007 to 13.4 years in Tawfik 2015.

Subtypes of haemangiomas

Different subtypes of infantile haemangiomas were assessed, including children with mixed or deep IH (Li 2016; Lu 2016; Pope 2007; Zhong 2015), ulcerated or problematic IH (Hogeling 2011; Malik 2013; Tiwari 2016; Zaher 2013; Zaher 2016), or high-risk haemangiomas (Abarzua-Araya 2014; Aly 2015; Asilian 2015; Hogeling 2011; Lu 2016; Zaher 2013; Zaher 2016; Zhu 2015). One study assessed facial haemangiomas (defined as "periorbital/orbital tumours with visual impairment and/or large size/disfiguring haemangiomas") (Pope 2007). Six studies exclusively assessed superficial haemangiomas (Asilian 2015; Batta 2002; Chan 2013; Gong 2015; Kessels 2013; Zhu 2015), while one trial evaluated mixed haemangiomas only (Li 2016). Jung 1977 assessed planotuberous or tuberocavernous haemangiomas. The remaining trials did not provide additional information about the type of IH included or included a mixture of subtypes (Bauman 2014; Ehsani 2014; Feng 2000; Fu 2012; Leaute-Labreze 2013; Leaute-Labreze 2015; Tan 2012; Tawfik 2015; Xu 2006; Zhang 2013).

Interventions

The included trials assessed the following interventions for treating infantile haemangiomas.

- Lasers: pulsed dye laser (PDL), Nd:YAG laser, sequential/concurrent dual-wavelength laser.
- Beta blockers: oral/topical propranolol, topical timolol maleate.
- Steroids: oral prednisolone.
- Other treatments: topical bleomycin, intralesional methylene blue.
- High-intensity focused ultrasound (HIFU).
- Radiation therapy: soft X-ray radiation, ^{90}SR-^{90}Y radiation.

Some treatments were used in combination.

Comparators included active monitoring (observation), placebo, sham radiation, and the following interventions (single or in combination with another intervention).

- Beta blockers: intralesional/oral/topical propranolol, topical timolol maleate, oral atenolol.
- Oral ibuprofen plus oral paracetamol, oral captopril.
- Lasers: concurrent dual-wavelength laser, PDL alone, Nd:YAG laser.
- Steroids: oral prednisolone, intralesional triamcinolone, methylprednisolone (infusion).
- HIFU.
- Radiation therapy: ^{90}SR-^{90}Y radiation.

We identified no evidence for argon laser, carbon dioxide laser, erbium laser, excision, cryotherapy, imiquimod, interferon alpha, vincristine, or rapamycin. We found the following treatment comparisons.

- PDL versus wait-and-see (i.e active monitoring) (Batta 2002; Kessels 2013).
- Oral propranolol versus placebo (Hogeling 2011; Leaute-Labreze 2013; Leaute-Labreze 2015).
- Topical timolol maleate versus placebo (Chan 2013).
- Topical bleomycin versus placebo (Xu 2006).
- X-ray radiation versus sham radiation (Jung 1977).
- Nd:YAG laser versus topical timolol maleate (Tawfik 2015).
- Nd:YAG laser versus oral propranolol (Tan 2012; Zhong 2015).
- PDL + topical propranolol versus PDL alone (Ehsani 2014).
- PDL + topical timolol maleate versus PDL alone (Asilian 2015).
- Nd:YAG laser + oral propranolol versus Nd:YAG laser (Tan 2012; Zhong 2015).
- Nd:YAG laser + oral propranolol versus oral propranolol (Tan 2012; Zhong 2015).
- ^{90}SR-^{90}Y radiation + topical timolol maleate versus ^{90}SR-^{90}Y radiation (Zhu 2015).

- Sequential dual-wavelength laser + oral propranolol versus concurrent dual-wavelength laser + oral propranolol (Lu 2016).
- Oral propranolol versus topical propranolol (Zaher 2013).
- Oral propranolol versus intralesional propranolol (Zaher 2013).
- Topical propranolol versus intralesional propranolol (Zaher 2013).
- Oral propranolol versus oral atenolol (Abarzua-Araya 2014).
- Oral propranolol versus oral prednisolone (Bauman 2014; Malik 2013).
- Oral propranolol versus oral captopril (Zaher 2016).
- Oral propranolol versus topical timolol maleate (Gong 2015).
- Oral propranolol versus oral propranolol + oral prednisolone (Aly 2015; Malik 2013).
- Oral propranolol versus oral ibuprofen + oral paracetamol (Tiwari 2016).
- Oral propranolol + topical timolol maleate versus oral propranolol (Gong 2015; Li 2016).
- Oral propranolol + topical timolol maleate versus topical timolol maleate (Gong 2015).
- Oral propranolol + oral prednisolone versus oral prednisolone (Malik 2013).
- Intralesional methylene blue versus intralesional triamcinolone (Feng 2000).
- Oral prednisolone versus oral methylprednisolone (Pope 2007).
- HIFU at 3.5 W versus HIFU at 4.5 W (Fu 2012).
- HIFU at 3.5 W versus HIFU at 4.0 W (Fu 2012).
- HIFU at 4.0 W versus HIFU at 4.5 W (Fu 2012).

Duration of treatment and follow-up

The most common duration of treatment was 24 weeks, found in five trials (Abarzua-Araya 2014; Aly 2015; Chan 2013; Hogeling 2011; Tan 2012). In six trials, there was no fixed length of intervention for all children; the intervention was stopped for the following reasons: when the lesion was cleared; there was no clear improvement; in the presence of important side effects; or for parent's/clinician request, among other reasons (Batta 2002; Bauman 2014; Gong 2015; Kessels 2013; Zaher 2013; Zaher 2016). In 11 trials, this information was unclear or poorly reported (Asilian 2015; Ehsani 2014; Feng 2000; Fu 2012; Li 2016; Lu 2016; Malik 2013; Pope 2007; Tawfik 2015; Tiwari 2016; Zhang 2013).

Duration of follow-up ranged from 7 days in Xu 2006 to 72 months in Jung 1977. The most frequent duration of follow-up was six months, found in nine trials (Abarzua-Araya 2014; Asilian 2015; Chan 2013; Fu 2012; Hogeling 2011; Tan 2012; Zaher 2013; Zhong 2015; Zhu 2015). In three trials this information was unclear (Feng 2000; Lu 2016; Zhang 2013).

Outcomes

Fourteen trials assessed our primary outcome measure of clearance (Abarzua-Araya 2014; Asilian 2015; Batta 2002; Ehsani 2014; Feng 2000; Fu 2012; Jung 1977; Leaute-Labreze 2015; Tan 2012; Tawfik 2015; Tiwari 2016; Zaher 2013; Zaher 2016; Zhu 2015).

One trial reported a subjective measure of improvement (Pope 2007). Adverse events were fully reported in 20 trials (Abarzua-Araya 2014; Aly 2015; Asilian 2015; Batta 2002; Bauman 2014; Chan 2013; Ehsani 2014; Fu 2012; Gong 2015; Hogeling 2011; Kessels 2013; Leaute-Labreze 2015; Li 2016; Malik 2013; Tan 2012; Tiwari 2016; Zaher 2013; Zaher 2016; Zhong 2015; Zhu 2015). Other measures of resolution such as redness, reduction of volume, colour fading, haemoglobin levels, or mean size reduction were assessed in 16 trials (Aly 2015; Asilian 2015; Batta 2002; Bauman 2014; Chan 2013; Gong 2015; Hogeling 2011; Kessels 2013; Li 2016; Lu 2016; Malik 2013; Pope 2007; Tawfik 2015; Tiwari 2016; Xu 2006; Zhong 2015). One trial reported the proportion of parents who consider their child still has a problem (Batta 2002); the same trial also reported on requirement for surgical correction. No trials reported the proportion of children who consider they still have a problem. In addition, one trial reported findings related to aesthetic appearance (Kessels 2013).

Excluded studies

Among the 45 studies excluded after full-text assessment, six were excluded due to ineligible population or other diseases (Liu 2009; Midena 2008; Pancar 2011; Rouvas 2009; Tierney 2009; Zhou 2002), and one for being developed in animals (Zhou 2015). The remaining 38 excluded studies were not randomised trials. Details of these studies and reasons for exclusion are listed in the Characteristics of excluded studies tables.

Studies awaiting classification

We assessed seven studies as awaiting classification because only partial information was available for these references (from abstracts, conference proceedings, or registration entries in trial platforms, among other reasons) (Kuang 2014; Maier 2012; NCT00004436; NCT00555464; NCT00744185; NCT01072045; Pandey 2010). Preliminary details are reported in the Characteristics of studies awaiting classification tables.

Ongoing studies

We identified two ongoing trials from the updated searches (NCT01147601; NCT02913612). The designs of the trials are listed below.

- NCT01147601: topical 0.5% timolol maleate versus placebo, 2 to 3 drops to cover the haemangioma, twice daily.
- NCT02913612: timolol maleate gel forming solution drug versus wait-and-see (i.e. active monitoring).

Risk of bias in included studies

We summarised the risk of bias of all the studies in the Characteristics of included studies section. The 'Risk of bias' graph (review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies) is presented in Figure 2. The 'Risk of bias' summary (review authors' judgements about each 'Risk of bias' item for each included study) is presented in Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

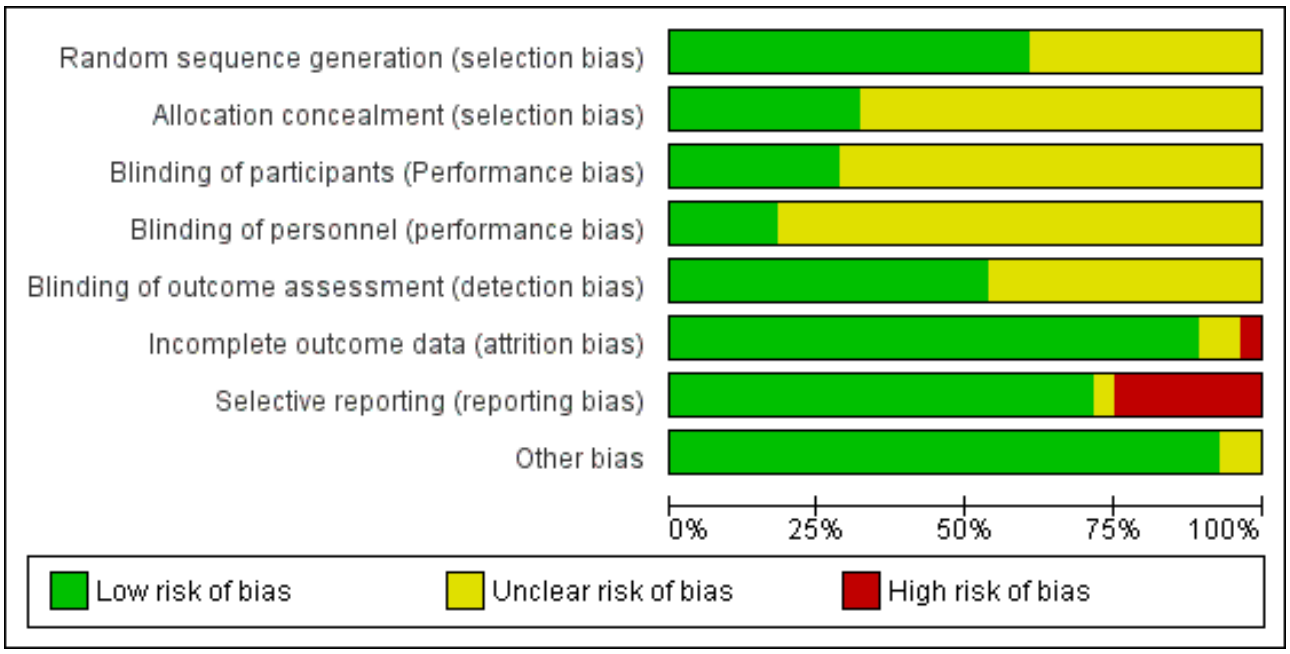


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

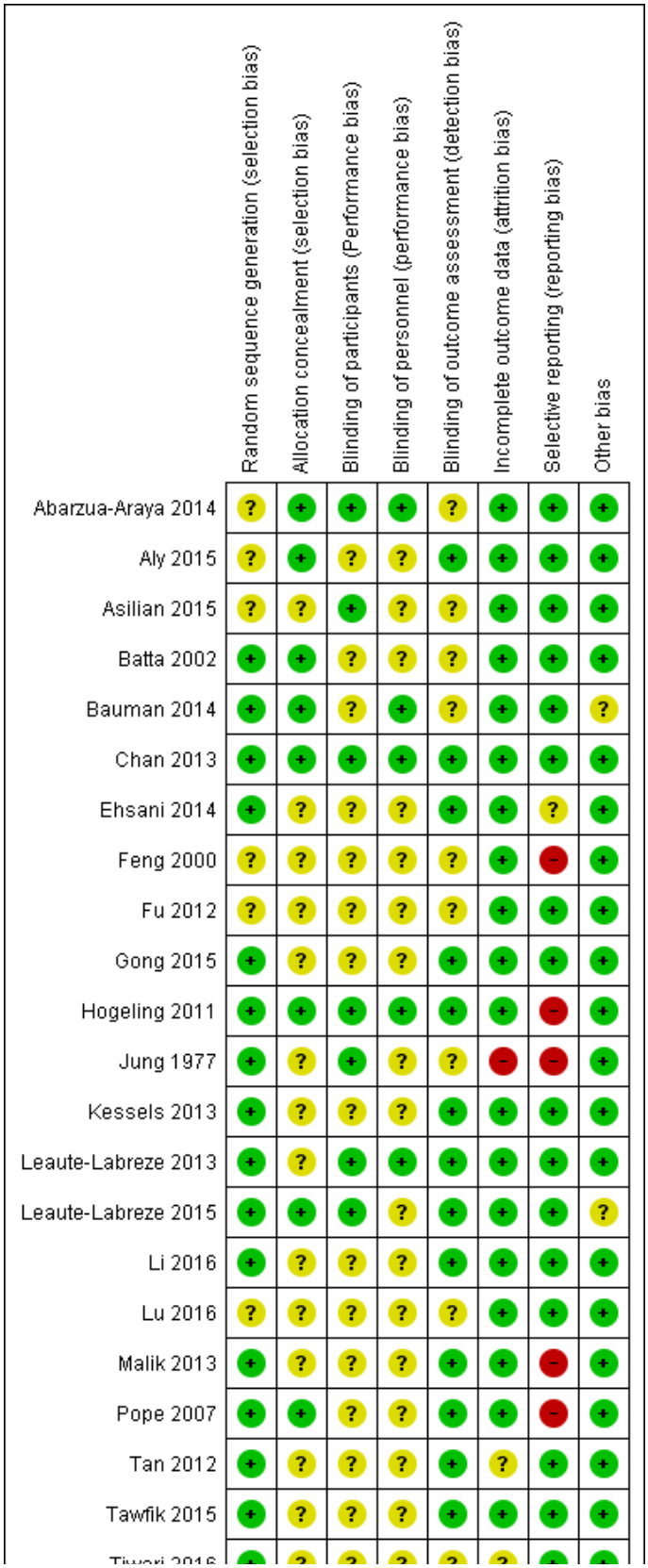
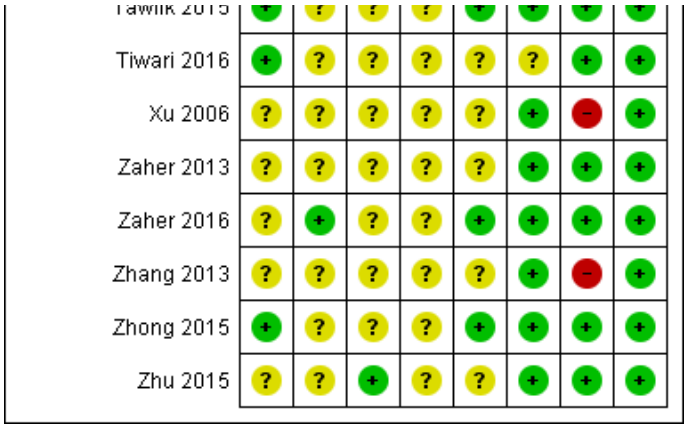


Figure 3. (Continued)



Allocation

Seventeen trials used an adequate method of randomisation and were hence rated as at low risk of bias (Batta 2002; Bauman 2014; Chan 2013; Ehsani 2014; Gong 2015; Hogeling 2011; Jung 1977; Kessels 2013; Leaute-Labreze 2013; Leaute-Labreze 2015; Li 2016; Malik 2013; Pope 2007; Tan 2012; Tawfik 2015; Tiwari 2016; Zhong 2015), while the other 11 did not provide sufficient information about the sequence generation process to permit judgement (unclear risk of bias) (Abarzua-Araya 2014; Aly 2015; Asilian 2015; Feng 2000; Fu 2012; Lu 2016; Xu 2006; Zaher 2013; Zaher 2016; Zhang 2013; Zhu 2015).

Nine studies specified adequate methods of allocation concealment and were hence rated as at low risk of bias (Abarzua-Araya 2014; Aly 2015; Batta 2002; Bauman 2014; Chan 2013; Hogeling 2011; Leaute-Labreze 2015; Pope 2007; Zaher 2016). The remaining trials (n = 19) did not specify allocation concealment methods and so were assessed as at unclear risk of bias.

Blinding

Eight trials reported blinding of participants (Abarzua-Araya 2014; Asilian 2015; Chan 2013; Hogeling 2011; Jung 1977; Leaute-Labreze 2013; Leaute-Labreze 2015; Zhu 2015), and we judged these trials to be at a low risk of performance bias. The remaining studies (n = 20) did not report this information clearly and so were judged to be at unclear risk of performance bias in relation to participants.

Five trials reported blinding of study personnel and so were rated as at low risk of performance bias (Abarzua-Araya 2014; Bauman 2014; Chan 2013; Hogeling 2011; Leaute-Labreze 2013). We rated the remaining 23 trials as at unclear risk of performance bias in relation to personnel.

Fifteen trials reported blinding of outcome assessment and so were rated as at low risk of bias (Aly 2015; Chan 2013; Ehsani 2014; Gong 2015; Hogeling 2011; Kessels 2013; Leaute-Labreze 2013; Leaute-Labreze 2015; Li 2016; Malik 2013; Pope 2007; Tan 2012; Tawfik 2015; Zaher 2016; Zhong 2015). The remaining trials (n = 13) did not report this information explicitly and so were rated as at unclear risk of bias.

We rated only three trials as at low risk of bias for all three of the blinding items assessed (Chan 2013; Hogeling 2011; Leaute-Labreze 2013).

Incomplete outcome data

Risk of attrition bias was high in Jung 1977 because of a high dropout rate (47% in the intervention group and 44% in the control group) with no reasons given. We assessed two trials as at unclear risk of bias (Tan 2012; Tiwari 2016). The risk of attrition bias was low in the remaining 25 trials due to a low or null dropout rate.

Selective reporting

There was evidence of selective omissions of outcomes or critical information from the publications of seven trials (Feng 2000; Hogeling 2011; Jung 1977; Malik 2013; Pope 2007; Xu 2006; Zhang 2013). In the Pope 2007 trial, the scores for a subjective measure of improvement as rated by the parents were not presented; the authors instead presented the correlation between the scores of the parents and the scores of the outcome assessors (intraclass correlation coefficient: 0.92). The choice of selective omission of the outcome did not appear to be based on outcome result, since highly significant findings were seen for the reported outcomes. We judged Ehsani 2014 to be at unclear risk of selective reporting because an outcome in their protocol was not included in their study report. We judged the remaining trials (n = 20) as at low risk of reporting bias.

Other potential sources of bias

There may be other sources of bias in one study related to the role of the sponsors in the development of the research (Leaute-Labreze 2015); hence we rated this trial as at unclear risk of bias for this domain. We found Bauman 2014 to be at unclear risk of other potential sources of bias due to the termination of the trial, which might generate biases in the results. We identified no additional sources of bias in the remaining studies (n = 26).

Effects of interventions

See: **Summary of findings for the main comparison** Oral propranolol compared to placebo for infantile haemangiomas of the skin; **Summary of findings 2** Topical timolol compared to placebo for infantile haemangiomas of the skin; **Summary**

of findings 3 Oral propranolol compared to topical timolol for infantile haemangiomas of the skin

Comparison 1. Interventions versus placebo: PDL versus wait-and-see (i.e. active monitoring)

For this comparison, we included the information from two trials with a total of 143 children (Batta 2002; Kessels 2013). Both authors included children with superficial early haemangiomas in the preproliferative or early proliferative growth phase. Batta 2002 used Chromos 585 nm wavelength venous flash-lamp pulsed dye laser without epidermal cooling (SLS Biophile, Dyfed, Wales, UK) at a pulse duration of 0.45 ms, with spot diameter of 3 to 5 mm, and energy fluence of 6.0 to 7.5 J/cm^2, and the treatment was repeated every 2 to 4 weeks. Duration of treatment was until the lesion cleared, stopped proliferating, stopped responding, or if the parents discontinued treatment (treatment maximum of one year), and children were followed until six months. Kessels 2013 used 595 nm PDL (Vbeam, Syneron Candela, Wayland, MA, USA) with 7-millimetre spot diameter, 30/10 to 40/10 epidermal cooling, at fluence range of 7 to 15 J/cm^2 and a pulse duration of 0.45 to 40.0 ms. The treatment was repeated every two to six weeks. The intervention ended when the child had complete remission, stop of proliferation, or no response of the haemangioma. Children were followed until 12 months.

Primary outcome 1: Clearance, as assessed by a clinician

One trial provided information about this outcome and reported a total of 52 cases of clearance (121 children; percentage of clearance: 42.9%) (Batta 2002): 25 children out of 60 (41.6%) in the PDL group and 27 out of 61 (44.2%) in the wait-and-see group reached clearance of lesions. This study found no differences in terms of clearance when comparing PDL with wait-and-see (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.62 to 1.42; Analysis 1.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Two trials provided information for four different adverse events. Batta 2002 provided information about 22 cases of skin atrophy (121 children; percentage of skin atrophy: 18.1%) and 36 cases of skin hypopigmentation (121 children; percentage of skin hypopigmentation: 29.7%). Seventeen children out of 60 (28.3%) in the PDL group and 5 out of 61 (8.1%) in the wait-and-see group had skin atrophy. The risk of skin atrophy after PDL was 3.46 times that after wait-and-see (RR 3.46, 95% CI 1.36 to 8.77; Analysis 1.2). In addition, 27 children out of 60 (45%) in the PDL group and 9 out of 61 (14.7%) in the wait-and-see group had skin hypopigmentation. The risk of skin hypopigmentation after PDL was 3.05 times that after wait-and-see (RR 3.05, 95% CI 1.57 to 5.93; Analysis 1.3).

Likewise, Kessels 2013 provided information about two cases of minimal crusting (22 children; percentage of minimal crusting: 9.09%) and two cases of pain (22 children; percentage of skin hypopigmentation: 9.09%). Two children out of 11 (18%) in the PDL group and 0 out of 11 (0%) in the wait-and-see group had minimal crusting. This study found no clear differences in terms of these adverse events when comparing PDL with wait-and-see, due to imprecision (RR 5.00, 95% CI 0.27 to 93.5; Analysis 1.4; and RR 5.00, 95% CI 0.27 to 93.5; Analysis 1.5).

Secondary outcome 1: Other measures of resolution

Batta 2002 provided information about 23 cases of no-redness (121 children; percentage of no-redness: 19%). Nineteen children out of 60 (31.6%) in the PDL group and 4 out of 61 (6.5%) in the wait-and-see group had no-redness. The risk of absence of redness after PDL was 4.83 times that after wait-and-see (RR 4.83, 95% CI 1.75 to 13.36; Analysis 1.6). Batta 2002 provided information about surface area after follow-up, reporting a median of 113 mm^2 (range 0 to 150) for the PDL group and a median of 146 mm^2 (range 0 to 2403) for the group under observation. Kessels 2013 provided information about median change in surface area at the age of 1 year, reporting a median of 0.20 cm^2 (interquartile range (IQR) -0.10 to 0.58) for the group receiving PDL versus a median of 0.00 cm^2 (IQR -0.10 to 0.4) for the group under observation.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

One trial provided information for this outcome with 20 cases (121 participants; percentage of parents: 16.5%) (Batta 2002). Eleven participants out of 60 (18.3%) in the PDL group and 9 out of 61 (14.7%) in the wait-and-see group considered their child still has a problem. This study found no clear differences for this outcome when comparing PDL with wait-and-see (RR 1.24, 95% CI 0.56 to 2.78; Analysis 1.7).

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

One trial provided information for this outcome with nine cases (22 children; percentage of aesthetic appearance: 40.9%) (Kessels 2013). A better cosmetic outcome was reported for 7 children out of 11 (63%) in the PDL group and 4 out of 11 (36%) in the wait-and-see group. This study found no clear differences for this outcome when comparing PDL with wait-and-see (RR 1.75, 95% CI 0.71 to 4.31; Analysis 1.8).

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

In Batta 2002, 7 out of 60 children in the PDL group compared with 3 out of 61 children in the wait-and-see group required surgical correction at 5 years' follow-up. There was no significant difference between groups for this outcome (RR 2.37, 95% CI 0.64 to 8.75; Analysis 1.9).

Comparison 2. Interventions versus placebo: oral propranolol versus placebo

For this comparison, we included information from three trials (312 children) (Hogeling 2011; Leaute-Labreze 2013; Leaute-Labreze 2015). Hogeling 2011 enrolled 40 children between the ages of 9 weeks and 5 years with facial infantile haemangioma or infantile haemangiomas in sites with potential for disfigurement. Children were randomly assigned to receive propranolol or placebo. Administration was initiated at a dosage of 1 mg/kg per day divided 3 times daily and then increased to 2 mg/kg per day divided 3 times daily from weeks 2 to 24. The children were followed up at weeks 0, 4, 8, 12, 16, 20, and 24. Duration of treatment and follow-up was 24 weeks in both cases. Leaute-Labreze 2013 enrolled 14 children

younger than 16 weeks with one or more non-threatening infantile haemangiomas of more than 1 cm in diameter, without vital or functional impairment. Children were randomly assigned to receive placebo or propranolol 3 mg/kg daily for 15 days, then 4 mg/kg daily for 15 additional days. Duration of treatment and follow-up was one month in both cases. Finally, Leaute-Labreze 2015 enrolled 456 infants between 35 and 150 days old with proliferating infantile haemangioma requiring systemic therapy. Children were randomly assigned to receive propranolol 1 mg/kg per day, 3 mg/kg per day, or placebo for 3 or 6 months. We reported data for the groups followed for six months in this analysis.

Primary outcome 1: Clearance, as assessed by a clinician

One trial provided information for this outcome (Leaute-Labreze 2015). Fifty children out of 102 (49%) in the oral propranolol group (1 mg/kg/day) and 2 out of 55 (3.6%) in the placebo group reached clearance of lesions. The risk of clearance after oral propranolol 1 mg/kg/day was 13.48 times that after placebo (RR 13.48, 95% CI 3.41 to 53.30; Analysis 2.1). Likewise, 61 children out of 101 (60.3%) in the oral propranolol group (3 mg/kg/day) and 2 out of 55 (3.6%) in the placebo group reached clearance of lesions. The risk of clearance after oral propranolol 3 mg/kg/day was 16.61 times that after placebo (RR 16.61, 95% CI 4.22 to 65.34; Analysis 2.1). We downgraded the quality of the evidence from high to moderate due to imprecision (see Summary of findings for the main comparison).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Three trials reported information about 26 cases of serious adverse events in general, but this was based only on information from a single trial (Leaute-Labreze 2015; percentage of cases: 5.1%), as the other two trials had zero events in both arms (Hogeling 2011; Leaute-Labreze 2013). Twenty-three children out of 427 (5.3%) in the oral propranolol group and 3 out of 82 (3.6%) in the placebo group had serious adverse events. This study found no differences in terms of adverse events when comparing oral propranolol with placebo (RR 1.05, 95% CI 0.33 to 3.39; Analysis 2.2). We downgraded the quality of the evidence from high to low due to imprecision (see Summary of findings for the main comparison). Likewise, we did not find a significant difference between oral propranolol and placebo at any doses, in terms of serious cardiovascular adverse events (Analysis 2.3) and other adverse events, including bronchospasm and hypoglycaemia (Analysis 2.4).

Secondary outcome 1: Other measures of resolution

Hogeling 2011 provided information about other measures of resolution, including per cent change in volume at 24 weeks and redness. For change in volume, the authors reported a reduction of mean haemangioma volume at 24 weeks of 45.9% (95% CI 11.60% to 80.20%) comparing oral propranolol with placebo (Analysis 2.5). We downgraded the quality of the evidence from high to moderate due to imprecision (See Summary of findings for the main comparison). Likewise, Hogeling 2011 reported improvement in redness at week 24 in 4 children out of 20 (20%) in the oral propranolol group and 0 out of 20 (0%) in the placebo group. This study found no clear difference in terms of redness improvement when comparing oral propranolol with placebo due to imprecision (RR 9.00, 95% CI 0.52 to 156.9; Analysis 2.6).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 3. Interventions versus placebo: topical timolol maleate versus placebo

For this comparison, we included the information from one trial (Chan 2013), with 41 children between the ages of 5 weeks and 24 weeks with small, focal superficial infantile haemangiomas. Children were randomly assigned to receive placebo or timolol maleate 0.5% gel. Administration was initiated by applying, with a fingertip, part of one drop of the gel onto the surface of the IH twice a day. Duration of treatment and follow-up was six months in both cases.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Chan 2013 provided information about serious cardiovascular events, reporting zero events of bradycardia and zero of hypotension (41 children). We downgraded the quality of the evidence from high to low due to imprecision (see Summary of findings 2).

Secondary outcome 1: Other measures of resolution

Chan 2013 provided information about absence of redness at the end of follow-up, reporting eight cases (41 children; percentage of absence of redness: 19.5%). Seven children out of 19 (36.8%) in the topical timolol maleate group and 1 out of 22 (4.5%) in the placebo group reached clearance of lesions. The absence of redness after topical timolol maleate was 8.11 times that after placebo (RR 8.11, 95% CI 1.09 to 60.09; Analysis 3.1). We downgraded the quality of the evidence from high to low due to imprecision (see Summary of findings 2). Chan 2013 also provided information about cases of volume reduction (equal to or more than 5%), reporting 11 cases (41 children; percentage of volume reduction: 26.8%). Nine children out of 19 (47.3%) in the topical timolol maleate group and 2 out of 22 (9%) in the placebo group reached clearance of lesions. Volume reduction after topical timolol maleate was 5.21 times that after placebo (RR 5.21, 95% CI 1.28 to 21.21; Analysis 3.1). We downgraded the quality of the evidence from high to low due to imprecision (see Summary of findings 2).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 4. Interventions versus placebo: topical bleomycin versus placebo

For this comparison, we included information from one trial with 30 children (Xu 2006). Thirty infants with "capillary hemangioma" at body surface aged less than six months were enrolled in this study. Children were randomly assigned to receive placebo or bleomycin emulsion 2 mg/dL by the ultrasound-atomised technique three times per day for one week and made a biopsy. Duration of treatment and follow-up was seven days in both cases.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

We found no information on this outcome for this comparison.

Secondary outcome 1: Other measures of resolution

In Xu 2006, two-thirds of the 15 haemangiomas treated with bleomycin, a very toxic agent, became deep red and their surfaces began to shrink slightly at day 7 (10 cases; 30 children). Ten children out of 15 (66%) in the topical bleomycin group and 0 out of 15 (0%) in the placebo group reached clearance of lesions. The shrink of lesions after topical bleomycin was 21 times greater than after placebo, but the 95% CI was wide, showing imprecision (RR 21.00, 95% CI 1.34 to 328.86; Analysis 4.1).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 5. Interventions versus placebo: X-ray radiation versus sham radiation

For this comparison, we included the information from one trial with 100 children (Jung 1977). The infantile haemangiomas were irradiated 2 or 3 times with 400 rad (rad = unit of absorbed radiation dose) at intervals of 4 to 8 weeks. For more than 4 cm of diameter, the 400 rad was dissolved in 3 x 200 rad at weekly intervals. Follow-up was performed at the end of each month, then monitored on an outpatient basis in six-month intervals. Duration of treatment ranged from 4 to 7 weeks; children were followed until 72 months.

Primary outcome 1: Clearance, as assessed by a clinician

Jung 1977 provided information on this outcome, reporting a total of 34 cases of clearance (100 children; percentage of clearance: 34%). Eighteen children out of 51 (35.2%) in the X-ray radiation group and 16 out of 49 (32.6%) in the sham radiation group reached clearance of lesions. This study found no differences in terms of clearance when comparing X-ray radiation with sham radiation (RR 1.08, 95% CI 0.63 to 1.87; Analysis 5.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

We found no information on this outcome for this comparison.

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 6. Laser comparisons: Nd:YAG laser versus topical timolol maleate

For this comparison, we included information from one trial with 60 children (Tawfik 2015). Children were randomly allocated into two groups. Group 1 was assigned to receive timolol maleate 0.5% drops (5 mg/mL) to apply twice a day. Group 2 was treated using combined sequential dual-wavelength 585 nm PDL and 1064 nm Nd:YAG laser (Synergy Multiplex, Cynosure, Westford, MA, USA) to flat superficial haemangiomas. The parameters were: PDL

with a 7-millimetre spot size, 6-millisecond pulse duration, and fluence of 4.5 to 6 J/cm^2. After a 1-second delay, Nd:YAG laser was administered at 15-millisecond pulse duration and fluence of 25 to 35 J/cm^2. Parameters for children with mixed haemangiomas were: PDL with a 7-millimetre spot size, 10-millisecond pulse duration, and fluence of 6 to 7.5 J/cm^2. After a 1-second delay, Nd:YAG laser was administered at 15-millisecond pulse duration and fluence of 30 to 40 J/cm^2. Interventions were administered in a maximum of six sessions; children were followed until three months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Tawfik 2015 narratively reported four cases of crusts and hyperpigmentation in the laser group after the first session. One child in the timolol maleate group reported shortness of breath and insomnia.

Secondary outcome 1: Other measures of resolution

Tawfik 2015 provided information on mean haemoglobin level after treatment with timolol maleate or laser, reporting a mean of 1.67 (standard deviation (SD) = 0.54) for the timolol maleate group versus a mean of 2.58 (SD = 0.86) for the laser group. Mean haemoglobin levels after topical timolol maleate were 0.91 units smaller than after Nd:YAG laser treatment (mean difference (MD) -0.91, 95% CI -1.27 to -0.55; Analysis 6.1).

Tawfik 2015 also provided information on children with an improvement between 76% and 100% (excellent improvement), reporting 12 cases (60 children; 20%). Nine children out of 30 (30%) in the Nd:YAG laser group and 3 out of 30 (10%) in the topical timolol maleate group reported excellent improvement. No clear differences in terms of this score were found when comparing Nd:YAG laser with topical timolol maleate due to imprecision (RR 3.00, 95% CI 0.90 to 10.01; Analysis 6.2).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 7. Laser comparisons: Nd:YAG laser versus oral propranolol

For this comparison, we included information from two trials with a total of 105 children (Tan 2012; Zhong 2015). In Tan 2012, Group B received Nd:YAG laser with spot diameter of 1.5- to 3.0-millimetre handle; energy density at 170 to 240 J/cm^2 range; width from 20 to 50 each session every 6 weeks. Group C received only twice-daily dose of 0.5 mg/kg oral propranolol, increased two weeks later to 0.8 mg/kg, and four weeks later to 1.0 mg/kg. Duration of treatment and follow-up were six months in both cases. In Zhong 2015, Group C received Nd:YAG once, with parameters adjusted according to lesion depth. Group B received propranolol 1.5 mg/kg over 3 divided doses per day for a total of 6 months. Treatment ranged from three to six months. Follow-up was six months.

Primary outcome 1: Clearance, as assessed by a clinician

Tan 2012 provided information on this outcome, reporting a total of 4 cases of clearance out of 65 children (percentage of clearance: 6.1%). Three children out of 35 (8.5%) in the Nd:YAG laser group and 1 out of 30 (3.3%) in the oral propranolol group reached complete clearance of lesions. This study found no clear differences in terms of clearance when comparing Nd:YAG laser with oral propranolol due to imprecision (RR 2.57, 95% CI 0.28 to 23.44; Analysis 7.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Tan 2012 provided information about cases of hyperpigmentation, reporting a total of 4 cases out of 65 children (6.1%). Three children out of 35 (8.5%) in the Nd:YAG laser group and 1 out of 30 (3.3%) in the oral propranolol group reported hyperpigmentation. This study found no clear differences in terms of hyperpigmentation when comparing Nd:YAG laser with oral propranolol (RR 2.57, 95% CI 0.28 to 23.44; Analysis 7.2). Zhong 2015 also provided information about cases of pigmentation and thinning, reporting a total of 12 cases (40 children, 30%). Three children out of 20 (15%) in the Nd:YAG laser group and 9 out of 20 (45%) in the oral propranolol group reported this combined outcome. This study found no clear differences in terms of pigmentation and thinning when comparing Nd:YAG laser with oral propranolol (RR 0.33, 95% CI 0.11 to 1.05; Analysis 7.3).

Both studies provided information about cases of superficial scar, reporting a total of 11 cases out of 105 children (10.4%). Seven children out of 55 (12.2%) in the Nd:YAG laser group and 4 out of 50 (8%) in the oral propranolol group reported superficial scars. These studies found no clear differences in terms of superficial scars when comparing Nd:YAG laser with oral propranolol (RR 1.52, 95% CI 0.24 to 9.58; I^2 = 48%; Analysis 7.4). Zhong 2015 also reported that no cases of severe hypoglycaemia, hypotension, or Reynauld's syndrome (extremity coldness) were found.

Secondary outcome 1: Other measures of resolution

Zhong 2015 provided information about "excellent response", defined as an improvement equal or superior to 95% performed by two clinicians, reporting a total of eight cases (40 children; 20%). Two children out of 20 (10%) in the Nd:YAG laser group and 6 out of 20 (30%) in the oral propranolol group reported this response. This study found no clear differences when comparing Nd:YAG laser with oral propranolol (RR 0.33, 95% CI 0.08 to 1.46; Analysis 7.5).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 8. Laser comparisons: PDL + topical propranolol versus PDL alone

For this comparison, we included information from one trial with 19 children (Ehsani 2014). Children were randomly divided into two groups: the first group (nine children) were treated with PDL (spot size 7 mm, fluence 12 J/cm^2, pulse duration 1.5 ms, dynamic cooling device 40/40), while second group (10 children) were treated with the same PDL sessions together with topical ointment of propranolol hydrochloride 1% applied twice a day for at least 12 weeks. Duration of treatment was at least 12 weeks; children were followed until four months.

Primary outcome 1: Clearance, as assessed by a clinician

Ehsani 2014 provided information on this outcome, reporting a total of seven cases of clearance (19 children; percentage of clearance: 36.8%). Five children out of 10 (50%) in the PDL + topical propranolol group and 2 out of 9 (22%) in the PDL group reached complete clearance of lesions. This study found no clear differences in terms of clearance when comparing PDL + topical propranolol with PDL alone (RR 2.25, 95% CI 0.57 to 8.86; Analysis 8.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Ehsani 2014 provided information about serious cardiovascular events and other adverse events, reporting zero cases for both outcomes.

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 9. Laser comparisons: PDL + topical timolol maleate versus PDL alone

For this comparison, we included information from one trial with 32 children (Asilian 2015). Children were divided into two groups: one group was treated with four sessions of PDL (585 nm, spot size 5 mm, fluence 9 J/cm^2, pulse duration 450 ms, without cooling, and spot overlap 20%) plus administration of timolol maleate gel 0.5%, while the other group received PDL plus lubricant gel as placebo. Duration of treatment was unclear; children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Asilian 2015 provided information on this outcome, reporting a total of two cases of clearance (32 children; percentage of clearance: 6.2%). One child out of 16 (6.2%) in the PDL + topical timolol maleate group and 1 out of 16 (6.2%) in the PDL group reached complete clearance of lesions. This study found no differences in terms of clearance when comparing PDL + topical timolol maleate with PDL alone (RR 1.00, 95% CI 0.07 to 14.64; Analysis 9.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Asilian 2015 provided information about severe adverse events such as hypotension, bradycardia, sleep disturbance, and anxiety, reporting zero cases.

Secondary outcome 1: Other measures of resolution

Asilian 2015 provided information about mean size reduction after treatment, reporting a mean of 17.62 cm (SD = 6.97) for the PDL + timolol maleate group versus a mean of 12 cm (SD = 5.71) for the PDL-alone group. The mean size reduction after PDL + timolol maleate was 5.62 cm greater than after PDL alone (MD 5.62, 95% CI 1.21 to 10.03; Analysis 9.2).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 10. Laser comparisons: Nd:YAG laser + oral propranolol versus Nd:YAG laser

For this comparison, we included information from two trials with a total of 107 children (Tan 2012; Zhong 2015). In Tan 2012, one of the groups received Nd:YAG laser using spot diameter of 1.5- to 3.0-millimetre handle; energy density at 170 to 240 J/cm^2 range; width from 20 to 50 each session every 6 weeks; the first 2 days after laser treatment start oral propranolol 0.5 mg/kg/day (twice daily) increased dosage 2 weeks later to 0.8 mg/kg/day, 4 weeks later increased to 1.0 mg/kg/day. The other group received only Nd:YAG laser with same parameters, one session every six weeks. Duration of treatment and follow-up was six months in both cases. In Zhong 2015, Group C received Nd:YAG once, with parameters adjusted according to lesion depth. Group B received propranolol 1.5 mg/kg/day over three doses per day for a total of six months. Treatment ranged from three to six months. Follow-up was six months.

Primary outcome 1: Clearance, as assessed by a clinician

Tan 2012 provided information on this outcome, reporting a total of 12 cases of clearance (67 children; percentage of clearance: 17.9%). Nine children out of 32 (28%) in Nd:YAG laser + oral propranolol group and 3 out of 35 (8.5%) in Nd:YAG laser group reached complete clearance of lesions. This study found no clear differences in terms of clearance when comparing Nd:YAG laser + oral propranolol with Nd:YAG laser alone, as the 95% confidence interval marginally included 1 (RR 3.28, 95% CI 0.97 to 11.06; Analysis 10.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Tan 2012 provided information about hyperpigmentation, reporting a total of seven cases (67 children; 10.4%). Four children out of 32 (12.5%) in the Nd:YAG laser + oral propranolol group and 3 out of 35 (8.5%) in the Nd:YAG laser group reported hyperpigmentation. This study found no differences in terms of hyperpigmentation when comparing Nd:YAG laser + oral propranolol with Nd:YAG laser alone (RR 1.46, 95% CI 0.35 to 6.02; Analysis 10.2). In addition, Zhong 2015 provided information on cases of pigmentation and thinning, reporting a total of five cases (40 children; 12.5%). Two children out of 20 (10%) in the Nd:YAG laser + oral propranolol group and 3 out of 20 (15%) in the Nd:YAG laser group reported this combined outcome. This study found no clear differences in terms of pigmentation and thinning when comparing Nd:YAG laser with oral propranolol (RR 0.67, 95% CI 0.12 to 3.57; Analysis 10.3).

Both studies provided information about superficial scars, reporting a total of nine cases (107 children; 8.4%). Two children out of 52 (3.8%) in the Nd:YAG laser + oral propranolol group and 7 out of 55 (12.7%) in the Nd:YAG laser group reported superficial scars. This study found no clear difference in terms of superficial scars when comparing Nd:YAG laser + oral propranolol with Nd:YAG laser alone (RR 0.37, 95% CI 0.09 to 1.48; Analysis 10.4).

Secondary outcome 1: Other measures of resolution

Zhong 2015 provided information about "excellent response", defined as an improvement equal or superior to 95% performed by two clinicians, reporting a total of eight cases (40 children; 20%). Two children out of 20 (10%) in the Nd:YAG laser+ oral propranolol group and 6 out of 20 (30%) in the Nd:YAG laser-alone group reported this response. The risk of excellent response after Nd:YAG laser + oral propranolol was 8.5 times that after Nd:YAG laser alone (RR 8.50, 95% CI 2.25 to 32.06; Analysis 10.5).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 11. Laser comparisons: Nd:YAG laser + oral propranolol versus oral propranolol

For this comparison, we included information from two trials with a total of 102 children (Tan 2012; Zhong 2015). In Tan 2012, one of the groups received Nd:YAG laser using spot diameter of 1.5- to 3.0-millimetre handle; energy density at 170 to 240 J/cm^2 range; width from 20 to 50 each session every 6 weeks; the first 2 days after laser treatment start oral propranolol 0.5 mg/kg/day (twice daily) increased dosage 2 weeks later to 0.8 mg/kg/day, 4 weeks later increased to 1.0 mg/kg/day. The other group received only oral propranolol with the same scheme. Duration of treatment and follow-up was six months in both cases. In Zhong 2015, Group C received Nd:YAG once, with parameters adjusted according to lesion depth. Group B received propranolol 1.5 mg/kg/day over three doses per day for a total of six months. Treatment ranged from three to six months. Follow-up was six months.

Primary outcome 1: Clearance, as assessed by a clinician

Tan 2012 provided information on this outcome, reporting a total of 10 cases of clearance (62 children; percentage of clearance: 16.1%). Nine children out of 32 (28%) in the Nd:YAG laser + oral propranolol group and 1 out of 30 (3.3%) in the oral propranolol group reached complete clearance of lesions. The risk of clearance after Nd:YAG laser + oral propranolol was 8.44 times that after oral propranolol alone (RR 8.44, 95% CI 1.14 to 62.66; Analysis 11.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Tan 2012 provided information about hyperpigmentation, reporting a total of five cases (62 children; 8.06%). Four children out of 32 (12.5%) in the Nd:YAG laser + oral propranolol group

and 1 out of 30 (3.3%) in the oral propranolol group reported hyperpigmentation. This study found no clear differences in terms of hyperpigmentation when comparing Nd:YAG laser + oral propranolol with oral propranolol (RR 3.75, 95% CI 0.44 to 31.68; Analysis 11.2). In addition, Zhong 2015 provided information on cases of pigmentation and thinning, reporting a total of 11 cases (40 children; 27.5%). Two children out of 20 (10%) in the Nd:YAG laser + oral propranolol group and 9 out of 20 (45%) in the oral propranolol group reported this combined outcome. The risk of this combined outcome after Nd:YAG laser + oral propranolol was 78% lower than after oral propranolol alone (RR 0.22, 95% CI 0.05 to 0.90; Analysis 11.3).

Both studies provided information about superficial scars, reporting a total of six cases (102 children; 5.8%). Two children out of 52 (3.8%) in the Nd:YAG laser + oral propranolol group and 4 out of 50 (8%) in the oral propranolol group reported superficial scars. This study found no clear differences in terms of superficial scars when comparing Nd:YAG laser + oral propranolol with oral propranolol (RR 0.60, 95% CI 0.05 to 7.63; Analysis 11.4).

Secondary outcome 1: Other measures of resolution

Zhong 2015 provided information about "excellent response", defined as an improvement equal or superior to 95% performed by two clinicians, reporting a total of 23 cases (40 children; 57.5%). Seventeen children out of 20 (85%) in the Nd:YAG laser group and 6 out of 20 (30%) in the oral propranolol group reported this response. Excellent response after Nd:YAG laser + oral propranolol was 2.83 times greater than after oral propranolol alone (RR 2.83, 95% CI 1.42 to 5.67; Analysis 11.5).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 12. Laser comparisons: ^{90}SR-^{90}Y radiation + topical timolol maleate versus ^{90}SR-^{90}Y radiation

For this comparison, we included information from one trial with 72 children (Zhu 2015). One of the groups received 1 to 2 courses of ^{90}SR-^{90}Y (applicator area of 2x2 and a surface-absorbed dose rate of 2.2 Gy/min) contact therapy and local external application of 0.5% topical timolol maleate solution on the area for 3 to 6 months. Children in the control group received an identical dosage and treatment course of ^{90}SR-^{90}Y contact therapy with local topical application of normal saline for three to six months. In cases with a total haemangioma area of < 20 cm^2, a single course of treatment consisted of a radiation dose of 2 to 2.4 Gy, once per day, for 5 consecutive days. In cases with a total haemangioma area of > 20 cm^2, a single course of treatment consisted of a radiation dose of 1 to 1.2 Gy, once per day, for 10 consecutive days. Duration of treatment ranged from three to six months; children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Zhu 2015 provided information on this outcome, reporting a total of 55 cases of clearance (72 children; percentage of clearance: 76.3%). Thirty-three children out of 37 (89.1%) in the ^{90}SR-^{90}Y radiation + topical timolol maleate group and 22 out of 35 (62.8%) in the ^{90}SR-^{90}Y radiation group reached complete clearance of lesions. Clearance after ^{90}SR-^{90}Y radiation + topical timolol maleate was 1.42 times greater than after ^{90}SR-^{90}Y radiation alone (RR 1.42, 95% CI 1.07 to 1.87; Analysis 12.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Zhu 2015 provided information about adverse events in general, such as mild itching, mild skin flaking, and pruritus, reporting a total of 22 cases (72 children; 30.5%). Twelve children out of 37 (32.4%) in the ^{90}SR-^{90}Y radiation + topical timolol maleate group and 10 out of 35 (28.5%) in the ^{90}SR-^{90}Y radiation group reported adverse events. This study found no differences in terms of adverse events when comparing ^{90}SR-^{90}Y radiation + topical timolol maleate with ^{90}SR-^{90}Y radiation alone (RR 1.14, 95% CI 0.56 to 2.29; Analysis 12.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 13. Laser comparisons: sequential dual-wavelength laser + oral propranolol versus concurrent dual-wavelength laser + oral propranolol

For this comparison, we included information from one trial with 61 children (Lu 2016). One of the groups received dual-wavelength laser therapy after discontinuation of oral propranolol (1 to 2 mg/kg/d). Propranolol treatment was stopped when maximised treatment effect was achieved. The second group were treated with oral propranolol for one week before laser therapy was added concurrently. Duration of treatment and follow-up was unclear.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Lu 2016 narratively described general information about adverse events. The authors reported two cases of upper respiratory tract infection, three cases of mild hyperkalaemia, and one case with decreased appetite.

Secondary outcome 1: Other measures of resolution

Lu 2016 provided information about the efficacy rating between the two groups evaluated by means of a 0-to-10 scale. Three researchers independently scored the treatment effect (changes of lesions appearance by digital photograph) by each month, and the average of these scores was reported. Complete resolution of the haemangioma was considered if the lesion achieved 1 or 0 points. At 3 months, the sequential-treatment group obtained a mean score of 6.23 units (SD = 0.99), and the concurrent-treatment group obtained a mean score of 7 units (SD = 0.46). The mean score after sequential dual-wavelength laser + oral propranolol was 0.77 units lower than after concurrent dual-wavelength laser + oral propranolol (MD -0.77, 95% CI -1.16 to -0.38; Analysis 13.1).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 14. Propranolol comparisons: oral propranolol versus topical propranolol

For this comparison, we included information from one trial with 30 children (Zaher 2013). Children with problematic infantile haemangioma (rapidly progressive, compromising vital functions, or causing cosmetic disfigurement) were randomised into three groups. Group A received oral propranolol, 2 mg/kg/day divided into two daily doses. Group B received topical propranolol 1% ointment in a hydrophilic base, applied twice daily. The intervention ended if "complete resolution occurred, if a sustained plateau in the size of the hemangioma was reached for a period of 2 months of treatment or if any intolerable side effects from propranolol developed". Children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Zaher 2013 provided information on this outcome, reporting a total of 12 cases of clearance (30 children; percentage of clearance: 40%). Nine children out of 15 (60%) in the oral propranolol group and 3 out of 15 (20%) in the topical propranolol group reached complete clearance of lesions. The risk of clearance after oral propranolol was three times that after topical propranolol (RR 3.00, 95% CI 1.01 to 8.95; Analysis 14.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Zaher 2013 provided information about syncopal attack, reporting a total of three cases (30 children; 10%). Three children out of 15 (60%) in the oral propranolol group and 0 out of 15 (0%) in the topical propranolol group reported syncopal attack. This study found no clear differences (due to imprecision) in terms of syncopal attack when comparing oral propranolol with topical propranolol (RR 7.00, 95% CI 0.39 to 124.83; Analysis 14.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 15. Propranolol comparisons: oral propranolol versus intralesional propranolol

For this comparison, we included information from one trial with 30 children (Zaher 2013). Children with problematic infantile haemangioma (rapidly progressive, compromising vital functions, or causing cosmetic disfigurement) were randomised into three groups. Group A received oral propranolol, 2 mg/kg/day divided into two daily doses. Group C received intralesional propranolol. The intervention ended if "complete resolution occurred, if a sustained plateau in the size of the hemangioma was reached for a period of 2 months of treatment or if any intolerable side effects from propranolol developed". Children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Zaher 2013 provided information on this outcome, reporting a total of 11 cases of clearance (30 children; percentage of clearance: 36.6%). Nine children out of 15 (60%) in the oral propranolol group

and 2 out of 15 (13.3%) in the intralesional propranolol group reached complete clearance of lesions. The risk of clearance after oral propranolol was 4.5 times that after intralesional propranolol (RR 4.50, 95% CI 1.16 to 17.44; Analysis 15.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Zaher 2013 provided information about syncopal attack, reporting a total of three cases (30 children; 10%). Three children out of 15 (20%) in the oral propranolol group and 0 out of 15 (0%) in the intralesional propranolol group reported syncopal attack events. This study found no clear differences (due to imprecision) in terms of syncopal attack when comparing oral propranolol with intralesional propranolol (RR 7.00, 95% CI 0.39 to 124.83; Analysis 15.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 16. Propranolol comparisons: topical propranolol versus intralesional propranolol

For this comparison, we included information from one trial with 30 children (Zaher 2013). Children with problematic infantile haemangioma (rapidly progressive, compromising vital functions, or causing cosmetic disfigurement) were randomised into three groups. Group B received topical propranolol 1% ointment in a hydrophilic base, applied twice daily. Group C received intralesional propranolol. The intervention ended if "complete resolution occurred, if a sustained plateau in the size of the hemangioma was reached for a period of 2 months of treatment or if any intolerable side effects from propranolol developed". Children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Zaher 2013 provided information on this outcome, reporting a total of five cases of clearance (30 children; percentage of clearance: 16.6%). Three children out of 15 (20%) in the topical propranolol group and 2 out of 15 (13.3%) in the intralesional propranolol group reached complete clearance of lesions. This study found no clear differences in terms of clearance when comparing topical propranolol with intralesional propranolol (RR 1.50, 95% CI 0.29 to 7.73; Analysis 16.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Zaher 2013 provided information about syncopal attack, reporting zero events for this comparison.

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 17. Propranolol comparisons: oral propranolol versus oral atenolol

For this comparison, we included information from one trial with 23 children (Abarzua-Araya 2014). Children were randomised to receive either atenolol or propranolol. Thirteen children receive propranolol in a dose of 2 mg/kg/d in three daily doses for 6 months, and 10 children receive atenolol in a dose of 1 mg/kg/d in a single daily dose for 6 months. Duration of treatment and follow-up was six months in both cases.

Primary outcome 1: Clearance, as assessed by a clinician

Abarzua-Araya 2014 provided information on this outcome, reporting a total of 13 cases of clearance (23 children; percentage of clearance: 56.5%). Six children out of 10 (60%) in the oral propranolol group and 7 out of 13 (53.8%) in the oral atenolol group reached complete clearance of lesions. This study found no differences in terms of clearance when comparing oral propranolol with oral atenolol (RR 1.11, 95% CI 0.55 to 2.27; Analysis 17.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Abarzua-Araya 2014 provided information about adverse events in general and serious cardiovascular events, reporting zero events for this comparison.

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 18. Propranolol comparisons: oral propranolol versus oral prednisolone

For this comparison, we included information from two trials with a total of 39 children (Bauman 2014; Malik 2013). In Bauman 2014, participants were infants aged from two weeks to six months with actively proliferating and symptomatic IH. Nineteen were enrolled and randomly assigned to prednisolone (n = 8) or propranolol (n = 11), both treatments given at a dose of 2 mg/kg/d until halted owing to toxic effects or clinical response. Treatment was stopped if IH resolved; no measurable improvement was noted in the lesion at two sequential monthly evaluations; in the presence of severe adverse events; at caretaker's or physician request; or no clinical improvement after one month. Children were followed for at least four months.

In Malik 2013, 30 children aged from one week to eight months with potentially disfiguring or functionally threatening IH were randomised into three equal groups: Group A, propranolol (2 to 3 mg/kg/d); Group B, prednisolone (1 to 4 mg/kg/d); and Group C, receiving both for a minimum duration of three months. After discharge, all children were re-evaluated after eight days of treatment and then every month for a minimum of three months. Duration of treatment was three months or more; children were followed until 18 months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Bauman 2014 provided information about severe adverse events, such as Cushingoid appearance and gastrointestinal upset, reporting a total of six cases (19 children; 31.5%). One child out of 11 (9%) in the oral propranolol group and 5 out of 8 (62.5%) in the oral prednisolone group reported severe adverse events, and the corresponding risk ratio favoured the oral propranolol group; however, the confidence interval was wide and did marginally include 1 showing some uncertainty (RR 0.15, 95% CI 0.02 to 1.02; Analysis 18.1).

Likewise, Malik 2013 provided information about complications in general, reporting a total of 11 cases (20 children; 55%). Two children out of 10 (20%) in the oral propranolol group and 9 out of 10 (90%) in the oral prednisolone group reported complications. The risk of complications after oral propranolol was 78% lower than after oral prednisolone (RR 0.22, 95% CI 0.06 to 0.78; Analysis 18.2). Malik 2013 also assessed the incidence of serious cardiovascular events such as bradycardia and hypotension, reporting zero events for both adverse events.

Secondary outcome 1: Other measures of resolution

Malik 2013 provide information about two measures of resolution. The authors stated that "Measure of assessment for colour and size was based on Visual Analogue Scale (VAS) ranging from −10 to +10 by comparing follow-up images to the baseline photograph pretreatment. Here, 0 represented the baseline photograph, a decrease resulting in a minus number and an increase in a + number" (Malik 2013). Regarding colour fading, Malik 2013 reported a mean score of -9 units (SD = 1.7) in the visual analogue scale for the propranolol group, versus a mean of -8 units (SD = 2.9) for the prednisolone group. This study found no clear difference in terms of colour fading score when comparing oral propranolol with oral prednisolone (MD -1.00, 95% CI -3.08 to 1.08; Analysis 18.3). Malik 2013 also assessed the percentage of mean size reduction after treatment, reporting a mean size of 89.8 (SD = 10.3) for the propranolol group, versus a mean size of 66.6 (SD = 41.6) for the prednisolone group. This study found no clear differences (due to imprecision) in terms of size reduction when comparing oral propranolol with oral prednisolone (MD 23.2, 95% CI -3.36 to 49.76; Analysis 18.4).

Likewise, Bauman 2014 reported information about the proportional change in the total surface area at four months. They found a mean of 0.64 (SD = 0.29) for the propranolol group, versus a mean of 0.41 (SD = 0.37) for the prednisolone group. This study found no differences in terms of changes in the total surface area when comparing oral propranolol with oral prednisolone (MD 0.23, 95% CI -0.08 to 0.54; Analysis 18.5).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 19. Propranolol comparisons: oral propranolol versus oral captopril

For this comparison, we included information from one trial with 30 children (Zaher 2016). Children with problematic infantile haemangiomas were enrolled and randomly divided into two

groups. Group A (n = 15) received oral propranolol (2 mg/kg/d, divided into two daily doses). Group B (n = 15) received oral captopril (0.5 to 1 mg/kg/d, in a titrating dose). Children were discharged and followed up on a weekly basis for the first month, every two weeks in the second month, and finally at four-week intervals until four months after stopping treatment. The intervention ended if there was "complete resolution of IH, no initial or further improvement of IH (for 2 months), or intolerable side effects". Children were followed until four months.

Primary outcome 1: Clearance, as assessed by a clinician

Zaher 2016 provided information on this outcome, reporting a total of seven cases of clearance (30 children; percentage of clearance: 23.3%). Seven children out of 15 (46.6%) in the oral propranolol group and 0 out of 15 (0%) in the oral captopril group reached complete clearance of lesions. Due to the large 95% confidence interval, it is uncertain whether there is a difference in terms of clearance when comparing oral propranolol with oral captopril (RR 15.00, 95% CI 0.93 to 241.2; Analysis 19.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Gong 2015 provided information about cardiac side effects such as hypotension and dizziness, reporting a total of four cases (30 children; 13.3%). No children out of 15 (0%) in the oral propranolol group and 4 out of 15 (26.6%) in the oral captopril group reported cardiac side effects. This study found no clear difference (due to imprecision) in terms of cardiac side effects when comparing oral propranolol with oral captopril (RR 0.11, 95% CI 0.01 to 1.90; Analysis 19.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 20. Propranolol comparisons: oral propranolol versus topical timolol maleate

For this comparison, we included information from one trial with 26 children (Gong 2015). Children with superficial infantile haemangiomas were randomised into three equal groups: one group received oral propranolol, and a second group received topical timolol maleate. Treatment efficacy was evaluated based on clinical photographs taken at the onset of treatment, during treatment, and at the end of treatment. Treatment ended if lesions had regressed or after 6 months without improvement; children were followed from 3 to 12 months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Gong 2015 provided information about adverse events in general, such as severe diarrhoea, lethargy, and loss of appetite, reporting a total of three cases (26 children; 11.5%). Three children out of 13 (23%) in the oral propranolol group and 0 out of 13 (0%) in the topical timolol maleate group reported adverse events. This study found no clear difference in terms of adverse events when comparing oral propranolol with topical timolol maleate (RR 7.00, 95% CI 0.40 to 123.35; Analysis 20.1). We downgraded the quality of the evidence from high to very low due to unclear risk of selection and performance bias, as well as imprecision (see Summary of findings 3).

Secondary outcome 1: Other measures of resolution

Gong 2015 provided information about size reduction equal or superior to 50% after treatment, reporting a total of 17 cases (26 children; 65.3%). Nine children out of 13 (69.2%) in the oral propranolol group and 8 out of 13 (61.5%) in the topical timolol maleate group reached size reduction of ≥ 50% . This study found no differences in terms of this measurement when comparing oral propranolol with topical timolol maleate (RR 1.13, 95% CI 0.64 to 1.97; Analysis 20.2). We downgraded the quality of the evidence from high to low due to unclear risk of selection and performance bias, as well as imprecision (see Summary of findings 3).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 21. Propranolol comparisons: oral propranolol versus oral propranolol + oral prednisolone

For this comparison, we included information from two trials with a total of 60 children (Aly 2015; Malik 2013). In Aly 2015, infants aged less than 9 months with cutaneous haemangiomas were randomly assigned into 2 groups: Group A received oral prednisolone 2 mg/kg/day in 2 divided doses for the initial 2 weeks combined with

oral propranolol 2 mg/kg/day in 3 divided doses for 6 months, while Group B received oral propranolol alone in the same dose for 6 months. Duration of treatment was 24 weeks; children were followed until 9 months.

In Malik 2013, children aged from 1 week to 8 months with potentially disfiguring or functionally threatening IH were randomised into 3 equal groups: Group A, propranolol (2 to 3 mg/kg/d); Group B, prednisolone (1 to 4 mg/kg/d); and Group C, receiving both for a minimum duration of 3 months. After discharge, all children were re-evaluated after eight days of treatment and then every month for a minimum of three months. Duration of treatment was three months or more; children were followed until 18 months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Both studies provided information about adverse events in general, including bronchiolitis, upper respiratory tract infection, and Cushingoid appearance, reporting a total of 13 cases (60 children; 21.6%). Three children out of 30 (10%) in the oral propranolol group and 10 out of 30 (33.3%) in the oral propranolol + oral prednisolone group reported adverse events. The risk of adverse events after oral propranolol was 70% lower that after oral propranolol + oral prednisolone (RR 0.30, 95% CI 0.10 to 0.91; I^2 = 0%; Analysis 21.1).

Secondary outcome 1: Other measures of resolution

Malik 2013 provided information about the percentage of mean size reduction on a visual analogue scale at 1.5 years' follow-up, reporting a mean of 89.8 (SD = 10.3) for the propranolol group, versus a mean of 82.6 (SD = 10.4) for the propranolol + prednisolone group. This study found no clear differences in terms of size reduction when comparing oral propranolol with oral propranolol + oral prednisolone (MD 7.20, 95% CI -1.87 to 16.27; Analysis 21.2).

Likewise, Aly 2015 reported decrease in redness in 23 children (40 children; 57.5%). Ten children out of 20 (50%) in the oral propranolol group and 13 out of 20 (65%) in the oral propranolol + oral prednisolone group reported decrease in redness. This study found no clear differences in terms of redness when comparing oral propranolol with oral propranolol + oral prednisolone (RR 0.77, 95% CI 0.45 to 1.32; Analysis 21.3).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 22. Propranolol comparisons: oral propranolol versus oral ibuprofen + oral paracetamol

For this comparison, we included information from one trial with 64 children (Tiwari 2016). Children with ulcerated infantile haemangiomas of the head and neck region, without any prior treatment and with age older than one month, were randomised into two groups. Group A received oral propranolol at a dose of 2 mg/kg per day in three divided doses. Group B received oral ibuprofen and paracetamol in doses of 10 and 16.2 mg/kg 8-hourly. Duration of treatment was unclear; follow-up was performed until 12 months.

Primary outcome 1: Clearance, as assessed by a clinician

Tiwari 2016 provided information on this outcome, reporting a total of 11 cases of clearance (64 children; percentage of clearance: 17.1%). Eight children out of 32 (25%) in the oral propranolol group and 3 out of 32 (9.3%) in the oral ibuprofen + oral paracetamol group reached clearance of lesions. This study found no clear differences in terms of clearance when comparing oral propranolol with oral ibuprofen + oral paracetamol (RR 2.67, 95% CI 0.78 to 9.15; Analysis 22.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Tiwari 2016 provided information about adverse events in general, including maculopapular generalised rash, reporting a total of three cases (64 children; 4.6%). Three children out of 32 (9.3%) in the oral propranolol group and 0 out of 32 (0%) in the oral ibuprofen + oral paracetamol group reported adverse events. This study found no clear differences (due to imprecision) in terms of adverse events when comparing oral propranolol with oral ibuprofen + oral paracetamol (RR 7.00, 95% CI 0.38 to 130.26; Analysis 22.2).

Secondary outcome 1: Other measures of resolution

Tiwari 2016 assessed the mean size of ulceration, reporting a mean of 3.25 cm (SD = 0.75) for the propranolol group, versus a mean of 2.94 cm (SD = 0.42) for the ibuprofen + paracetamol group. The mean size of ulceration after oral propranolol was 0.31 cm greater than after oral ibuprofen + oral paracetamol (MD 0.31, 95% CI 0.01 to 0.61; Analysis 22.3).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 23. Propranolol comparisons: oral propranolol + topical timolol maleate versus oral propranolol

For this comparison, we included information from two trials with a total of 57 children (Gong 2015; Li 2016). In Gong 2015, children with superficial infantile haemangiomas were randomised into three equal groups: one group received topical timolol maleate together with oral propranolol, and a second group received only oral propranolol. Treatment ended if lesions had regressed or after 6 months without improvement; children were followed from 3 to 12 months.

In Li 2016, children with mixed infantile haemangiomas in the oral and maxillofacial regions were randomised into two groups. Children in the experimental group (A) were treated with oral propranolol in combination with topical timolol maleate, and children in the control group (B) were treated with oral propranolol alone. Treatment was administered "for a maximum period of 8 months or complete regression of lesions". Children were followed until eight months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Gong 2015 provided information about adverse events in general, including severe diarrhoea, lethargy, and loss of appetite, reporting a total of four cases (26 children; 15.3%). One child out of 13 (7.6%) in the oral propranolol + topical timolol maleate group and 3 children out of 13 (23%) in the oral propranolol group reported adverse events. This study found no clear differences in terms of adverse events when comparing oral propranolol + topical timolol maleate with oral propranolol (RR 0.33, 95% CI 0.04 to 2.80; Analysis 23.1). Likewise, Li 2016 assessed the incidence of severe adverse events, finding zero events in both study arms.

Secondary outcome 1: Other measures of resolution

Li 2016 reported information about colour fading and size reduction, based on visual analogue scale scores. For colour fading, the authors reported a mean of 8.36 (SD = 1.39) for the propranolol + timolol maleate group, versus a mean of 7.18 (SD = 1.71) for the propranolol group. The mean score for colour fading after oral propranolol + topical timolol maleate was 1.18 units greater than after oral propranolol (MD 1.18, 95% CI 0.09 to 2.27; Analysis 23.2). Regarding size reduction, Li 2016 found a mean of 8.0 (SD = 1.75) for the propranolol + timolol maleate group, versus a mean of 7.59 (SD = 1.8) for the propranolol group. This study found no clear difference in terms of size reduction when comparing oral propranolol + topical timolol maleate with oral propranolol (MD 0.41, 95% CI -0.84 to 1.66; Analysis 23.3).

Likewise, Gong 2015 provided information on the number of cases with size reduction ≥ 50% after treatment, reporting a total of 20 cases (26 children; 76.9%). Eleven children out of 13 (84.6%) in the oral propranolol + topical timolol maleate group and 9 out of 13 (69.2%) in the oral propranolol group reached size reduction ≥ 50%. This study found no significant differences in terms of size reduction when comparing oral propranolol + topical timolol maleate with oral propranolol (RR 1.22, 95% CI 0.79 to 1.88; Analysis 23.4).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 24. Propranolol comparisons: oral propranolol + topical timolol maleate versus topical timolol maleate

For this comparison, we included information from one trial with 26 children (Gong 2015). Children with superficial infantile haemangiomas were randomised into three equal groups: one group received topical timolol maleate together with oral propranolol, and a second group received only topical timolol maleate. Treatment ended if lesions had regressed or after 6 months without improvement; children were followed from 3 to 12 months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Gong 2015 provided information about adverse events in general, including severe diarrhoea, lethargy, and loss of appetite, reporting one case that developed loss of appetite and vomiting (26 children; 3.84%). One child out of 13 (7.6%) in the oral propranolol + topical timolol maleate group and 0 out of 13 (0%) in the topical timolol maleate group reported adverse events. This study found no clear differences (due to imprecision) in terms of adverse events when comparing oral propranolol + topical timolol maleate with topical timolol maleate (RR 3.00, 95% CI 0.13 to 67.51; Analysis 24.1).

Secondary outcome 1: Other measures of resolution

Gong 2015 provided information on the number of cases with size reduction ≥ 50% after treatment, reporting a total of 19 cases (26 children; 73%). Eleven children out of 13 (84.6%) in the oral propranolol + topical timolol maleate group and 8 out of 13 (61.5%) in the topical timolol maleate group reached size reduction ≥ 50%. This study found no significant differences in terms of size reduction when comparing oral propranolol + topical timolol maleate with topical timolol maleate (RR 1.38, 95% CI 0.84 to 2.24; Analysis 24.2).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 25. Propranolol comparisons: oral propranolol + oral prednisolone versus oral prednisolone

For this comparison, we included information from one trial with 20 children (Malik 2013). Children aged from 1 week to 8 months with potentially disfiguring or functionally threatening IH were randomised into 3 groups: Group A, propranolol (2 to 3 mg/kg/d); Group B, prednisolone (1 to 4 mg/kg/d); and Group C, propranolol + prednisolone for a minimum duration of 3 months. After discharge, all children were re-evaluated after eight days of treatment and then every month for a minimum of three months. Duration of treatment was three months or more; children were followed until 18 months.

Primary outcome 1: Clearance, as assessed by a clinician

We found no clear information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Malik 2013 provided information about complications in general, including Cushingoid appearance and gastrointestinal upset, reporting a total of 16 cases (20 children; 80%). Nine children out of 10 (90%) in the oral propranolol + oral prednisolone group and 7 out of 10 (70%) in the oral prednisolone group reported adverse events. This study found no significant differences in terms of adverse events when comparing oral propranolol + oral prednisolone with oral prednisolone (RR 1.29, 95% CI 0.82 to 2.03; Analysis 25.1).

Secondary outcome 1: Other measures of resolution

Malik 2013 provided information on two measures of resolution. Regarding colour fading, Malik 2013 reported a mean score of -8 units (SD = 2.9) in the visual analogue scale for the propranolol + prednisolone group, versus a mean of -9 units (SD = 1.5) for the prednisolone group. This study found no differences in terms of colour-fading score when comparing oral propranolol + oral prednisolone with oral prednisolone (MD 1.00, 95% CI -1.02 to 3.02; Analysis 25.2). Malik 2013 also assessed the percentage of mean size reduction after treatment, reporting a mean size of 66.6 (SD = 41.6) for the propranolol + prednisolone group, versus a mean size of 82.6 (SD = 10.4) for the prednisolone group. This study found no clear differences (due to imprecision) in terms of size reduction when comparing oral propranolol + oral prednisolone with oral prednisolone (MD -16.00, 95% CI -42.58 to 10.58; Analysis 25.3).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 26. Other comparisons: intralesional methylene blue versus intralesional triamcinolone

For this comparison, we included information from one trial with 268 children (Feng 2000). In this trial, children were randomised into two groups. Group A received methylene blue 1% injection doses from 10 to 20 mg, once a week for four weeks. Group B received triamcinolone injection doses from 20 to 50 mg, once a week for four weeks. Duration of treatment was unclear; children were followed from one to three years.

Primary outcome 1: Clearance, as assessed by a clinician

Fu 2012 provided information on this outcome, reporting a total of 172 cases of clearance (268 children; percentage of clearance: 64.1%). In this study, 129 children out of 150 (86%) in the intralesional methylene blue group and 43 out of 118 (36.4%) in the intralesional triamcinolone group reached clearance of lesions. Clearance after intralesional methylene blue was 2.36 times greater than after intralesional triamcinolone (RR 2.36, 95% CI 1.84 to 3.02; Analysis 26.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

We found no information on this outcome for this comparison.

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 27. Other comparisons: oral prednisolone versus intravenous methylprednisolone

For this comparison, we included information from one trial with 20 children (Pope 2007). Children with problematic haemangiomas from one to four months of age were randomised into two groups. In the oral group, infants received oral prednisolone, 2 mg/kg per day, in two divided doses for 3 months. This dose was followed by a tapering schedule (decreasing the dose by 1 mg per month) over 6 to 9 months to prevent rebound. The intravenous group received pulses of intravenous high-dose corticosteroids monthly for three months. A pulse consisted of methylprednisolone in doses of 30 mg/kg per day infused over 1 hour daily for 3 days. Treatment was administered for at least three months; children were followed from three months to one year of life.

Primary outcome 1: Clearance, as assessed by a clinician

We found no information on this outcome for this comparison.

Primary outcome 2: A subjective measurement of improvement

The trial by Pope 2007 found a good correlation between the visual analogue scale scores of the size of the haemangioma as reported by the parents of the children and the blinded outcome assessors (correlation coefficient = 0.92).

Primary outcome 3: Adverse events

In the Pope 2007 trial, adverse events in the 20 children were recorded by the parents (parent diaries) and the clinicians (monitoring). Parental reports of adverse events were reported as median and range along with a P value for the following eight types.

- Irritability: median 1 (range 0 to 3) for oral group and 1.5 (0 to 3) for IV group (P = 0.85).
- Crying: median 1 (range 0 to 3) for oral group and 0.5 (0 to 2) for IV group (P = 0.58).
- Hyperactivity: both groups had a median 0 (range 0 to 2) (P = 1.00).
- Apathy: median 0 (range 0) for oral group and 0 (0 to 1) for IV group (P = 0.32).
- Insomnia: median 1 (range 0 to 3) for oral group and 0 (0 to 1) for IV group (P = 0.08).
- Vomiting: both groups had a median 0 (range 0 to 2) (P = 1.00).
- Abdominal pains: median 0 (range 0 to 2) for both groups (P = 0.34).
- Behavioural changes: median 0 (range 0) for oral group and 0 (0 to 1) for IV group (P = 0.32).

One child in the oral prednisolone group required antihypertensive medication for persistent high blood pressure, and one child in each of the treatment groups experienced serious respiratory distress, but both made a full recovery. Although no difference in the children's growth factors (height and weight) were seen at 3 months, by 1 year children in the oral prednisolone group had evidence of growth retardation as compared to the intravenous methylprednisolone group (weight, P = 0.003; height, P < 0.001).

Secondary outcome 1: Other measures of resolution

In the Pope 2007 trial, the 10 children in the oral prednisolone group had significantly greater reductions in the size of the haemangioma when compared to the 10 children in the intravenous methylprednisolone group at 1 year of age (MD 51.50 mm, 95% CI 21.49 to 81.51; Analysis 27.1).

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 28. Other comparisons: HIFU at 3.5 W versus HIFU at 4.5 W

For this comparison, we included information from one trial with 40 children (Fu 2012). In Fu 2012, the lesion surface was irradiated with 3 to 5 mm/second continuously by ultrasonic therapeutic apparatus at frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap. The ultrasound was used three times as a course of treatment, with one-month interval. Duration of treatment was unclear; children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Fu 2012 provided information on this outcome, reporting a total of 15 cases of clearance (40 children; percentage of clearance: 37.5%). Seven children out of 20 (35%) in HIFU at 3.5 W group and 8 out of 20 (40%) in HIFU at 4.5 W group reached clearance of lesions. This study found no significant differences in terms of clearance when comparing HIFU at 3.5 W with HIFU at 4.5 W (RR 0.88, 95% CI 0.39 to 1.95; Analysis 28.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Fu 2012 provided information about cases of ulceration or scars, reporting a total of seven cases (40 children; Analysis 28.2). No children out of 20 (0%) in HIFU at 3.5 W group and 7 out of 20 (35%) in HIFU at 4.5 W group reported ulcerations or scars. This study found no clear differences (due to imprecision) in terms of adverse events when comparing HIFU at 3.5 W with HIFU at 4.5 W (RR 0.07, 95% CI 0.00 to 1.09; Analysis 28.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 29. Other comparisons: HIFU at 3.5 W versus HIFU at 4.0 W

For this comparison, we included information from one trial with 40 children (Fu 2012). In Fu 2012, the lesion surface was irradiated with 3 to 5 mm/second continuously by ultrasonic therapeutic apparatus at frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap. The ultrasound was used three times as a course of treatment, with one-month interval. Duration of treatment was unclear; children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Fu 2012 provided information on this outcome, reporting a total of 16 cases of clearance (40 children; percentage of clearance: 40%). Seven children out of 20 (35%) in HIFU at 3.5 W group and 9 out of 20 (45%) in HIFU at 4.0 W group reached clearance of lesions. This study found no significant differences in terms of clearance when comparing HIFU at 3.5 W with HIFU at 4.0 W (RR 0.78, 95% CI 0.36 to 1.68; Analysis 29.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Fu 2012 provided information about cases of ulceration or scars, reporting a total of four cases (40 children; 10%). No children out of 20 (0%) in HIFU at 3.5 W group and 4 out of 20 (20%) in HIFU at 4.0 W group reported ulceration or scars. This study found no clear differences (due to imprecision) in terms of adverse events when comparing HIFU at 3.5 W with HIFU at 4.0 W (RR 0.11, 95% CI 0.01 to 1.94; Analysis 29.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

Comparison 30. Other comparisons: HIFU at 4.0 W versus HIFU at 4.5 W

For this comparison, we included information from one trial with 40 children (Fu 2012). In Fu 2012, the lesion surface was irradiated with 3 to 5 mm/second continuously by ultrasonic therapeutic apparatus at frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap. The ultrasound was used three times as a course of treatment, with one-month interval. Duration of treatment was unclear; children were followed until six months.

Primary outcome 1: Clearance, as assessed by a clinician

Fu 2012 provided information on this outcome, reporting a total of 17 cases of clearance (40 children; percentage of clearance: 42.5%). Nine children out of 20 (45%) in HIFU at 4.0 W group and 8 out of 20 (40%) in HIFU at 4.5 W group reached clearance of lesions. This study found no differences in terms of clearance when comparing HIFU at 4.0 W with HIFU at 4.5 W (RR 1.13, 95% CI 0.55 to 2.32; Analysis 30.1).

Primary outcome 2: A subjective measurement of improvement

We found no information on this outcome for this comparison.

Primary outcome 3: Adverse events

Fu 2012 provided information about cases of ulceration or scars, reporting a total of 11 cases (40 children; 27.5%). Four children out of 20 (20%) in HIFU at 4.0 W group and 7 out of 20 (35%) in HIFU at 4.5 W group reported ulceration or scars. This study found no clear differences in terms of adverse events when comparing HIFU at 4.0 W with HIFU at 4.5 W (RR 0.57, 95% CI 0.20 to 1.65; Analysis 30.2).

Secondary outcome 1: Other measures of resolution

We found no information on this outcome for this comparison.

Secondary outcome 2: Proportion of parents who consider their child still has a problem

We found no information on this outcome for this comparison.

Secondary outcome 3: Proportion of children who consider they still have a problem, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 4: Aesthetic appearance as assessed by physician, child, or parent, at any follow-up

We found no information on this outcome for this comparison.

Secondary outcome 5: Requirement for surgical correction, as assessed by a physician, at any follow-up

We found no information on this outcome for this comparison.

DISCUSSION

Summary of main results

This systematic review identified 28 controlled trials with 1728 children enrolled and randomised.

We selected information for three important comparisons, which we summarised in three tables: Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3.

Oral propranolol versus placebo (3 parallel studies; 312 children)

Moderate-quality evidence showed that compared with placebo, 3 mg/kg/day of propranolol probably improves clinician-assessed clearance at 24 weeks (based on 156 children, from one study) and probably leads to a clinician-assessed change in mean haemangioma volume at 24 weeks, as another measure of resolution (based on 40 children, from one study). We found no evidence of a difference in terms of short- or long-term severe adverse events between the two groups (based on 509 children, from three studies) or in terms of cardiovascular adverse events, bronchospasm, or hypoglycaemia events (based on low-quality evidence).

Topical timolol maleate versus placebo (1 parallel study; 41 children)

Clinician-assessed clearance was not reported for this comparison. Low-quality evidence indicated that achieving clinician-confirmed reduction of redness at 24 weeks (used as a measure of resolution) may be increased with topical timolol maleate 0.5% gel applied twice daily, as opposed to placebo (based on 41 children, from one study). Regarding short- or long-term serious cardiovascular events, in both groups there were zero events of bradycardia and hypotension (based on low-quality evidence from 41 children in one study). No other safety data were assessed.

Oral propranolol versus topical timolol maleate (1 parallel study; 26 children)

Clinician-assessed clearance was not reported for this comparison. There was no evidence of a difference between oral propranolol (via a tablet, at a 1.0 mg/kg dose, taken once per day) and topical timolol maleate (0.5% eye drops applied twice daily) in producing a 50% or greater reduction in haemangioma size at 24 weeks (based on 26 children from one study; low-quality evidence). Regarding short- or long-term general adverse events, although there were more events in the oral propranolol group such as severe diarrhoea, lethargy, and loss of appetite, this result was based on a low number of events and very low-quality evidence; therefore, we are uncertain about the safety implications (based on 26 children from one study).

For the three comparisons just discussed, the following outcomes, measured at any follow-up, were not reported.

- A subjective measure of improvement, as assessed by the parent or child.
- Proportion of parents who consider their child still has a problem.
- Proportion of children who consider they still have a problem.
- Aesthetic appearance as assessed by physician, child, or parent.

We found little evidence for a number of outcomes, especially patient-reported outcomes, such as subjective measure of improvement, proportion of children who consider they still have a problem, proportion of parents who consider their child still has a problem, and aesthetic appearance. Furthermore, we included no trials assessing a large number of haemangioma treatments, such as argon laser, carbon dioxide laser, erbium laser, excision, cryotherapy, imiquimod, interferon alpha, vincristine, and rapamycin.

Overall completeness and applicability of evidence

We aimed to include all interventions recommended for the management of infantile haemangiomas in children, and found a wide variety of different interventions and comparisons. We included a total of 12 interventions (not including combinations of these interventions) and 30 comparisons. Most of the included interventions were evaluated in single studies, precluding meta-analysis. Due to the low quality of the evidence found for our key comparisons and incomplete coverage in terms of outcomes of interest and interventions, the external validity of the review is poor.

Propranolol (oral, topical, and intralesional), currently the first-line recommended intervention for IH, was the most assessed intervention (in 16 studies). However, some trials included in this systematic review assessed the efficacy of less used, and perhaps less important, treatments, such as bleomycin and radiation, whilst we found no evidence from randomised trials related to efficacy and safety of potential interventions such as argon laser, carbon dioxide laser, erbium laser, excision, cryotherapy, imiquimod, interferon alpha, vincristine, or rapamycin. Information about ongoing trials may be useful in clarifying the role of these potential treatments in the management of infantile haemangiomas in children (NCT01147601; NCT02913612).

Data were lacking for a number of outcomes, especially patient-relevant outcomes, such as reports of improvement by parents/children or aesthetic/cosmetic assessment, among others. Results for these outcomes could provide critical information about the patient/carer perspective on the benefits and harms of the proposed interventions for the treatment of this condition.

Furthermore, it is difficult to ascertain the applicability of the results in terms of population because the age of the children was reported inconsistently; numerous subtypes of haemangiomas were included; and some trials did not provide information on haemangioma type. Lack of data also meant we were unable to undertake subgroup analysis by haemangioma type, although we did note that evidence was scarce for complicated scenarios such as ulcerated or problematic IH.

Quality of the evidence

This systematic review included only randomised controlled trials, as this design is considered the gold-standard for assessing the efficacy of an intervention. However, although we included 28 trials that were eligible according to the inclusion criteria, we

considered the quality of the evidence for the three most important comparisons mainly moderate or low. One of the reasons for this rating was the unclear risk of bias in several elements related to the methodological quality of included trials. For example, blinding of outcomes assessment was reported for 13 trials (Aly 2015; Chan 2013; Ehsani 2014; Gong 2015; Hogeling 2011; Kessels 2013; Leaute-Labreze 2013; Leaute-Labreze 2015; Li 2016; Malik 2013; Pope 2007; Tan 2012; Zaher 2016), whereas the remaining trials did not report this information in a clear way. We considered only three studies at low risk of bias for the three blinding items (Chan 2013; Hogeling 2011; Leaute-Labreze 2013). Likewise, there was some evidence of selective omissions of outcomes from publications for six trials (Feng 2000; Hogeling 2011; Jung 1977; Malik 2013; Pope 2007; Xu 2006; Zhang 2013), especially concerning the safety of the assessed interventions. In addition, one of the factors that led to us downgrading the quality of evidence was small sample sizes. As mentioned above, most of the comparisons were based on a single trial with a small number of recruited children; only four trials recruited more than 100 children (Batta 2002; Feng 2000; Jung 1977; Leaute-Labreze 2015). Due to these limitations, our confidence in the effect estimate is limited, and we considered that the true effect may be different from the estimate of the effect showed in this present review.

Potential biases in the review process

We aimed to minimise potential biases during the development of this review. We followed the methodology for systematic reviews outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We feel that this review was comprehensive in identifying clinical trials addressing the issue of efficacy and safety of suggested interventions for the management of infantile haemangiomas. However, insufficient information was available for seven studies to classify them as included or excluded, because they were published only as conference proceedings, or because we did not have access to the full texts. The fact that these studies have not yet been incorporated into the review may be a potential source of bias. In addition, we considered two of the studies as 'ongoing' due to their date of publication as abstracts. We may be able to decide whether or not to include them once they are published as full texts.

We modified some of the methods planned for and used in the original review published by Leonardi-Bee 2011: changes included the need to add current interventions used in the treatment of IH (such as oral propranolol), modification of primary and secondary outcomes, and assessment of evidence using the GRADE approach, among other changes (see Differences between protocol and review for more information). These modifications could be a potential source of bias in the review process. In addition, due to scarcity of data for most of the comparisons, we did not perform the planned investigation of heterogeneity and sensitivity analysis.

Agreements and disagreements with other studies or reviews

We identified and selected five reviews published in the last five years on the management of IH in children. A recent systematic review of the literature highlighted several potential pharmacotherapy treatments for management of IH (Chinnadurai 2016b); the authors of this review included randomised trials as well as observational evidence to address several potential interventions for the management of infantile haemangiomas, and found evidence that propranolol had the highest clearance rate, with high variability, under a network meta-analysis approach. These findings are also in agreement with Izadpanah 2013, a systematic review and meta-analysis, which suggests that propranolol therapy could potentially be superior to other alternatives of management of IH in children. Our results also found propranolol to be one of the interventions with clear evidence of benefits, a comprehensive assessment of adverse events, as well as a considerable number of studies focused on its efficacy and safety. However, unlike Chinnadurai 2016b and Izadpanah 2013, we added an assessment of the evidence using the GRADE approach, finding issues related to potential risk of bias and imprecision, which raise uncertainty in the estimated effect, especially those effects related to adverse events (see Quality of the evidence).

Regarding laser treatments, other authors have remarked that evidence is limited by low sample size, lack of comparisons of the same modalities, and variations in the used laser settings including wavelength and cooling protocols (Chinnadurai 2016a). However, in an additional systematic review and meta-analysis, Shen 2015 found that despite the few trials included in the review, PDL should be considered as a treatment modality, especially for superficial haemangiomas. Our findings from Batta 2002, an included study, suggested that there was no evidence of a difference in achieving clearance of the haemangioma between PDL and wait-and-see (i.e. active monitoring), but fewer adverse events were generally observed with wait-and-see.

Xu 2014 gathered evidence under a systematic approach related to the efficacy and safety of propranolol versus corticosteroids for the treatment of periorbital infantile haemangiomas, finding only case series addressing this comparison. The authors concluded that propranolol may be an effective and even safer intervention for periorbital IHs compared with corticosteroids. This conclusion was based on the results of studies some of which were neither randomised nor controlled. We did not find evidence from randomised trials addressing this issue.

AUTHORS' CONCLUSIONS

Implications for practice

Our Cochrane Review updated the evidence on the effects of different interventions for the management of infantile haemangiomas (IHs). We included 12 interventions, 28 studies, and 30 comparisons. We assessed the quality of the evidence underlining three key treatment comparisons, and have been able to draw the following conclusions.

- There is moderate-quality evidence that, when compared with placebo, oral propranolol is probably beneficial in terms of complete or almost complete clearance and probably reduces haemangioma volume more than placebo. We found no evidence of a difference in terms of short- or long-term adverse events between the groups (low-quality evidence).
- Low-quality evidence indicates that topical timolol maleate may reduce IH redness more than placebo, with possibly no accompanying cardiovascular events, although no other safety data were assessed for this comparison.
- There was no evidence of a difference between oral propranolol and topical timolol maleate in their ability to generate a 50% or greater reduction in IH size, based on low-quality evidence. We

were unable to draw conclusions about adverse events for this comparison due to very low-quality evidence.

All outcomes reported for these comparisons were measured at 24 weeks' follow-up and were clinician assessed, except for the safety outcomes. We are unable to present evidence on the following key outcomes for our key comparisons because they were not reported.

- A subjective measure of improvement, as assessed by the parent or child.
- Proportion of parents who consider their child still has a problem.
- Proportion of children who consider they still have a problem.
- Aesthetic appearance as assessed by physician, child, or parent.

As the evidence underlying our results for propranolol and timolol maleate was allocated a GRADE rating no higher than moderate, we cannot make qualitative statements with high certainty. However, propranolol remains the standard treatment for infantile haemangiomas, and clinicians should be aware that clinical management of haemangiomas depends on the following risk factors, amongst others: the grade of complication, presence of comorbidities, clinician experience, need for hospitalisation versus ambulatory care, and patient factors.

A large number of interventions were not assessed by any included study: argon laser, carbon dioxide laser, erbium laser, excision, cryotherapy, imiquimod, interferon alpha, vincristine, and rapamycin.

Implications for research

Despite the fact that there was a considerable increase in the number of trials since the publication of the first version of this review (from 4 trials/271 children to 28 trials/1728 children), the certainty of the evidence was reduced due to issues such as the sample size of the included studies and risk of bias in, for example, blinding and selective reporting domains. Furthermore, scarce or non-existent evidence for certain interventions and outcomes means that there is still a need for high-quality randomised controlled trials (RCTs) to assess interventions for IH.

Participants

Randomised controlled trials are needed for all types of haemangiomas, especially complicated scenarios such as ulcerated or problematic IH, where evidence is lacking. It is important that the haemangioma subtype is clearly reported in trial publications.

Interventions

There is a need for RCTs related to the efficacy and safety of the following interventions:

- oral propranolol and topical timolol maleate (assessed separately);
- combination of oral propranolol with other interventions (such as laser or corticosteroids);
- combination of topical timolol maleate with other interventions;
- other potential interventions, such as imiquimod, interferon alpha, excision, cryotherapy, vincristine, and rapamycin; and
- new interventions, such as beta blockers.

The evaluation of different dosages and duration, which will vary according to treatment, should also be taken into account.

Comparators

High-quality trials should assess oral propranolol and topical timolol maleate against each other. Other interventions should also be compared against oral propranolol and topical timolol maleate, as beta blockers are currently approved as standard care both by the US Food and Drug Administration and the European Medicines Agency.

Outcomes

Important outcomes to assess include the incidence and types of adverse events experienced by trial participants, as well as other patient-reported outcomes, or those pertaining to parents and carers, such as the proportion of participants that feel they still have a problem (either reported by the child or the parent/carer), the requirement for surgical correction, and aesthetic appearance. These outcomes should ensure follow-up in both the short term and the long term. Furthermore, objective outcomes such as resolution need further assessment.

Methodology

A sufficient sample size to enable the detection of a clinically important effect size is crucial when conducting future trials; this could perhaps be achieved using a multicentre approach. Trials must be rigorously reported to help overcome methodological issues associated with poor RCTs in this field, such as selective reporting of outcomes and unclear blinding (outcomes, participants, and personnel). Furthermore, thorough reporting with regard to the nature of the interventions, the age of participants, and the type of haemangiomas included will ensure the applicability of future trial results.

ACKNOWLEDGEMENTS

We would like to thank Cochrane Skin for their help during all stages of this review. Cochrane Skin wishes to thank Urbá González, who was the Dermatology Editor for this review; Thomas Chu and Ching-Chi Chi, who were the Statistical and Methods Editors, respectively; the clinical referees, Lea Solman and another who wishes to remain anonymous; and the consumer referee, Anne Lyddiatt. We would also like to thank Aidan Tan for his help with papers in data extraction of Zhong 2015.

REFERENCES

References to studies included in this review

Abarzua-Araya 2014 *{published data only}*

* Abarzua-Araya A, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. *Journal of the American Academy of Dermatology* 2014;**70**(6):1045-9. [CENTRAL: CN-00993183; PUBMED: 24656727]

Aly 2015 *{published data only}*

Aly MMD, Hamza AF, Abdel Kader HM, Saafan HA, Ghazy MS, Ragab IA. Therapeutic superiority of combined propranolol with short steroids course over propranolol monotherapy in infantile hemangioma. *European Journal of Pediatrics* 2015;**174**(11):1503-9. [CENTRAL: CN-01106020; PUBMED: 25982338]

Asilian 2015 *{published data only}*

Asilian A, Mokhtari F, Kamali AS, Abtahi-Naeini B, Nilforoushzadeh MA, Mostafaie S. Pulsed dye laser and topical timolol gel versus pulse dye laser in treatment of infantile hemangioma: A double-blind randomized controlled trial. *Advanced Biomedical Research.* 2015;**4**:257. [PUBMED: 26918239]

Batta 2002 *{published data only}*

Batta K, Goodyear H, Moss C, Williams H, Hiller L, Waters R. Randomized controlled study of early pulsed dye laser treatment of uncomplicated infantile haemangiomas: results of a 5-year analysis. *British Journal of Dermatology* 2008;**159**(Suppl 1):113-27. [CENTRAL: CN-00784022]

* Batta K, Goodyear HM, Moss C, Williams HC, Hiller L, Waters R. Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002;**360**(9332):521-7. [CENTRAL: CN-00410133]

Batta K, Waters R, Titley M, Goodyear H, Moss C. Experience in the very early treatment of childhood haemangiomas with the 585 nm pulsed dye laser (PDL). *British Journal of Dermatology* 2000;**143**(Suppl 57):42-85. [CENTRAL: CN-00783264]

Bauman 2014 *{published data only}*

* Bauman NM, McCarter RJ, Guzzetta PC, Shin JJ, Oh AK, Preciado DA, et al. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: A randomized clinical trial. *JAMA Otolaryngology, Head & Neck Surgery.* 2014;**140**(4):323-30. [CENTRAL: CN-00988156; PUBMED: 24526257]

NCT00967226. Propranolol versus prednisolone for treatment of symptomatic hemangiomas. clinicaltrials.gov/ct2/show/NCT00967226 (accessed 23 April 2010).

Chan 2013 *{published data only}*

* Chan H, McKay C, Adams S, Wargon O. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. *Pediatrics* 2013;**131**(6):e1739-47. [CENTRAL: CN-00876607]

Ehsani 2014 *{published data only}*

* Ehsani AH, Noormohammadpoor P, Abdolreza M, Balighi K, Arianian Z, Daklan S. Combination therapy of infantile hemangioma with pulsed dye laser with topical propranolol: a randomized clinical trial. *Archives of Iranian Medicine* 2014;**17**(10):657-60. [CENTRAL: CN-01042472; PUBMED: 25305763]

Feng 2000 *{published data only}*

Feng LL, Wang XJ, Sun LQ, Zhang ZR, Ma CH. Clinical observation on efficacy of methylthionine chloride in the treatment of hemangiomas in children. *Chinese Journal of Dermatology* 2000;**33**(4):284. [CENTRAL: CN-00843680]

Fu 2012 *{published data only}*

Fu S, Wang B, Huang H, Huang L. Primary clinical application of high-intensity focused ultrasound on infant hemangiomas. *Chung-Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih/Chinese Journal of Reparative & Reconstructive Surgery* 2011;**25**(12):1477-80. [CENTRAL: CN-00896632]

Fu SZ, Wang B, Huang HP, Huang LL. Clinical study on hemangiomas treatment with high-intensity focused ultrasound (60 cases). *Zhonghua Zheng Xing Wai Ke za Zhi = Zhonghua Zhengxing Waike Zazhi [Chinese Journal of Plastic Surgery]* 2012;**28**(4):252-5. [CENTRAL: CN-00966758]

Gong 2015 *{published data only}*

Gong H, Xu D-P, Li Y-X, Cheng C, Li G, Wang X-K. Evaluation of the efficacy and safety of propranolol, timolol maleate, and the combination of the two, in the treatment of superficial infantile haemangiomas. *British Journal of Oral & Maxillofacial Surgery* 2015;**53**(9):836-40. [CENTRAL: CN-01125564; PUBMED: 26427968]

Hogeling 2011 *{published data only}*

Hogeling M, Adams S, Wargon O. A randomized controlled trial of Propranolol for infantile haemangiomas. *Australasian Journal of Dermatology* 2011;**52**(Suppl 2):4. [EMBASE: 70558759]

* Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. *Pediatrics* 2011;**128**(2):e259-66. [PUBMED: 21788220]

Wargon O. Randomised placebo controlled trial: Safety and efficacy of topical timolol maleate gel vs placebo for small superficial infantile haemangiomas. *Australasian Journal of Dermatology* 2013;**54**(Suppl 2):22-3. [EMBASE: 71067708]

Jung 1977 *{published data only}*

Jung EG. X-ray therapy for hemangiomatas [Die strahlentherapie der hamangiome]. *Dermatologica* 1976;**153**(2):86-7. [CENTRAL: CN-00784697]

* Jung EG, Kohler U. Regression of haemangiomata in infants after x-ray treatment and mock-radiation [Rückbildung frühkindlicher hämangiome nach röntgen- und pseudobestrahlung]. *Archives of Dermatological Research* 1977;**259**(1):21-8. [CENTRAL: CN-00614355]

Kessels 2013 *{published data only}*

Kessels JP, Hamers ET, Ostertag JU. Superficial hemangioma: pulsed dye laser versus wait-and-see. *Dermatologic Surgery* 2013;**39**(3 Pt 1):414-21. [CENTRAL: CN-00966183; PUBMED: 23279058]

Leaute-Labreze 2013 *{published data only}*

* Leaute-Labreze C, Dumas de la Roque E, Nacka F, Abouelfath A, Grenier N, Rebola M, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. *British Journal of Dermatology* 2013;**169**(1):181-3. [CENTRAL: CN-00977604; PUBMED: 23301692]

Leaute-Labreze 2015 *{published data only}*

* Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *New England Journal of Medicine.* 2015;**372**(8):735-46. [CENTRAL: CN-01052642; PUBMED: 25693013]

Li 2016 *{published data only}*

Li G, Xu DP, Tong S, Xue L, Sun NN, Wang XK. Oral propranolol with topical timolol maleate therapy for mixed infantile hemangiomas in oral and maxillofacial regions. *Journal of Craniofacial Surgery* 2016;**27**(1):56-60. [CENTRAL: CN-01195472; PUBMED: 26716547]

Lu 2016 *{published data only}*

Lu J, Kuang X, Zhao J, Xiang Y, Huang J, Zeng Q, et al. Concurrent versus sequential combination of propranolol and dual-wavelength laser (585 nm and 1064 nm) to treat complicated infantile hemangiomas. *International Journal of Clinical and Experimental Medicine* 2016;**9**(8):16132-16138. [EMBASE: 20160650632]

Malik 2013 *{published data only}*

* Malik MA, Menon P, Rao KL, Samujh R. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: A randomized controlled study. *Journal of Pediatric Surgery* 2013;**48**(12):2453-9. [CENTRAL: CN-00921325; PUBMED: 24314186]

Pope 2007 *{published data only}*

* Pope E, Krafchik BR, Macarthur C, Stempak D, Stephens D, Weinstein M, et al. Oral versus high-dose pulse corticosteroids for problematic infantile hemangiomas: a randomized controlled trial. *Pediatrics* 2007;**119**(6):e1239-e1247. [CENTRAL: CN-00588641; PUBMED: 17485449]

Tan 2012 *{published data only}*

* Tan M, Duan B, Zhou CM, Gong H. The therapeutic effect of propranolol with 1064 nm Nd: YAG laser on proliferating hemangioma in body surface. *Zhonghua Zheng Xing Wai Ke za Zhi = Zhonghua Zhengxing Waike Zazhi [Chinese Journal of Plastic Surgery]* 2012;**28**(3):164-8. [CENTRAL: CN-01124671; PUBMED: 22870700]

Tawfik 2015 *{published data only}*

Tawfik AA, Alsharnoubi J. Topical timolol solution versus laser in treatment of infantile hemangioma: a comparative study. *Pediatric dermatology* 2015;**32**(3):369-76. [CENTRAL: CN-01102313; PUBMED: 25740672]

Tiwari 2016 *{published data only}*

Tiwari P, Pandey V, Gangopadhyay AN, Sharma SP, Gupta DK. Role of propranolol in ulcerated haemangioma of head and neck: a prospective comparative study. *Oral & Maxillofacial Surgery* 2016;**20**(1):73-7. [PUBMED: 26481918]

Xu 2006 *{published data only}*

Xu WL. The research of pingyangmycin emulsion on proliferation of tumor cell apoptosis in capillary hemangiomas [translation]. Shijiazhuang, Hebei, China: Hebei Medical University, 2003.

Xu WL, Niu AG, Li SL, Li ZD. Pingyangmycin emulsion inducing apoptosis in infantile proliferating capillary hemangiomas. *Zhonghua Zheng Xing Wai Ke za Zhi = Zhonghua Zhengxing Waike Zazhi [Chinese Journal of Plastic Surgery]* 2006;**22**(5):362-4. [CENTRAL: CN-00730309]

* Xu WL, Niu AG, Li ZD, Li SL, Shi BJ, Zhang YB, et al. Effect of pingyangmycin emulsion on the microenvironment of infantile proliferating capillary hemangioma. *World Journal of Pediatrics* 2006;**2**(3):217-22.

Zaher 2013 *{published data only}*

Zaher H, Rasheed H, Esmat S, Gawdat HI, Hegazy RA, El-Komy M, et al. Propranolol and infantile hemangiomas: Different routes of administration, a randomized clinical trial. *European Journal of Dermatology* 2013;**23**(5):646-52. [CENTRAL: CN-00961393; PUBMED: 24135427]

Zaher 2016 *{published data only}*

Zaher H, Rasheed H, El-Komy MM, Hegazy RA, Gawdat HI, Abdel Halim DM, et al. Propranolol versus captopril in the treatment of infantile hemangioma (IH): A randomized controlled trial. *Journal of the American Academy of Dermatology* 2016;**74**(3):499-505. [CENTRAL: CN-01138323; PUBMED: 26685718]

Zhang 2013 *{published data only}*

Zhang L, Mai HM, Zheng J, Zheng JW, Chen ZG, Wang YA, et al. Preliminary study on plasma RPN concentration of patients with infantile hemangioma treated with propranolol. *International journal of clinical and experimental medicine* 2013;**6**(5):342-5. [CENTRAL: CN-00906420; PUBMED: 23724152]

Zhong 2015 *{published data only}*

Zhong S, Tao Y, Zhou J, Yao L, Uu Y, Yan D, et al. Evaluation on efficacy of low dose propranolol combined with 1 064 nm Nd: YAG laser on mixed and deeper infantile hemangioma. *Journal of Jilin University Medicine Edition* 2015;**41**(5):1032-5. [CENTRAL: CN-01177799]

Zhu 2015 *{published data only}*

Zhu HJ, Liu Q, Deng XL, Guan YX. Efficacy of low-dose 90Sr-90Y therapy combined with topical application of 0.5% timolol

maleate solution for the treatment of superficial infantile hemangiomas. *Experimental and Therapeutic Medicine* 2015;**10**(3):1013-8. [PUBMED: 26622431]

References to studies excluded from this review

Ahn 2004 *{published data only}*

* Ahn H, Kim YJ, Hwang ES, Kim IH. Clinical trial of 5% imiquimod cream for eleven cases of infantile hemangioma. *Korean Journal of Dermatology* 2004;**42**(6):718-23. [EMBASE: 2004354455]

Ambika 2013 *{published data only}*

* Ambika H, Sujatha C, Kumar YH. Topical timolol: A safer alternative for complicated and un-complicated infantile hemangiomas. *Indian Journal of Dermatology* 2013;**58**(4):330. [PUBMED: 23919041]

Anonymous 2002 *{published data only}*

* Anonymous. Assessing early laser treatment of strawberry naevi. *Medicine Today* 2002;**3**(12):10.

Anonymous 2011 *{published data only}*

* Anonymous. Propranolol effective in shrinking infantile hemangioma. *Contemporary Pediatrics* 2011;**28**:11-2.

Baselga 2014 *{published data only}*

* Baselga E. IS-065: Hemangiomas: Oral propanolol and beyond. *Archives of Disease in Childhood* 2014;**99**:A20-A21.

Bozena 2012 *{published data only}*

* Bozena DB. HEMANGIOL Study: The first worldwide dose-effect study concerning propranolol in infantile hemangiomas [Badanie HEMANGIOL - pierwsze ogolnoswiatowe badanie zaleznosci dawka-efekt dotyczace stosowania propranololu u pacjentow z naczyniakami niemowlecymi]. *Przeglad Dermatologiczny* 2012;**99**(4):419. [CENTRAL: CN-01028347]

Branco 2008 *{published data only}*

* Branco DFR, Goldenberg DC, Heitor BS, Bastos EO, Alonso N. Early surgical resection of nasal hemangiomas: indications and results [Ressecção cirúrgica precoce de hemangiomas nasais: indicações e resultados]. *Revista da Sociedade Brasileira de Cirurgia Craniomaxilofacial.* 2008;**11**(3 Suppl):23.

Chang 2008 *{published data only}*

* Chan CJ, Hsiao YC, Mihm MC Jr, Nelson JS. Pilot study examining the combined use of pulsed dye laser and topical Imiquimod versus laser alone for treatment of port wine stain birthmarks. *Lasers in Surgery & Medicine* 2008;**40**(9):605-10. [CENTRAL: CN-00708211; PUBMED: 18951427]

Chen 2013 *{published data only}*

* Chen XD, Ma G, Huang JL, Chen H, Jin YB, Ye XX, et al. Serum-level changes of vascular endothelial growth factor in children with infantile hemangioma after oral propranolol therapy. *Pediatric Dermatology* 2013;**30**(5):549-53. [CENTRAL: CN-01122228; PUBMED: 23909679]

Costinescu 1981 *{published data only}*

* Costinescu V, Dinu C, Martu D. Clinical trial of sodium morrhuate in the treatment of ORL angiomas [Experimentarea clinica a moruatului de sodiu in tratamentul angioamelor din sfera O.R.L]. *Revista de Chirurgie, Oncologie, Radiologie, O.r.l., Oftalmologie, Stomatologie. Oto-rino-laringologia* 1981;**26**(1):61-2. [PUBMED: 6454221]

Dalby 2013 *{published data only}*

* Dalby TK, Lester-Smith D. Propranolol for the treatment of infantile haemangioma. *Journal of Paediatrics & Child Health* 2013;**49**(2):148-51. [PUBMED: 23418706]

Ferahbas 2008 *{published data only}*

* Ferahbas A, Kartal D, Taslider N, Utas S. The effectiveness of contact cryotherapy in treatment of infantile hemangiomas. *Turkish Journal of Dermatology* 2008;**2**(4):107-10.

Frieden 2009 *{published data only}*

* Frieden IJ, Drolet BA. Propranolol for infantile hemangiomas: promise, peril, pathogenesis. *Pediatric Dermatology* 2009;**26**(5):642-4. [PUBMED: 19840341]

Gajbhiye 2011 *{published data only}*

* Gajbhiye V, Nath S, Chatterjee S, De A, Ghosh D, Das SK. Role of propranolol in hemangiomas. *Journal of Indian Association of Pediatric Surgeons* 2011;**16**(4):173-4. [PUBMED: 22121324]

Goelz 2014 *{published data only}*

Goelz R, Moll M, Meisner C, Rocken M, Poets CF, Moehrle MC. Prospective controlled study to evaluate cryocontact therapy for infantile haemangioma in preterm infants. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2014;**99**(4):F345-6. [CENTRAL: CN-01042486]

Incesoy 2011 *{published data only}*

* Incesoy Ozdemir S, Bozkurt C, Orun UA, Sahin G, Yuksek N, Cetinkaya S, et al. Successful treatment of pulmonary arteriovenous malformation and infantile hepatic hemangioendothelioma with alpha-interferon. *Anadolu Kardiyoloji Dergisi [Anatolian Journal of Cardiology]* 2011;**11**(2):181-3. [PUBMED: 21362599]

Jalil 2006 *{published data only}*

* Jalil S, Akhtar J, Ahmed S. Corticosteroids therapy in the management of infantile cutaneous hemangiomas. *Journal of the College of Physcians & Surgeons - Pakistan* 2006;**16**(10):662-665. [CENTRAL: CN-00608871; PUBMED: 17007757]

Jesitus 2011 *{published data only}*

* Jesitus J. Lack of data: More controlled trials needed for infantile hemangioma therapies, experts say. *Dermatology Times* 2011;**32**:28-34.

Jha 2012 *{published data only}*

* Jha AK, Mallik SK, Raihan M. Topical ophthalmic solution in infantile hemangioma. *Journal of Postgraduate Medicine* 2012;**58**(2):163-5. [PUBMED: 22718070]

Jiang 2011 *{published data only}*

* Jiang C, Hu X, Ma G, Chen D, Jin Y, Chen H, et al. A prospective self-controlled phase II study of imiquimod 5% cream in the treatment of infantile hemangioma. *Pediatric Dermatology* 2011;**28**(3):259-66. [CENTRAL: CN-00799727; PUBMED: 21615472]

Kunzi-Rapp 2012 *{published data only}*

* Kunzi-Rapp K. Topical propranolol therapy for infantile hemangiomas. *Pediatric Dermatology* 2012;**29**(2):154-9. [CENTRAL: CN-00900917]

Liu 2009 *{published data only}*

Liu XJ, Quin ZP, Tai MZ. Angiographic classification and sclerotic therapy of maxillofacial cavernous haemangiomas: a report of 204 cases. *Journal of International Medical Research* 2009;**37**(5):1285-92. [PUBMED: 19930833]

McCuaig 2009 *{published data only}*

McCuaig CC, Dubois J, Powell J, Belleville C, David M, Rousseau E, et al. A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma. *Pediatric Dermatology* 2009;**26**(2):203-12. [PUBMED: 19419474]

Menezes 2011 *{published data only}*

Menezes MD, McCarter R, Greene EA, Bauman NM. Status of propranolol for treatment of infantile hemangioma and description of a randomized clinical trial. *Annals of Otology, Rhinology, and Laryngology* 2011;**120**(10):686-95. [CENTRAL: CN-00804792]

Michel 1998 *{published data only}*

Michel S, Wlotzke U, Hohenleutner U, Landthaler M. Laser and cryotherapy of hemangioma in infants in a direct comparison [Laser- und kryotherapie der Sauglingshamangiome im direckten vergleich]. *Hautarzt* 1998;**49**(3):192-6. [CENTRAL: CN-00509698]

Midena 2008 *{published data only}*

Midena E, Pilotto E, Radin PP, de Belvis V. Bolus vs standard photodynamic therapy in the treatment of circumscribed choroidal hemangioma: a randomized, masked study. *Investigative Ophthalmology & Visual Science* 2004;**45**:3154. [CENTRAL: CN-00598352]

* Urban F, Pilotto E, Parrozzani R, Midena E. Photodynamic therapy of circumscribed choroidal hemangioma: comparison of dosage and timing. *Acta Ophthalmologica* 2008;**86**:s243.

Miranda 2005 *{published data only}*

Miranda Madinya Ricardo, Vásquez Beckmann Carlos. Importance of absolute alcohol in the treatment of infantile capillary hemangiomas. Dr. Francisco de Ycaza Bustamanteö Hospital, Guayaquil [Valor del alcohol absoluto en el tratamiento de los hemangiomas capilares infantiles. Hospital Dr. Francisco de Ycaza Bustamante, Guayaquil]. *Medicina* 2005;**10**:203-6.

NCT01074437 *{published data only}*

NCT01074437. Corticosteroids with placebo versus corticosteroids with propranolol treatment of infantile hemangiomas. clinicaltrials.gov/ct2/results?term=NCT01074437 (accessed 23 April 2010).

Pancar 2011 *{published data only}*

Pancar GS, Aydin F, Senturk N, Bek Y, Canturk MT, Turanli AY. Comparison of the 532-nm KTP and 1064-nm Nd:YAG lasers for the treatment of cherry angiomas. *Journal of Cosmetic and Laser Therapy* 2011;**13**(4):138-41. [CENTRAL: CN-00811208]

Poetke 2000 *{published data only}*

Poetke M, Philipp C, Berlien HP. Flashlamp-pumped pulsed dye laser for hemangiomas in infancy: treatment of superficial vs mixed hemangiomas. *Archives of Dermatology* 2000;**136**(5):628-32. [CENTRAL: CN-00277983]

Pope 2013 *{published data only}*

* Pope E, Chakkittakandiyil A, Lara-Corrales I, Maki E, Weinstein M. Expanding the therapeutic repertoire of infantile haemangiomas: Cohort-blinded study of oral nadolol compared with propranolol. *British Journal of Dermatology* 2013;**168**(1):222-4. [CENTRAL: CN-00912475]

Pope E, Chakkittakandiyil A, Weinstein M. Expanding the therapeutic repertoire of infantile hemangiomas: Prospective pilot study using oral nadolol. *Pediatric Dermatology* 2011;**28**(5):510. [EMBASE: 70661234]

Rouvas 2009 *{published data only}*

Rouvas AA, Papakostas TD, Vavvas D, Vergados I, Moschos MM, Kotsolis A, et al. Intravitreal ranibizumab, intravitreal ranibizumab with PDT, and intravitreal triamcinolone with PDT for the treatment of retinal angiomatous proliferation: a prospective study. *Retina* 2009;**29**(4):536-44. [CENTRAL: CN-00704491]

Sadan 1996 *{published data only}*

Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. *Journal of Pediatrics* 1996;**128**(1):141-6. [CENTRAL: CN-00122746]

Schlosser 2009 *{published data only}*

Schlosser KA. Infantile hemangioma: how to treat this benign neoplasm of childhood. *JAAPA: Journal of the American Academy of Physician Assistants* 2009;**22**(5):46-9. [PUBMED: 19469391]

Smit 2005 *{published data only}*

Smit JM, Bauland CG, Wijnberg DS, Spauwen PH. Pulsed dye laser treatment, a review of indications and outcome based on published trials. *British Journal of Plastic Surgery* 2005;**58**(7):981-7. [PUBMED: 16039628]

Song 2015 *{published data only}*

Song H, Shi H, Zhang X, Wang J, Yu Y, Chen W, et al. Safety profile of a divided dose of propranolol for heart rate in children with infantile haemangioma during 16 weeks of treatment. *British Journal of Dermatology* 2015;**172**(2):444-9. [CENTRAL: CN-01052634]

Thaivalappil 2013 *{published data only}*

Thaivalappil S, Bauman N, Saieg A, Movius E, Brown KJ, Preciado D. Propranolol-mediated attenuation of MMP-9 excretion in infants with hemangiomas. *JAMA Otolaryngology--Head & Neck Surgery* 2013;**139**(10):1026-31. [CENTRAL: CN-00921293]

Tierney 2009 *{published data only}*

Tierney E, Barker A, Ahdout J, Hanke CW, Moy RL, Kouba DJ. Photodynamic therapy for the treatment of cutaneous neoplasia, inflammatory disorders, and photoaging. *Dermatologic Surgery* 2009;**35**(5):725-46. [PUBMED: 19309338]

Weienstein 2012 *{published data only}*

Weissenstein A, Villalon G, Luchter E, Bittmann S. Children's haemangiomas: use of new topical therapies. *British Journal of Nursing* 2012;**21**(5):274. [PUBMED: 22398997]

Weissenstein 2015 *{published data only}*

Weissenstein A, Luchter E, Bittmann S. Successful treatment of infantile haemangioma with propranolol. *British Journal of Nursing* 2015;**24**(2):96-7. [PUBMED: 25615994]

Zhao 1997 *{published data only}*

Zhao YL, He CN, Zhi CF, Zhang YX, Wang HJ. Prednisolone acetate mixed up Morrhuate sodium for the treatment of hemangiomas in children. *Chinese Journal of Dermatology* 1997;**30**(6):414. [CENTRAL: CN-00844079]

Zhong 2014 *{published data only}*

Zhong SX, Tao YC, Zhou JF, Yao L, Li SS. Evaluation on efficacy of different doses of propranolol in treatment of infantile hemangioma. *Journal of Jilin University Medicine Edition* 2014;**40**(4):880-3. [CENTRAL: CN-01041728]

Zhou 2000 *{published data only}*

Zhou JY, Fang GJ, Wang XM. Clinical study of microwave operation in treating nasal hemangioma. International and 6th National Head and Neck Cancer Conference. Shanghai, china, 9-13 June, 2000. 2000:195. [CENTRAL: CN-00343206]

Zhou 2002 *{published data only}*

Zhou K, Liang C, Yang K, Wang L. A randomised controlled study on the efficacy of modified sclerotherapy in treating angioma of ear, nose and throat. *Lin Chuang Er Bi Yan Hou Ke za Zhi [Journal of Clinical Otorhinolaryngology]* 2002;**16**(12):681-3. [CENTRAL: CN-00436296]

Zhou 2015 *{published data only}*

Zhou W, He S, Yang Y, Jian D, Chen X, Ding J. Formulation, characterization and clinical evaluation of propranolol hydrochloride gel for transdermal treatment of superficial infantile hemangioma. *Drug Development & Industrial Pharmacy* 2015;**41**(7):1109-19. [CENTRAL: CN-01254273]

References to studies awaiting assessment

Kuang 2014 *{published data only}*

Kuang X, Lu J. Concurrent versus sequential combination therapy of propranolol and dual-wavelength laser (585nm and 1064nm) to treat refractory infantile hemangiomas. *Journal of Dermatology* 2014;**41**:100. [CENTRAL: CN-01055093]

Maier 2012 *{published data only}*

Maier H, Wanka A, Schmalwieser AW, Maier B, Dani T, Neumann R, et al. Prospective, randomized, investigator-blind, controlled therapy study on treatment of haemangioma of infancy: Pulsed dye laser versus cryotherapy versus observation. *Experimental Dermatology* 2012;**21**(3):e15. [EMBASE: 70792062]

NCT00004436 *{published data only}*

NCT00004436. Randomized study of hormonal regulation of infantile hemangioma. clinicaltrials.gov/ct2/show/NCT00004436 (accessed 23 April 2010).

NCT00555464 *{published data only}*

NCT00555464. Clinical Trial of Vincristine vs. Prednisolone for Treatment of Complicated Hemangiomas. clinicaltrials.gov/ct2/show/NCT00555464 (accessed 23 April 2010).

NCT00744185 *{published data only}*

NCT00744185. Propranolol on capillary hemangiomas. clinicaltrials.gov/ct2/show/NCT00744185 (accessed 23 April 2010).

NCT01072045 *{published data only}*

NCT01072045. Comparative Study of the Use of Beta Blocker and Oral Corticosteroid in the Treatment of Infantile Hemangioma. clinicaltrials.gov/ct2/show/NCT01072045 (accessed 23 April 2010).

Pandey 2010 *{published data only}*

Pandey A, Gangopadhyay AN, Sharma SP, Kumar V, Gupta DK, Gopal SC. Evaluation of topical steroids in the treatment of superficial hemangioma. *SKINmed* 2010;**8**(1):9-11. [CENTRAL: CN-00760496]

References to ongoing studies

NCT01147601 *{published data only}*

NCT01147601. Topical Timolol 0.5% solution for proliferating infantile haemangiomas. clinicaltrials.gov/ct2/show/NCT01147601?term=NCT01147601 (accessed 25 March 2011).

NCT02913612 *{published data only}*

NCT02913612. Efficacy, Safety and Pharmacokinetics of Topical Timolol in Infants With Infantile Hemangioma (IH) (TIM01). clinicaltrials.gov/ct2/show/NCT02913612 Date first received: 12 August 2016.

Additional references

Abramson 1989

Abramson S, Weissmann G. The mechanisms of action of nonsteroidal antiinflammatory drugs. *Clinical and experimental rheumatology* 1989;**7 Suppl 3**:S163-70. [PUBMED: 2557993]

Achauer 1997

Achauer BM, Chang CJ, Vander Kam VM. Management of hemangioma of infancy: review of 245 patients. *Plastic & Reconstructive Surgery* 1997;**99**(5):1301-8.

Al 2003

Al Buainian H, Verhaeghe E, Dierckxsens L, Naeyaert JM. Early treatment of hemangiomas with lasers. A review. *Dermatology (Basel, Switzerland)* 2003;**206**(4):370-3. [PUBMED: 12771489]

Anderson 1981

Anderson RR, Parrish JA. The optics of human skin. *Journal of Investigative Dermatology* 1981;**77**(1):9-13.

Antonelli 1991

Antonelli G, Currenti M, Turriziani O, Dianzani F. Neutralizing antibodies to interferon-alpha: relative frequency in patients treated with different interferon preparations. *Journal of Infectious Diseases* 1991;**163**(4):882-885.

Azzopardi 2012

Azzopardi S, Wright TC. Novel strategies for managing infantile hemangiomas: a review. *Annals of plastic surgery* 2012;**68**(2):226-8. [PUBMED: 21629088]

Baselga 2016

Baselga E, Roe E, Coulie J, Munoz FZ, Boon LM, McCuaig C, et al. Risk factors for degree and type of sequelae after involution of untreated hemangiomas of infancy. *JAMA Dermatology* 2016;**152**(11):1239-43. [PUBMED: 27540637]

Bauland 2011

Bauland CG, Luning TH, Smit JM, Zeebregts CJ, Spauwen PH. Untreated hemangiomas: growth pattern and residual lesions. *Plastic and Reconstructive Surgery* 2011;**127**(4):1643-8. [PUBMED: 21460670]

Bayart 2017

Bayart CB, Tamburro JE, Vidimos AT, Wang L, Golden AB. Atenolol Versus Propranolol for Treatment of Infantile Hemangiomas During the Proliferative Phase: A Retrospective Noninferiority Study. *Pediatric dermatology* 2017;**34**(4):413-21. [PUBMED: 28556385]

Bennett 2001

Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. *Archives of Dermatology* 2001;**137**(9):1208-1213.

Bruckner 2006

Bruckner AL, Frieden IJ. Infantile hemangiomas. *Journal of the American Academy of Dermatology* 2006;**55**(4):671-82. [PUBMED: 17010748]

Castren 2016

Castren E, Salminen P, Gissler M, Stefanovic V, Pitkaranta A, Klockars T. Risk factors and morbidity of infantile haemangioma: preterm birth promotes ulceration. *Acta Paediatrica* 2016;**105**(8):940-5. [PUBMED: 27146410]

Chang 1997

Chang E, Boyd A, Nelson CC, Crowley D, Law T, Keough KM, et al. Successful treatment of infant hemangiomas with interferon alpha-2b. *Journal of Pediatric Hematology/Oncology* 1997;**19**(3):237-244.

Chinnadurai 2016a

Chinnadurai S, Sathe NA, Surawicz T. Laser treatment of infantile hemangioma: A systematic review. *Lasers in Surgery & Medicine* 2016;**48**(3):221-233. [PUBMED: 26711436]

Chinnadurai 2016b

Chinnadurai S, Snyder K, Sathe N, Fonnesbeck C, Morad A, Likis FE, et al. In: Agency for Healthcare Research and Quality, editor(s). Diagnosis and Management of Infantile Hemangioma. Vol. **AHRQ Publication No.16-EHC002-EF**, Rockville MD: Agency for Healthcare Research and Quality, 2016.

Christou 2012

Christou EM, Wargon O. Effect of captopril on infantile haemangiomas: a retrospective case series. *The Australasian journal of dermatology* 2012;**53**(3):216-8. [PUBMED: 22671578]

Couto 2012

Couto RA, Maclellan RA, Zurakowski D, Greene AK. Infantile hemangioma: clinical assessment of the involuting phase and implications for management. *Plastic and reconstructive surgery* 2012;**130**(3):619-24. [PUBMED: 22575857]

Csoma 2017

Csoma ZR, Dalmady S, Abraham R, Rozsa T, Racz K, Kemeny L. Infantile haemangioma: clinical and demographic characteristics, experiences in the treatment [Infantilis haemangioma: klinikai es demografiai jellemzok, kezelesi-gondozasi tapasztalatok.]. *Orvosi Hetilap* 2017;**158**(39):1535-44. [PUBMED: 28942665]

Danarti 2016

Danarti R, Ariwibowo L, Radiono S, Budiyanto A. Topical timolol maleate 0.5% for infantile hemangioma: its effectiveness compared to ultrapotent topical corticosteroids - a single-center experience of 278 cases. *Dermatology (Basel, Switzerland)* 2016;**232**(5):566-71. [PUBMED: 27592104]

Daramola 2012

Daramola OO, Chun RH, Kerschner JE. Surgical management of auricular infantile hemangiomas. *Archives of otolaryngology--head & neck surgery* 2012;**138**(1):72-5. [PUBMED: 22249633]

Darrow 2015

Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Diagnosis and management of infantile hemangioma. *Pediatrics* 2015;**136**(4):e1060-104. [PUBMED: 26416931]

Dinehart 2001

Dinehart SM, Kincannon J, Geronemus R. Hemangiomas: evaluation and treatment. *Dermatologic Surgery* 2001;**27**(5):475-85. [PUBMED: 11359498]

Doshan 1986

Doshan HD, Rosenthal RR, Brown R, Slutsky A, Applin WJ, Caruso FS. Celiprolol, atenolol and propranolol: a comparison of pulmonary effects in asthmatic patients. *Journal of cardiovascular pharmacology* 1986;**8 Suppl 4**:S105-8. [PUBMED: 2427836]

EMC 2018

EMC. Summary of product characteristics. www.medicines.org.uk/emc/medicine/1730/SPC/Roferon-A+Pre-Filled+Syringe/#INTERACTIONS (accessed prior to 21 February 2018).

Ezekowitz 1992

Ezekowitz RA, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *The New England journal of medicine* 1992;**326**(22):1456-63. [PUBMED: 1489383]

Fragu 1991

Fragu P, Lemarchand-Venencie F, Benhamou S, François P, Jeannel D, Benhamou E, et al. Long-term effects in skin and thyroid after radiotherapy for skin angiomas: a French retrospective cohort study. *European Journal of Cancer* 1991;**27**(10):1215-22. [PUBMED: 1835589]

George 2004

George ME, Sharma V, Jacobson J, Simon S, Nopper AJ. Adverse effects of systemic glucocorticosteroid therapy in infants with hemangiomas. *Archives of Dermatology* 2004;**140**(8):963-9. [PUBMED: 15313812]

Ginimuge 2010

Ginimuge PR, Jyothi SD. Methylene blue: revisited. *Journal of anaesthesiology, clinical pharmacology* 2010;**26**(4):517-20. [PUBMED: 21547182]

Glade 2010

Glade RS, Vinson K, Becton D, Bhutta S, Buckmiller LM. Management of complicated hemangiomas with vincristine/vinblastine: Quantitative response to therapy using MRI. *International journal of pediatric otorhinolaryngology* 2010;**74**(11):1221-5. [PUBMED: 20884067]

Glassberg 1989

Glassberg E, Lask G, Rabinowitz LG, Tunnessen WW Jr. Capillary hemangiomas: case study of novel laser treatment and a review of therapeutic options. *Journal of Dermatologic Surgery & Oncology* 1989;**15**(11):1214-23. [PUBMED: 2808890]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed prior to 27/03/2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grantzow 2001

Grantzow R. [Differential therapy of hemangiomas--when cryotherapy, laser therapy or operation?] [Differentialtherapie von Hamangiomen--Wann Kryo, Laser oder Operation?]. *Kongressband. Deutsche Gesellschaft fur Chirurgie. Kongress* 2001;**118**:521-4. [PUBMED: 11824311]

Greinwald 1999

Greinwald JH Jr, Burke DK, Bonthius DJ, Bauman NM, Smith RJ. An update on the treatment of hemangiomas in children with interferon alfa-2a. *Archives of Otolaryngology - Head and Neck Surgery* 1999;**125**(1):21-7. [PUBMED: 9932582]

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651):995-8. [PUBMED: 18456631]

Guyatt 2011a

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294-302. [PUBMED: 21803546]

Guyatt 2011b

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277-82. [PUBMED: 21802904]

Guyatt 2011c

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303-10. [PUBMED: 21802903]

Guyatt 2011d

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407-15. [PUBMED: 21247734]

Guyatt 2011e

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311-6. [PUBMED: 21802902]

Guyatt 2011f

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93. [PUBMED: 21839614]

Guyatt 2011g

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PUBMED: 21195583]

Guyatt 2011h

Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395-400. [PUBMED: 21194891]

Hansson 1975

Hansson L, Aberg H, Karlberg BE, Westerlund A. Controlled study of atenolol in treatment of hypertension. *British medical journal* 1975;**2**(5967):367-70. [PUBMED: 236810]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011.

Holland 2013

Holland KE, Drolet BA. Approach to the patient with an infantile hemangioma. *Dermatologic Clinics* 2013;**31**(2):289-301. [PUBMED: 23557656]

Hopewell 1990

Hopewell JW. The skin: its structure and response to ionizing radiation. *International journal of radiation biology* 1990;**57**(4):751-73. [PUBMED: 1969905]

Hu 2015

Hu L, Huang HZ, Li X, Lin XX, Li W. Open-label nonrandomized left-right comparison of imiquimod 5% ointment and timolol maleate 0.5% eye drops in the treatment of proliferating superficial infantile hemangioma. *Dermatology (Basel, Switzerland)* 2015;**230**(2):150-5. [PUBMED: 25633200]

Itinteang 2011

Itinteang T, Brasch HD, Tan ST, Day DJ. Expression of components of the renin-angiotensin system in proliferating infantile haemangioma may account for the propranolol-induced accelerated involution. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2011;**64**(6):759-65. [PUBMED: 20870476]

Izadpanah 2013

Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plastic Reconstructive Surgery* 2013;**131**(3):601-13. [PUBMED: 23142941]

Ji 2015

Ji Y, Chen S, Xu C, Li L, Xiang B. The use of propranolol in the treatment of infantile haemangiomas: an update on potential mechanisms of action. *British Journal of Dermatology* 2015;**172**(1):24-32. [PUBMED: 25196392]

Kaplan 1990

Kaplan P, Normandin J Jr, Wilson GN, Plauchi H, Lippman A, Vekemans M. Malformations and minor anomalies in children whose mothers had prenatal diagnosis: comparison between CVS and amniocentesis. *American Journal of Medical Genetics* 1990;**37**(3):366-70. [PUBMED: 2260567]

Kennedy 2005

Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. Nature reviews. Cancer 2005; Vol. 5, issue 4:321-7. [PUBMED: 15776004]

Krupa 2009

Krupa Shankar D, Chakravarthi M, Shilpakar R. Carbon dioxide laser guidelines. *Journal of cutaneous and aesthetic surgery* 2009;**2**(2):72-80. [PUBMED: 20808594]

Li 2017

Li B, Li Z, Wang P, Huang Q, Xu L, He R, et al. Mammalian target of rapamycin complex 1 signalling is essential for germinal centre reaction. *Immunology* 2017;**152**(2):276-86. [PUBMED: 28557002]

Liang 2014

Liang MG, Frieden IJ. Infantile and congenital hemangiomas. *Seminars in pediatric surgery* 2014;**23**(4):162-7. [PUBMED: 25241092]

Luo 2011

Luo QF, Zhao FY. The effects of Bleomycin A5 on infantile maxillofacial haemangioma. *Head & face medicine* 2011;**7**:11. [PUBMED: 21736714]

Léauté-Labrèze 2015

Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *New England Journal of Medicine* 2015;**372**(8):735-46. [PUBMED: 25693013]

Ma 2017

Ma EH, Robertson SJ, Chow CW, Bekhor PS. Infantile hemangioma with minimal or arrested growth: further observations on clinical and histopathologic findings of this unique but underrecognized entity. *Pediatric Dermatology* 2017;**34**(1):64-71. [PUBMED: 27873347]

Marchuk 2001

Marchuk DA. Pathogenesis of hemangioma. *Journal of Clinical Investigation* 2001;**107**(6):665-6. [PUBMED: 11254664]

McDaniel 1997

McDaniel DH, Ash K, Lord J, Newman J, Zukowski M. The erbium: YAG laser: a review and preliminary report on resurfacing of the face, neck, and hands. *Aesthetic surgery journal* 1997;**17**(3):157-64. [PUBMED: 19327707]

Medicines.ie 2018

Medicines.ie. Summary of product characteristics. www.medicines.ie/medicine/15865/SPC/Capoten+25mg +Tablets/#INTERACTIONS (accessed prior to 21 February 2018).

Mulliken 2002

Mulliken JB, Rogers GF, Marler JJ. Circular excision of hemangioma and purse-string closure: the smallest possible scar. *Plastic and reconstructive surgery* 2002;**109**(5):1544-54; discussion 1555. [PUBMED: 11932595]

Orsi 2010

Orsi F, Arnone P, Chen W, Zhang L. High intensity focused ultrasound ablation: a new therapeutic option for solid tumors. *Journal of cancer research and therapeutics* 2010;**6**(4):414-20. [PUBMED: 21358073]

Pienaar 2006

Pienaar C, Graham R, Geldenhuys S, Hudson DA. Intralesional bleomycin for the treatment of hemangiomas. *Plastic and reconstructive surgery* 2006;**117**(1):221-6. [PUBMED: 16404271]

Probert 1975

Probert JC, Parker BR. The effects of radiation therapy on bone growth. *Radiology* 1975;**114**(1):115-62. [PUBMED: 813276]

Qiu 2015

Qiu Y, Lin X, Ma G, Chang L, Jin Y, Chen H, et al. Eighteen cases of soft tissue atrophy after intralesional bleomycin a5 injections for the treatment of infantile hemangiomas: a long-term follow-up. *Pediatric Dermatology* 2015;**32**(2):188-91. [PUBMED: 25640925]

Raphael 2011

Raphael MF, de Graaf M, Breugem CC, Pasmans SG, Breur JM. Atenolol: a promising alternative to propranolol for the treatment of hemangiomas. Journal of the American Academy of Dermatology 2011; Vol. 65, issue 2:420-1. [PUBMED: 21763565]

Review Manager 5.3 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration.. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration., 2014.

Rothfleisch 2002

Rothfleisch JE, Kosann MK, Levine VJ, Ashinoff R. Laser treatment of congenital and acquired vascular lesions. A review. *Dermatologic Clinics* 2002;**20**(1):1-18. [PUBMED: 11859585]

Sethuraman 2014

Sethuraman G, Yenamandra VK, Gupta V. Management of infantile hemangiomas: current trends. *Journal of cutaneous and aesthetic surgery* 2014;**7**(2):75-85. [PUBMED: 25136206]

Shen 2015

Shen L, Zhou G, Zhao J, Li P, Xu Q, Dong Y, et al. Pulsed dye laser therapy for infantile hemangiomas: a systemic review and meta-analysis. *QJM : Monthly Journal of the Association of Physicians* 2015;**108**(6):473-80. [PUBMED: 25376585]

Shorr 1986

Shorr N, Seiff SR. Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile haemangioma. *Ophthalmic Surgery* 1986;**17**(4):229-31. [PUBMED: 3714192]

Smolinski 2005

Smolinski KN, Yan AC. Hemangiomas of infancy: clinical and biological characteristics. *Clinical Pediatrics* 2005;**44**(9):747-66. [PUBMED: 16327961]

Syed 1999

Syed SB. Vascular birthmarks: update on presentation and management. *Current Paediatrics* 1999;**9**(1):20-6.

Tollefson 2012

Tollefson MM, Frieden IJ. Early growth of infantile hemangiomas: what parents' photographs tell us. *Pediatrics* 2012;**130**(2):e314-20. [PUBMED: 22826568]

van de Kerkhof 1998

van der Kerkhof PCM, de Rooij M, Steijlen PM. Spontaneous course of haemangiomas: facts and speculations. *International Journal of Dermatology* 1998;**37**(2):101-2.

Vega 2017

Vega Mata N, Lopez Gutierrez JC, Vivanco Allende B, Fernandez Garcia MS. Different clinical features of acral abortive hemangiomas. *Case Reports in Dermatological Medicine* 2017;**2017**:2897617. [PUBMED: 28785492]

Waeber 1980

Waeber B, Brunner HR, Brunner DB, Curtet AL, Turini GA, Gavras H. Discrepancy between antihypertensive effect and angiotensin converting enzyme inhibition by captopril. *Hypertension (Dallas, Tex. : 1979)* 1980;**2**(2):236-42. [PUBMED: 6247269]

Wang 2017

Wang C, Li Y, Xiang B, Xiong F, Li K, Yang K, et al. Quality of life in children with infantile hemangioma: a case control study. *Health and Quality of Life Outcomes* 2017;**15**(1):221. [PUBMED: 29145889]

Wnek 2017

Wnek A, Andrzejewska E, Kobos J, Taran K, Przewratil P. Molecular and immunohistochemical expression of apoptotic proteins Bax, Bcl-2 and Caspase 3 in infantile hemangioma tissues as an effect of propranolol treatment. *Immunology Letters* 2017;**185**:27-31. [PUBMED: 28279700]

Xu 2014

Xu S, Jia R, Ge S, Lin M, Fan X. Treatment of periorbital infantile haemangiomas: a systematic literature review on propranolol or steroids. *Journal of Paediatrics and Child Health* 2014;**50**(4):271-9. [PUBMED: 24754793]

Zhang 2017

Zhang L, Wu HW, Yuan W, Zheng JW. Propranolol therapy for infantile hemangioma: our experience. *Drug Design, Development and Therapy* 2017;**11**:1401-8. [PUBMED: 28507428]

Zheng 2018

Zheng L, Li Y. Effect of topical timolol on response rate and adverse events in infantile hemangioma: a meta-analysis. Archives of Dermatological Research 2018 Jan 23 [Epub ahead of print]. [DOI: 10.1007/s00403-018-1815-y]

Zimmermann 2010

Zimmermann AP, Wiegand S, Werner JA, Eivazi B. Propranolol therapy for infantile haemangiomas: review of the literature. *International Journal of Pediatric Otorhinolaryngology* 2010;**74**(4):338-42. [PUBMED: 20117846]

Zou 2013

Zou HX, Jia J, Zhang WF, Sun ZJ, Zhao YF. Propranolol inhibits endothelial progenitor cell homing: a possible treatment mechanism of infantile hemangioma. *Cardiovascular Pathology* 2013;**22**(3):203-10. [PUBMED: 23151525]

References to other published versions of this review

Leonardi-Bee 2011

Leonardi-Bee J, Batta K, O'Brien C, Bath-Hextall FJ. Interventions for infantile haemangiomas (strawberry birthmarks) of the skin. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD006545.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abarzua-Araya 2014

Methods	• Design: parallel - 2 arms • Country: Chile • Method of randomisation: simple randomisation • Blinding: double-blind/children – investigators • Location: Department of Dermatology, Universidad Católica de Chile • Length of follow-up: 6 months
Participants	• Diagnosis: IH needing treatment defined as functional impairment and aesthetic disfigurement • Sex. 65.2% were female and 34.7% were male. • Age: between 1 and 15 months • Inclusion criteria: infants and children from 1 to 15 months old with IH needing treatment, defined as functional impairment, aesthetic disfigurement, and if they were ulcerated or located on folds • Exclusion criteria: history of allergy or hypersensitivity to beta blockers, second- or third-degree atrioventricular block, heart failure, severe bradycardia, asthma or bronchial obstruction, and previous use of systemic corticosteroids or other beta blocker • Number of randomised children: 23
Interventions	• Intervention A (number of children: 13): atenolol 1 mg/kg/day for 6 months in a single daily dose • Intervention B (number of children: 10): propranolol in a dose of 2 mg/kg/day in 3 daily doses for 6 months
Outcomes	• Primary outcome: response classified as complete response, partial response, no response • Secondary outcomes: adverse events, heart rate, blood pressure, heart failure symptoms, and symptoms of bronchial obstruction
Notes	• Trial registration: not stated • Funder: none • Role of funder: none • A priori sample size estimation: not stated • Conducted: June 2012 to January 2013 • Declared conflicts of interest: no conflicts reported (page 1045)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who met inclusion criteria were randomised by simple randomisation (...)." Page 1046

Abarzua-Araya 2014 *(Continued)*

		Comment: There was insufficient information to rate this item as low or high risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was respected." Page 1046 Comment: Authors reported information about allocation concealment.
Blinding of participants (Performance bias)	Low risk	Quote: "The drugs were similar in aspect and the patients and main investigators were blind." Page 1046 Comment: Authors reported information about adequate blinding of participants and personnel.
Blinding of personnel (performance bias)	Low risk	Quote: "The drugs were similar in aspect and the patients and main investigators were blind." Page 1046 Comment: Authors reported information about adequate blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of information was not detected.
Other bias	Low risk	No other biases were detected.

Aly 2015

Methods	• Design: parallel - 2 arms • Country: Egypt • Method of randomisation: children were randomly assigned into 2 groups: Group A were given oral propranolol for 6 months combined with oral prednisolone for the initial 2 weeks, while Group B were given oral propranolol alone for 6 months. • Blinding: single-blind/assessors • Location: Pediatric Surgery Department, Ain Shams University, Egypt • Length of follow-up: 8 months
Participants	• Diagnosis: cutaneous haemangioma causing complications such as deformity, ulceration, bleeding, infection, or damage of orifices • Sex: not stated • Age: between 4 weeks and 8 months • Inclusion criteria: the included participants had an age less than 9 months, with cutaneous haemangioma causing complications such as deformity, ulceration, bleeding, infection, or damage of orifices. • Exclusion criteria: congenital haemangioma, main/extensive deep subcutaneous component, those receiving previous treatment for IH or with hypersensitivity to propranolol, known cardiac disease (heart failure or AV block), pulmonary disease (asthma or bronchiolitis), diabetes mellitus, visceral haemangiomas, or PHACE syndrome • Number of randomised children: 40

Aly 2015 *(Continued)*

Interventions	• Intervention A (Number of children: 20): children were given oral propranolol dosed as 2 mg/kg/day in 3 divided doses for 6 months combined with oral prednisolone dosed as 2 mg/kg/day in 2 divided doses for the initial 2 weeks, then stopped after gradual tapering over 1 week. Propranolol was gradually tapered over 2 weeks before stopping. • Intervention B (Number of children: 20): children were given oral propranolol monotherapy in the same previous dose for 6 months.
Outcomes	• Primary: decrease in the dimensions of the haemangiomas • Secondary: lightening of colour and flattening of their surfaces
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: December 2011 to March 2014 • Declared conflicts of interest: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All patients were randomly assigned into one of the two groups at equal probability using sealed envelope method." Page 1504 Comment: Insufficient information to rate this item as low or high risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "All patients were randomly assigned into one of the two groups at equal probability using sealed envelope method." Page 1504 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not in trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of intervention group assigned, but it is unclear whether this had an impact or not in trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Response to therapy was measured by blinded volume estimations at weeks (...)." Page 1504 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of information was not detected.
Other bias	Low risk	No other biases were detected.

Asilian 2015

Methods	• Design: parallel - 2 arms • Country: Iran • Method of randomisation: children were divided into 2 groups in double-blind manner. Each group had 16 haemangiomas. Group A was treated with 585 PDL and timolol maleate and Group B with 585 PDL plus lubricant gel as a placebo. • Blinding: double-blind • Location: Alzahra hospital (Referral Center for Treatment of Skin Diseases) • Length of follow-up: 6 months
Participants	• Diagnosis: cutaneous haemangioma causing complications such as deformity, ulceration, bleeding, infection, or damage of orifices • Sex: 24 female, 8 male • Age: between 1 and 12 months • Inclusion criteria: healthy infants between 1 month and 12 months old with superficial haemangioma ≤ 3 cm and with a history of sensitivity to beta blockers or asthma, renal disease, heart disease, hypoglycaemia, use of drugs that interact with beta blockers • Exclusion criteria: haemangiomas > 3 cm, infants older than 1 year, no sensitivity to beta blockers • Number of randomised children: 30 (2 children with 2 haemangiomas)
Interventions	• Intervention A (Number of children: 15): children were treated with 4 sessions of PDL and timolol maleate gel 0.05%. • Intervention B (Number of children: 15): PDL plus lubricant gel as placebo
Outcomes	• Primary: improvement in appearance, colour, and size. 2 forms of assessment were used: (1) clinical score for the overall change and (2) visual analogue scale similar to that employed in other objective studies. • Secondary: not stated
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: January 2011 to January 2012 • Declared conflicts of interest: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Then, patients were divided into two groups in [a] double blind manner." Comment: There was insufficient information to rate this item as low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Blinding of participants (Performance bias)	Low risk	Quote: " (...) Group B with 585 PDL plus lubricant gel as placebo." Page 2 Comment: Placebo intervention was used.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.

Asilian 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of information was not detected.
Other bias	Low risk	No other biases were detected.

Batta 2002

Methods	• Design: prospective, 2-arm, randomised controlled trial • Country: UK • Method of randomisation: block telephone randomisation • Blinding: only observer for secondary outcomes • Location: The Birmingham Children's Hospital NHS Trust • Length of follow-up: unclear: researchers followed children up at age 3, 6, 9, and 12 months.
Participants	• Diagnosis: children with superficial early haemangiomas, in the proliferative or early proliferative growth phase • Sex: male: 43; female: 78 • Age: between 1 and 14 weeks at start of trial • Inclusion criteria: children with superficial early haemangiomas, in the preproliferative or early proliferative growth phase • Exclusion criteria: children with mixed or deep haemangiomas, eyelid haemangiomas, large facial haemangioma at risk of causing great cosmetic deformity, and haemangiomas obstructing vital structures • Number of randomised children: 121
Interventions	• Intervention group (N = 60 children): PDL with 585 nm venous flash lamp pulsed dye laser at a pulse duration of 0.45 ms, spot diameter of 3 to 5 nm, and energy fluence of 6.0 to 7.5 J/cm^2 to produce purpura of the entire lesion, repeated every 2 to 4 weeks • Control group (N = 61 children): 'wait and see' approach
Outcomes	• Primary outcomes: proportion of children with lesions completely healed/minimal residual signs; proportion of parents who consider the child has a problem; adverse events • Secondary outcomes: objective measure of resolution by clinician using photographs (surface area and vertical height); average haemangioma problem grading of 5 independent parents
Notes	• Trial registration: not stated • Funder: Haemangioma and Laser Trust (HALT) and Sunday Mercury Newspaper • Role of funder: no role in study design, data collection, data analysis, data interpretation, or writing of report • A priori sample size estimation: not stated • Conducted: recruitment between May 1999 and May 2000 • Declared conflicts of interest: no conflicts reported (page 527)
Risk of bias	

Batta 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotation: "A block telephone randomisation was provided by the Birmingham Clinical trial unit. We stratified randomisation by completely flat and raised lesions (...)." Page 522 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quotation: "A block telephone randomisation was provided by the Birmingham Clinical trial unit. We stratified randomisation by completely flat and raised lesions (...)." Page 522 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of the intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of the intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Despite the fact that standardised methods were used, the lead author treated children with PDL and also assessed the primary outcome at 1 year.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors performed intention-to-treat analysis; all children were analysed for primary outcome.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods were reported on in the results.
Other bias	Low risk	No other biases were identified.

Bauman 2014

Methods	• Design: parallel, 2 arms • Country: USA • Method of randomisation: pre-generated encrypted schedule (Page 324) • Blinding: single-blind/investigator • Location: Children's National Medical Center • Length of follow-up: until 4 months
Participants	• Diagnosis: actively proliferating and symptomatic IH • Sex: females: 14; males: 5 • Age: 2 weeks to 6 months • Inclusion criteria: infants with symptomatic haemangiomas • Exclusion criteria: inadequate social support, non-proliferating IH, other treatment for IH, liver disease, abnormal blood glucose level (BG), hypertension, hypotension, reactive airway disease, cardiac anomalies, and PHACE • Number of randomised children: 19
Interventions	• Intervention A (number of children: 11): propranolol 2.0 mg/kg/d orally 3 times daily

Bauman 2014 *(Continued)*

	• Intervention B (number of children: 8): prednisolone 2.0 mg/kg/d orally twice daily
Outcomes	• Primary outcome: reduction in size of haemangioma, measured by the proportional change in the total surface area based on the lesion's outer margin dimensions at 4 months • Secondary outcome: adverse events, graded by severity (1 to 5)
Notes	• Trial registration: NCT00967226 • Funder: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Center for Research Resources of the National Institutes of Health (Page 330) • Role of funder: only financial support • A priori sample size estimation: yes (planned sample size: 55 children) • Conducted: between 1 September 2010 and 1 August 2012 • Declared conflicts of interest: yes (page 330)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " ...were randomised ... using a CNMC institutional tamper-proof, pre-generated encrypted schedule..." Page 324 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quotes: " ...were randomised ... using a CNMC institutional tamper-proof, pre-generated encrypted schedule..." Page 324. "The CNMC research pharmacy dispensed study drugs." Page 324 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Unclear risk	Quote: "Unblinded caretakers received counselling and written instructions to administer the medication 15 minutes before meals. (...) Caretakers were trained to recognize signs of hypoglycaemia, hypotension, and bradycardia that would warrant withholding of medication." Page 324 Comment: Unclear information was reported regarding the impact of lack of blinding for caretakers in the development of this trial.
Blinding of personnel (performance bias)	Low risk	Quote: "At enrolment, the blinded investigators assigned a number (...). The same blinded investigator repeated the measurements of size and skin involvement monthly." Page 324 Comment: Authors reported information about adequate blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Unblinded caretakers received counselling and written instructions to administer the medication 15 minutes before meals. (...) Caretakers were trained to recognize signs of hypoglycaemia, hypotension, and bradycardia that would warrant withholding of medication." Page 324 Comment: Unclear information was reported regarding the impact of lack of blinding for caretakers in the development of this trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors performed intention-to-treat analysis; all children were analysed for the primary outcome.

Bauman 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods were reported on in the results.
Other bias	Unclear risk	Quote: "The study was terminated prior to targeted enrolment at the DSMB's recommendation owing to severe AEs described herein that prompted early withdrawal of 6 of the 8 prednisolone participants." Page 325 Comment: Reason for termination of trial could be a potential source of bias.

Chan 2013

Methods	• Design: parallel, 2 arms • Country: Australia • Method of randomisation: method of minimisation • Blinding: children, caregivers, physicians, statistician • Location: Sydney Children's Hospital • Length of follow-up: 24 weeks
Participants	• Diagnosis: small, focal superficial IHs not requiring systemic therapy • Sex: female: 29; male: 12 • Age: between 5 and 24 weeks • Inclusion criteria: infants between the ages of 5 and 24 weeks with small, focal superficial IHs not requiring systemic therapy • Exclusion criteria: hypersensitivity to timolol maleate, wheezing, cardiac rhythm disturbances or congenital heart disease, or large, ulcerated, mucosal, or subcutaneous IHs • Number of children randomised: 41 infants
Interventions	• Intervention A (number of children: 19): timolol maleate 0.5% gel, 1 drop twice a day • Intervention B (number of children: 22): placebo gel, 1 drop twice a day
Outcomes	Outcomes were not classified as primary or secondary: • Volume estimation at weeks 0 ,1, 2, 3, 4, 8, 12, 16, 20, and 24 • Redness at weeks 0 ,1, 2, 3, 4, 8, 12, 16, 20, and 24 • Safety data: heart rate, systolic blood pressure, diastolic blood pressure, measured before first dose and 1 hour after the initial dose, and then at every visit
Notes	• Trial registration: ACTRN12610001069044 • Funder: Sydney Children's Hospital Foundation, Vascular Birthmark Research fellowship position • Role of funder: funds for statistical analysis • A priori sample size estimation: no • Conducted: from March 2011 to April 2012 • Declared conflicts of interest: yes (page e1739)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were enrolled in the trial by 1 of 2 study physicians and randomly assigned (by using a method of minimization) by the clinical trials pharmacist into 4 groups: age between 5 and 15 weeks or between 16 and 24 weeks and size of lesion, < or > 25 mm”. Page e1740

Chan 2013 *(Continued)*

		Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were enrolled in the trial by 1 of 2 study physicians and randomly assigned (by using a method of minimization) by the clinical trials pharmacist into 4 groups: age between 5 and 15 weeks or between 16 and 24 weeks and size of lesion, < or > 25 mm". Page e1740 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Low risk	Quote: "Participants, caregivers, and physicians were blinded to group status". Page e1740 Comment: Authors reported information about adequate blinding of participants.
Blinding of personnel (performance bias)	Low risk	Quote: "Participants, caregivers, and physicians were blinded to group status". Page e1740 Comment: Authors reported information about adequate blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Response to therapy was measured by (1) blinded predicted volume estimation at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 and (2) blinded scoring of clinical photographs at 0, 12, and 24 weeks". Page e1741 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were analysed using intention-to-treat approach.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods were reported on in the results.
Other bias	Low risk	No other biases were identified.

Ehsani 2014

Methods	• Design: parallel, 2 arms • Country: Iran • Method of randomisation: randomised number table • Blinding: single-blind • Location: Razi Hospital • Length of follow-up: 16 weeks
Participants	• Diagnosis: superficial or mixed IH • Sex: female: 16; male: 3 • Age: less than 2 years of age • Inclusion criteria: less than 2 years of age, having haemangioma in non-vital parts of the body including eyelids, ears, lips, and nose, and no previous treatment with systemic steroids or other modalities over the last 3 months • Exclusion criteria: patients with congenital heart or renal disease • Number of randomised children: 19

Ehsani 2014 *(Continued)*

Interventions	• Intervention A (number of children: 9): pulsed dye laser therapy (spot size 7 mm, fluence 12 J/cm^2, pulse duration 1.5 ms, dynamic cooling device 40/40) • Intervention B (number of children: 10): pulsed dye laser therapy + topical propranolol 1%, twice a day for at least 12 weeks
Outcomes	Outcomes were not classified as primary or secondary: • Clinical response: 0% to 25% = no response, 25% to 50% = poor response, 50% to 75% = good response, 75% to 100% = excellent response • Side effects reported by parents
Notes	• Trial registration: IRCT 201110137787N1 • Funder: not reported • Role of funder: not reported • A priori sample size estimation: no • Conducted: from January 2011 to July 2012 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "(...) and randomly divided into two treatment groups using a randomised number table." Page 658 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to classify this item as high or low risk of bias.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The clinical improvements of IH lesions were quantified using a visual score system after comparing pre- and post-treatment lesion photographs by two dermatologists who were blind to treatment regimens”. Page 659 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “All the 19 patients who were included to the study completed the treatment course.” Page 659 Comment: Authors reported complete data for all included children.
Selective reporting (reporting bias)	Unclear risk	In the protocol, the authors specified an outcome called “improvement of overall health of patient”. However, this outcome is not reported in the manuscript.
Other bias	Low risk	No other biases were identified.

Feng 2000

Methods	• Design: parallel, 2 arms • Country: China • Method of randomisation: unclear • Blinding: unclear • Location: unclear • Length of follow-up: not reported
Participants	• Diagnosis: haemangioma • Sex: female: 184; male: 84 • Age: from 2 months to 11 years old • Inclusion criteria: not reported • Exclusion criteria: not reported • Number of randomised children: 268
Interventions	• Intervention A (number of children: 150): methylene blue 1% injection (Shanghai Reagent Factory). Doses from 10 to 20 mg, once at week, for 4 weeks. A new course can start after 10 days. • Intervention B (number of children: 10): triamcinolone injection (Shanghai Ninth Pharmaceutical Products). Doses from 20 to 50 mg, once a week, for 4 weeks. A new course can start after 15 days.
Outcomes	Outcomes were not classified as primary or secondary: • Clinical results: cure = complete disappearance; effective = tumour regression > 30%
Notes	• Trial registration: not reported • Funder: not reported • Role of funder: not reported • A priori sample size estimation: no • Conducted: from February 1980 to December 1997 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "268 cases were randomly divided into two groups (...)." Page 284 Comment: Authors reported insufficient information about random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of personnel (performance bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to classify this item as high or low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.

Feng 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	Adverse events not reported.
Other bias	Low risk	No other biases were identified.

Fu 2012

Methods	• Design: parallel, 3 arms • Country: China • Method of randomisation: unclear • Blinding: unclear • Location: unclear • Length of follow-up: 6 months
Participants	• Diagnosis: haemangioma • Sex: female: 37; male: 23 • Age: from 3 to 30 months • Inclusion criteria: not reported • Exclusion criteria: not reported • Number of randomised children: 60
Interventions	• Intervention A (number of children: 20): HIFU, power of 3.5 W, 3 times as a course of treatment with a 1-month interval. Lesion surface was irradiated with 3 to 5 mm/second by ultrasonic therapeutic apparatus at a frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap. • Intervention B (number of children: 20): HIFU, power of 4.0 W, 3 times as a course of treatment with a 1-month interval. Lesion surface was irradiated with 3 to 5 mm/second by ultrasonic therapeutic apparatus at a frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap. • Intervention C (number of children: 20): HIFU, power of 4.5 W, 3 times as a course of treatment with a 1-month interval. Lesion surface was irradiated with 3 to 5 mm/second for by ultrasonic therapeutic apparatus at a frequency of 9 MHz, impulse of 1000, and 10% of scanning overlap.
Outcomes	Outcomes were not classified as primary or secondary: • Skin changes: cure = complete disappearance; basic cure = tumour regression > 80%; improvement = significant reduction but requiring treatment; invalid = no tumour shrinkage • Ulceration or scarring incidence
Notes	• Trial registration: not reported • Funder: not reported • Role of funder: not reported • A priori sample size estimation: no • Conducted: from January 2009 to September 2010 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 60 infants were randomly divided into 3 groups (...)." Page 1477 Comment: Authors reported insufficient information about random sequence generation.

Fu 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of personnel (performance bias)	Unclear risk	Insufficient information to classify this item as high or low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to classify this item as high or low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of data was not detected.
Other bias	Low risk	No other biases were identified.

Gong 2015

Methods	• Design: 3 arms • Country: China • Method of randomisation: 39 children with superficial infantile haemangiomas were randomised into 3 equal groups of 13 each: the first given topical timolol maleate together with oral propranolol, the second given only oral propranolol, and the third given only topical timolol maleate. • Blinding: double-blind • Location: Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University • Length of follow up: 3 to 12 months
Participants	• Diagnosis: children with superficial haemangiomas • Sex: 24 female, 15 male • Age: between 2 and 9 months • Inclusion criteria: children younger than 12 months with superficial haemangiomas with no previous treatment • Exclusion criteria: those with deep or mixed haemangiomas, bronchial asthma, pneumonia, sinus bradycardia or atrioventricular block (second degree and above), fever, and diarrhoea or respiratory infections • Number of randomised children: 39
Interventions	Intervention A (number of children: 13): propranolol oral (regimen below) + timolol maleate topical (regimen below) Intervention B (number of children: 13): propranolol oral: 10 mg tablet, at a 1.0 mg/kg dose orally once a day with food Intervention C (number of children: 13): timolol maleate topical: 0.5% timolol maleate eye drops to the lesion twice daily (25 mg/5 mL) with medical cotton swabs
Outcomes	Outcome A: the improvement in size after treatment was graded on a 4-point scale as proposed by Achauer and colleagues: class I (poor) - reduction in size of < 25%; class II (moderate) - reduction in size

Gong 2015 *(Continued)*

	of 25% to 50%; class III (good) - reduction in size of 50% to 75%; and class IV (excellent) - reduction in size of 75% to 100%. Classes I and II were considered ineffective treatment, and classes III and IV effective treatment.
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: October 2012 to August 2013 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a random sequence was generated using a computer program to assign patients in a 1:1:1 ratio to three groups of 13 patients each." Page 837 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A panel of three surgeons who were unaware of which treatment the infant had been given and the response rates, assessed the outcomes." Page 837 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of data was not detected.
Other bias	Low risk	No other biases were identified.

Hogeling 2011

Methods	• Design: parallel, 2 arms • Country: Australia • Method of randomisation: minimisation method • Blinding: participants, caregivers, physicians, statistician • Location: Sydney Children's Hospital • Length of follow-up: 6 months

Hogeling 2011 *(Continued)*

Participants	• Diagnosis: IHs that had a deep component or were located in sites that could impair function or result in aesthetic disfigurement • Sex: female: 27; male: 12 • Age: between 9 weeks and 5 years • Inclusion criteria: children between the ages of 9 weeks and 5 years with IHs that had a deep component or were located in sites that could impair function or result in aesthetic disfigurement, were too late for corticosteroid therapy, or that had failed to respond to corticosteroid therapy • Exclusion criteria: any children with IHs requiring urgent treatment due to impingement on vital structures, children with contraindications to propranolol, such as wheezing or PHACE syndrome, and those children with extracutaneous haemangiomas that could not be assessed by clinical photography and volume estimation • Number of randomised children: 40
Interventions	• Intervention A (number of children: 20): propranolol hydrochloride oral solution 2 mg/kg per day. Administration was initiated at a dosage of 1 mg/kg per day divided 3 times daily for 1 week, and then increased to 2 mg/kg per day divided 3 times daily from weeks 2 to 24. After 6 months of treatment, the trial medication was tapered by decreasing to one-half dose for 1 week followed by one-quarter dose for 1 week, and then discontinuing. • Intervention B (number of children: 20): placebo oral solution. The placebo oral solution had a similar taste and smell and an identical dispensing bottle.
Outcomes	Outcomes were not classified as primary or secondary: • Response to therapy: volume estimation at weeks 0, 4, 8, 12, 16, 20, and 24 by using serial hemispheric measurements of tumour volume. IH colour (redness or blueness) and elevation • Adverse events
Notes	• Trial registration: ACTRN12611000004965 • Funder: Sydney Children's Hospital Foundation • Role of funder: not reported • A priori sample size estimation: yes • Conducted: from June 2009 to December 2010 • Declared conflicts of interest: yes (page e259)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were enrolled in the trial by study physicians and randomised into 4 groups using minimization by the clinical trials pharmacist. The study physician telephoned the clinical trials pharmacist who then assigned sequence of randomisation.” Page 260 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: “Patients were enrolled in the trial by study physicians and randomised into 4 groups using minimization by the clinical trials pharmacist. The study physician telephoned the clinical trials pharmacist who then assigned sequence of randomisation.” Page 260 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Low risk	Quotes: “Participants, caregivers, and physicians were blinded to group status.” Page 260

Hogeling 2011 *(Continued)*

		"The placebo oral solution had a similar taste and smell and an identical dispensing bottle." Page 260 Comment: Authors reported information about adequate blinding of participants.
Blinding of personnel (performance bias)	Low risk	Quotes: "Participants, caregivers, and physicians were blinded to group status." Page 260 "The placebo oral solution had a similar taste and smell and an identical dispensing bottle." Page 260 Comment: Authors reported information about adequate blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The IH colour (redness or blueness) and elevation were assessed by the blinded investigator and were given scores by the investigators." Page 261 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% of children were lost at follow-up. Page 261
Selective reporting (reporting bias)	High risk	All outcomes were predefined and reported. However, information about variance of information (standard deviations) associated to mean estimation were ommited.
Other bias	Low risk	No other biases were identified.

Jung 1977

Methods	• Design: parallel, 2 arms • Country: Germany • Method of randomisation: table • Blinding: participants • Location: outpatient clinic, Department of Dermatology, Heidelberg University • Length of follow-up: 6 years
Participants	• Diagnosis: haemangioma • Sex: female: 70; male: 30 • Age: less than 9 months • Inclusion criteria: small children with planotuberous or tuberocavernous haemangiomas with growth tendency • Exclusion criteria: children older than 9 months, using active pretreatment, explicit therapy advice from referring physician, or haemangioma not accessible from radiation treatment • Number of randomised children: 100
Interventions	• Intervention A (N = 51 children): soft X-ray radiation, 400 rad (setting level 2, 29 kV, 0.3-millimetre AL-filter) 2 or 3 times per week for 4 to 7 weeks • Intervention B (N = 49 children): mock [sham] radiation 2 or 3 times per week for 4 to 7 weeks
Outcomes	Outcomes were not classified as primary or secondary: • Clearance: proportion of children with lesions completely healed/minimal residual signs

Jung 1977 *(Continued)*

Notes	Translation of original publication (article in German) • Trial registration: not stated • Funder: not reported • Role of funder: not reported • A priori sample size estimation: no • Conducted: from January 1966 to December 1969 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was according to "table of chance".
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Low risk	Participants were blinded by means of pseudo-radiation intervention.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to classify this item as high or low.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to classify this item as high or low.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis not used: • Intervention: 24 dropouts (47%; reasons not reported) • Control: 22 dropouts (44%; reasons not reported)
Selective reporting (reporting bias)	High risk	Adverse events were not reported in this trial.
Other bias	Low risk	No other biases were identified.

Kessels 2013

Methods	• Design: parallel, 2 arms • Country: the Netherlands • Method of randomisation: computer program (Page 415) • Blinding: single-blind; “The panel consisting of a dermatologist, physician assistant, dermatology resident, dermatology nurse, and plastic surgery resident to score improvement on a scale from 1 to 3 (1 = no improvement, 2 = moderate improvement, 3 = significant improvement) based on colour photographs taken at inclusion and at the age of 1 year. This panel was blinded to treatment group and when the photographs were taken” Page 416 • Location: Catharina Hospital Eindhoven, Netherlands • Length of follow-up: 12 months
Participants	• Diagnosis: early haemangiomas with a maximum diameter of 5 cm • Sex: male: 7; female: 16

Kessels 2013 *(Continued)*

	• Age: between 0 and 6 months • Inclusion criteria: non-treated superficial and cutaneous haemangioma with a maximum diameter of 5 cm, a maximum depth to the papillary dermis, and a maximum of 1 haemangioma per child, parents signed informed consent • Exclusion criteria: patients aged 6 months and older, subcutaneous or compound haemangioma, haemangioma with a diameter > 5 cm, haemangioma associated with neurocutaneous syndromes, ulcerating haemangioma, haemangioma at great risk for auditory or visual compromise, and previous treatment • Number of randomised children: 22
Interventions	• Intervention A (number of children: 11): PDL group, 595 nm PDL (Vbeam, Candela Corp., Wayland, MA, USA) with a 7-millimetre spot diameter, 30/10- to 40/10-millisecond epidermal cooling, a fluence range of 7 to 15 J/cm^2, and a pulse duration of 0.45 to 40.0 ms. Treatment was given every 2 to 6 weeks. • Intervention B (number of children: 11): wait-and-see group, no treatment. Children were followed until reaching 12 months.
Outcomes	Outcomes were not classified as primary or secondary: • Change in the echo thickness of the haemangiomas • Change in the surface area of the haemangioma • Change in the colour of the haemangiomas • Score improvement by an independent panel • Side effects
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: “A power analysis done before the start of the study calculated that a sample size of 70 infants (35 PDL treatment group, 35 observation group) was needed with 80% power and 5% significance.” • Conducted: May 2009 to December 2011 • Declared conflicts of interest: no "significant interest" (page 414)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were randomised using a computer program to two groups (...)." Page 415 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At the end of the study, we asked a panel consisting of a dermatologist, physician assistant, dermatology resident, dermatology nurse, and plastic surgery resident to score improvement on a scale from 1 to 3 (...) The panel was blinded to treatment group and when the photographs were taken." Page 416

Kessels 2013 *(Continued)*

		Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 children were lost at follow-up (13%) for such reasons as long travel distance between hospital and home and dissatisfaction with final group randomisation.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods were reported on in the results.
Other bias	Low risk	No other biases were identified.

Leaute-Labreze 2013

Methods	• Design: parallel, 2 arms • Country: France • Method of randomisation: randomisation list (Page 181) • Blinding: participants, caregivers, and physicians • Location: Pediatric Dermatology Centre, University Hospital of Bordeaux, France • Length of follow-up: 30 days
Participants	• Diagnosis: IH more than 1 cm in diameter • Sex: male: 4; female: 10 • Age: less than 16 weeks • Inclusion criteria: infants aged < 16 weeks, with 1 or more non-threatening IH of more than 1 cm in diameter, without vital or functional impairment, and not justifying oral corticosteroids • Exclusion criteria: (i) children with IHs requiring urgent treatment due to possible impact on vital structures; (ii) those with contraindications for propranolol (sinus bradycardia, partial atrioventricular block, previous history of wheezing); and (iii) those previously treated with propranolol, systemic steroids, vincristine, or interferon alpha • Number of randomised children: 14
Interventions	• Intervention A (number of children: 7): propranolol group, oral propranolol at 3 mg/kg/day for 15 days, then 4 mg/kg/day for 15 additional days • Intervention B (number of children: 11): placebo group, no further details provided
Outcomes	Outcomes were not classified as primary or secondary: • Diameter and thickness of IH, using ultrasonography • Measurements of blood pressure and heart rate • Adverse events
Notes	• Trial registration: NCT00744185 • Funder: University Hospital of Bordeaux, France • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: from October 2008 to April 2010 • Declared conflicts of interest: yes (page 183)

Risk of bias

Bias	Authors' judgement	Support for judgement

Leaute-Labreze 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Once enrolled, patients were subsequently randomised into two groups to receive either oral propranolol (3 mg kg 1 daily for 15 days then 4 mg kg 1 daily for 15 additional days) or a placebo, according to a predefined randomisation list." Page 169 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to classify this item as high or low.
Blinding of participants (Performance bias)	Low risk	Quote: "Participants, caregivers and physicians were blinded to group status." Page 169 Comment: Authors reported information about adequate blinding of participants.
Blinding of personnel (performance bias)	Low risk	Quote: "Participants, caregivers and physicians were blinded to group status." Page 169 Comment: Authors reported information about adequate blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, caregivers and physicians were blinded to group status." Page 169 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14% were lost at follow-up: 1 child in the propranolol group and 1 child in placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the trial protocol were reported.
Other bias	Low risk	No other biases were identified.

Leaute-Labreze 2015

Methods	• Design: parallel, 4 arms • Country: France • Method of randomisation: interactive voice-response system, with the use of block randomisation stratified according to age group (35 to 90 days vs 91 to 150 days) and haemangioma location (facial vs non-facial). Page 736 • Blinding: participants, outcome evaluators • Location: Unité de Dermatologie Pédiatrique, Hôpital Pellegrin- Enfants, Pl. Amélie Raba Léon, Bordeaux, France • Length of follow-up: 24 weeks (first measurement). Last follow-up was performed at week 96.
Participants	• Diagnosis: proliferating infantile haemangioma requiring systemic therapy (i.e. an evaluated lesion with a minimal diameter of 1.5 cm) • Sex: male: 131; female: 325 • Age: between 35 to 150 days of age

Leaute-Labreze 2015 *(Continued)*

- Inclusion criteria: a proliferating IH (target haemangioma) requiring systemic therapy present anywhere on the child's body except on the diaper area, with largest diameter of at least 1.5 cm; written informed consent; 35 to 150 days old
- Exclusion criteria: congenital haemangioma; Kasabach-Merritt syndrome; bronchial asthma; bronchospasm; hypoglycaemia (< 40 mg/dL or at risk); untreated phaeochromocytoma; hypotension (< 50/30 mmHg); second- or third-degree heart block; cardiogenic shock; metabolic acidosis; bradycardia (< 80 beats per minute); severe peripheral arterial circulatory disturbances; Raynaud's phenomenon; sick sinus syndrome; uncontrolled heart failure or Prinzmetal's angina; documented PHACE syndrome with central nervous system involvement; previously been treated for IH; child's mother had been breastfeeding the child while she was also being treated with beta blockers; known to have a hypersensitivity to propranolol and/or any other beta blockers; life-threatening IH; function-threatening IH (e.g. those causing impairment of vision, or respiratory compromise caused by airway lesions); ulcerated IH (whatever the localisation) with pain and lack of response to simple wound care measures; born prematurely and had not yet reached his/her term-equivalent age; left ventricular systolic function ≤ 40% and/or cardiomyopathy and/or hereditary arrhythmia disorder
- Number of randomised children: 460

Interventions

- Intervention A (number of children: 98): propranolol at 1 mg per kilogram per day for 3 months
- Intervention B (number of children: 102): propranolol at 1 mg per kilogram per day for 6 months
- Intervention C (number of children: 100): propranolol at 3 mg per kilogram per day for 3 months
- Intervention D (number of children: 101): propranolol at 3 mg per kilogram per day for 6 months
- Intervention E (number of children: 55): placebo at 3 mg per kilogram per day for 6 months

Outcomes

Primary

- Complete or nearly complete resolution of the target haemangioma (with nearly complete resolution defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks), haemangioma evolution (improvement, stabilisation, or worsening), and change in haemangioma size and colour were assessed centrally.

Secondary

- Centralised assessments of the target IH
- Investigator on-site qualitative assessments of the target IH at each postbaseline visit vs baseline
- Investigator on-site qualitative assessments of the target IH at paired consecutive patient visits (each scheduled postbaseline visit compared to the previous scheduled visit)
- Other investigator on-site qualitative assessments at each scheduled postbaseline visit
- Parent(s) or guardian(s) on-site qualitative assessments of the target IH at each scheduled postbaseline visit compared to the previous scheduled visit
- Intake of IH treatment (outside that assigned in the trial) during follow-up (systemic/local beta blockers, systemic/local corticoids, and laser)

Notes

- Trial registration: NCT01056341
- Funder: Pierre Fabre Dermatologie
- Role of funder: involved in study design, analysis, and manuscript production
- A priori sample size estimation: yes (page 737)
- Conducted: February 2010 to November 2011
- Declared conflicts of interest: stated in full text (supplementary appendix)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to treatment through an interactive voice-response system, with the use of block randomisation stratified according to age group (35 to 90 days vs. 91 to 150 days) and hemangioma location (facial vs. non-facial) and applied in a 2:2:2:2:1 ratio (propranolol at 1 mg per kilogram per day for 3 months, propranolol at 1 mg per kilogram per day for 6 months,

Leaute-Labreze 2015 *(Continued)*

		propranolol at 3 mg per kilogram per day for 3 months, propranolol at 3 mg per kilogram per day for 6 months, and placebo, respectively).” Page 736 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: “Patients were assigned to treatment through an interactive voice-response system, with the use of block randomisation stratified according to age group (35 to 90 days vs. 91 to 150 days) and hemangioma location (facial vs. non-facial) and applied in a 2:2:2:2:1 ratio (propranolol at 1 mg per kilogram per day for 3 months, propranolol at 1 mg per kilogram per day for 6 months, propranolol at 3 mg per kilogram per day for 3 months, propranolol at 3 mg per kilogram per day for 6 months, and placebo, respectively).” Page 736 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Low risk	Quote: “Different concentrations of propranolol were used (1.25, 2.50, or 3.75 mg per millilitre) in order to administer the same volume to each patient and thereby maintain blinding; patients assigned to 3-month propranolol regimens received placebo for the second 3 months.” Page 737 Comment: Authors reported information about adequate blinding of participants.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Primary efficacy was assessed by centralized evaluation of standardized digital photographs (taken by investigators at each visit) by two independent, trained, validated readers who were unaware of the study-group assignments, with adjudication for discrepancies; inter-reader and intra-reader reliability were assessed.” Page 737 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The percentage lost at follow-up was between 1% and 4%, respectively (intention-to-treat analysis with overrun).
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Unclear risk	Quote: “The sponsor (Pierre Fabre Dermatologie) was involved in the study design in collaboration with three of the academic authors and was responsible for trial management, analysis and interpretation of data, and the decision to submit the manuscript for publication.” Page 736 Comment: The industry sponsor was involved in the analysis and interpretation of the data, as well as the decision to submit the manuscript for publication. It is unclear what effect this may have on the study results.

Li 2016

Methods	• Design: 2 arms • Country: China

Li 2016 *(Continued)*

	• Method of randomisation: randomly divided into experimental and control groups using a randomised number table • Blinding: double-blind • Location: Department of Oral and Maxillofacial Surgery, China Medical University Stomatologic Hospital • Length of follow-up: 8 months
Participants	• Diagnosis: children with mixed IHs in the oral and maxillofacial regions • Sex: 18 female, 13 male • Age: between 2 and 11 months • Inclusion criteria: patients of less than 1 year of age, and the presence of mixed haemangioma (located in the papillary dermis, reticular dermis, and subcutaneous tissue) with functional or cosmetic deformity • Exclusion criteria: history of previous treatment for IHs (such as laser or steroid), heart disease, cardiac arrhythmia, asthma, broncho-obstructive disease, PHACE syndrome, and prematurity • Number of randomised children: 31
Interventions	Intervention A (number of children: 14): oral propranolol in combination with topical timolol maleate Intervention B (number of children: 17): oral propranolol treatment alone
Outcomes	**Primary** Outcome A: Changes of size and colour of the haemangioma were assessed by B-ultrasound and photographs at the onset of treatment, between treatment intervals, and at the conclusion of treatment. **Secondary** Outcome B: The visual analogue scale was compared with the response to treatment.
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: March 2013 to June 2014 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly divided into experimental and control groups using a randomised number table." Page 56 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	Despite participants being aware of intervention group assigned, it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	Despite researchers being aware of intervention group assigned, it is unclear whether this had an impact or not on the trial results.

Li 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three independent surgeons blind to the patients assessed the efficacy by analysing the clinical photograph at baseline and the end of the treatment." Page 57 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting was not detected.
Other bias	Low risk	No other biases were identified.

Lu 2016

Methods	• Design: 2 arms • Country: China • Method of randomisation: unclear • Blinding: unclear • Location: Department of Dermatology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, China • Length of follow-up: unclear
Participants	• Diagnosis: complicated infantile haemangiomas • Sex: 46 female, 15 male • Age: mean age of 3.55 (range 1 to 6 months) • Inclusion criteria: 1. the lesion in question had a distinct proliferative phase; 2. physicians determined topical treatment alone would not control the progression of the disease; 3. the thickness of lesions was ≥ 1 cm and confirmed by ultrasound • Exclusion criteria: patients who had taken or were taking systemic corticosteroids, as well as patients with a family history of asthma • Number of randomised children: 61
Interventions	• Intervention A (number of children: 30): local dual-wavelength laser therapy after discontinuation of oral propranolol (1 to 2 mg/kg/day). Propranolol treatment was stopped when maximised treatment effect was achieved. • Intervention B (number of children: 31): oral propranolol (1 to 2 mg/kg/day) for 1 week before laser therapy was added concurrently
Outcomes	• Change in lesions: scores from 0 to 10 points • Total treatment time • Medication time • Laser treatment times • Side effects
Notes	• Trial registration: not stated • Funder: Natural Science Foundation of Hunan Province and Bureau of Changsha Science and Technology • Role of funder: provision of grants • A priori sample size estimation: not stated

Lu 2016 *(Continued)*

- Conducted: 2009 to 2011
- Declared conflicts of interest: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomised into two groups." Page 16,135 Comment: There was insufficient information to rate this item as low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to rate this item as low or high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting of information was not detected.
Other bias	Low risk	No other biases were detected.

Malik 2013

Methods	• Design: parallel, 3 arms • Country: India • Method of randomisation: computer program • Blinding: double-blind/assessors • Location: Department of Pediatric Surgery, Advanced Pediatric Centre • Length of follow-up: 18 months
Participants	• Diagnosis: IHs • Sex: male: not stated; female: not stated • Age: 1 week to 8 months • Inclusion criteria: 1 week to 8 months of either sex and problematic IHs, with potentially disfiguring lesions in the face or functionally threatening lesions of the limbs, genitalia, or natural orifices • Exclusion criteria: uncomplicated lesions of trunk, extremities; presence of heart disease, cardiac arrhythmia; broncho-obstructive disease; history of hypoglycaemia; diabetes mellitus; hypertension; hypotension; liver failure; visceral lesions; and prematurity • Number of randomised children: 30
Interventions	• Group A (10 children): oral propranolol alone, 1 mg/kg per day, in 2 divided doses and increased to 2 mg/kg/day on the second day (max: 3 mg/kg/day)

Malik 2013 *(Continued)*

	• Group B (10 children): oral prednisolone alone; 1 mg/kg/day in 2 divided doses after feeding for a period of 3 weeks; discontinued for 3 weeks and then restarted in a similar on/off fashion to reduce drug side effects • Group C (10 children): combination of both drugs as per above protocol
Outcomes	**Primary outcome** • Complete or nearly complete resolution of the target haemangioma (with nearly complete resolution defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks), haemangioma evolution (improvement, stabilisation, or worsening), and changes in haemangioma size and colour were assessed centrally. **Secondary outcomes** • Centralised assessments of the target IH • Investigator on-site qualitative assessments of the target IH at each postbaseline visit vs baseline • Investigator on-site qualitative assessments of the target IH at paired consecutive patient visits (each scheduled postbaseline visit compared to the previous scheduled visit) • Other investigator on-site qualitative assessments at each scheduled postbaseline visit • Parent(s) or guardian(s) on-site qualitative assessments of the target IH at each scheduled postbaseline visit compared to the previous scheduled visit • Intake of IH treatment (outside that assigned in the trial) during follow-up (systemic/local beta blockers, systemic/local corticoids, and laser)
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: from January 2011 to July 2012 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Random sequence was generated using a computer program in a 1:1:1 ratio.” Page 2454 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The images were evaluated by two independent blinded examiners who scored the improvement (...)." Page 2454 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	No children were lost at follow-up.

Malik 2013 *(Continued)*

All outcomes

Selective reporting (reporting bias)	High risk	The primary outcome was not clearly reported in the Results section.
Other bias	Low risk	No other biases were detected.

Pope 2007

Methods	• Design: parallel, 2 arms • Country: Canada • Method of randomisation: performed by a research pharmacist who prepared blocks of 4 (Page 3) • Blinding: single-blind • Location: “The Hospital for Sick Children (SickKids), an academic paediatric tertiary referral centre”, Toronto, Canada • Length of follow-up: 3 months from the enrolment and at the child's first birthday
Participants	• Diagnosis: facial haemangiomas (defined as "peri-orbital/orbital tumours with visual impairment and/or large size/disfiguring hemangiomas”) • Sex: 17 females, 3 males • Age: from 1 to 4 months of age • Inclusion criteria: infants between 1 and 4 months of age, who had "problematic" facial infantile haemangiomas • Exclusion criteria: infants > 4 months of age, those with concomitant congenital heart disease, and those with non-facial IHs were excluded. • Number of randomised children: 20
Interventions	• Active intervention 1 (N = 10 children): prednisolone (2 mg/kg/day) orally divided into 2 doses for 3 months, then tapered schedule (decreasing dose by 1 mg per month over 6 to 9 months to prevent rebound). Children could have oral ranitidine to minimise steroid-related gastrointestinal adverse effects. • Active intervention 2 (N = 10 children): methylprednisolone (30 mg/kg/day) intravenously infused over 1 hour, daily for 3 days, given monthly for 3 months. Children could have oral steroids if significant rebound or worsening of the lesion, but they were counted as treatment failures.
Outcomes	• Primary outcome: change in the size of the haemangioma • Secondary outcomes: * Changes in visual function at 1 year in infants with periorbital haemangiomas * Report of adverse events using 1 of these: ☐ parent diaries (behaviour changes, irritability, crying, hyperactivity, apathy, insomnia, vomiting, and abdominal pains); ☐ medical charts (blood pressure, heart rate, and respiratory rate); ☐ investigations (complete blood cell count, blood sugar, renal function tests, electrolytes, and morning cortisol) * Changes in angiogenesis markers
Notes	• Trial registration: NCT 00312520 • Funder: not stated • Role of funder: not stated • A priori sample size estimation: yes • Conducted: the study was conducted between July 2002 and July 2005 at the Hospital for Sick Children (SickKids). • Declared conflicts of interest: not reported

Pope 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were allocated randomly to each group by the research pharmacist who prepared blocks of 4." Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were allocated randomly to each group by the research pharmacist who prepared blocks of 4." Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Unclear risk	Despite participants being aware of the intervention group assigned, it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	Despite researchers being aware of the intervention group assigned, it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "However, the assessors who measured the primary outcome were blinded to the patient's intervention allocation" Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children lost to follow-up.
Selective reporting (reporting bias)	High risk	Evidence of selective omissions of outcomes from the report (a subjective measure of improvement, as assessed by the parent or child), where only an interclass correlation is presented.
Other bias	Low risk	No other biases were detected.

Tan 2012

Methods	• Design: parallel, 3 arms • Country: China • Method of randomisation: random number table • Blinding: single-blind/the physician test packet inspection blinded • Duration of trial: from July 2010 to October 2011 • Location: Hubei Maternal and Child Health Hospital, China • Length of follow-up: 24 weeks
Participants	• Diagnosis: all diagnosed as haemangioma surface, all cases had not received treatment. • Sex: male: 28; female: 69 • Age: between 1 and 4 months • Inclusion criteria: 1 to 4 months of age, signed consent for • Exclusion criteria: refusal to participate; age > 4 months; children with chronic diseases of cardiovascular, respiratory, and other systems; merger vascular malformations; maximum tumour diameter < 1.0 cm

Tan 2012 *(Continued)*

	• Number of randomised children: 97
Interventions	• Intervention A (number of children: 32): propranolol, laser combined treatment. 1064 nm Nd:YAG laser therapy, once every 6 weeks; the first 2 days after laser treatment start propranolol 0.5 mg/kg/day, twice daily; increased dosage 2 weeks later to 0.8 mg/kg/day, 4 weeks later increased to 1.0 mg/kg/day • Intervention B (number of children: 35): 1064 nm Nd:YAG laser treatment, once every 6 weeks • Intervention C (number of children: 30): propranolol 0.5 mg/kg/day, orally twice daily; increased dosage 2 weeks later to 0.8 mg/kg/day, 4 weeks later increased to 1.0 mg/kg/day
Outcomes	• Primary outcome: clearance of lesions, measured by visual analogue scale score • Clinical response rate: (the number of recovery cases + the number of obvious improvement cases + the number of improvement cases)/total number of cases in each group *100% • Obvious improvement rate: (the number of recovery cases + the number of obvious improvement cases)/total number of cases in each group *100% • Adverse events
Notes	• Trial registration: unclear • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: from July 2010 to October 2011 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned based on random number table." Page 165 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome assessor was blinded." Page 165 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 (16%) children in the propranolol group left the study early; no intention-to-treat analysis was conducted.
Selective reporting (reporting bias)	Low risk	Selective reporting was not detected.
Other bias	Low risk	No other biases were identified.

Tawfik 2015

Methods	• Design: parallel, 2 arms • Country: Egypt • Method of randomisation: coin-toss method • Blinding: single-blind • Location: National Institute of Laser Enhanced Sciences • Length of follow-up: 3 months
Participants	• Diagnosis: infantile haemangioma • Sex: male: 15; female: 45 • Age: not specified • Inclusion criteria: no history of previous treatment, no concomitant active treatment for IH, and no evidence of short-term regression • Exclusion criteria: asthma, sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of timolol maleate • Number of randomised participants: 60
Interventions	• Intervention A (number of participants: 30): timolol maleate 0.5% (5 mg/mL) ophthalmic solution, twice daily for 6 months. The dose was given according to the size and depth of the haemangiomas. • Intervention B (number of participants: 30): PDL with a 7-millimetre spot size, 6-millisecond pulse duration, and fluence of 4.5 to 6 J/cm^2. After a 1-second delay, Nd:YAG laser was administered at a 15-millisecond pulse duration and fluence of 25 to 35 J/cm^2.
Outcomes	Outcomes were not classified as primary or secondary: • Clinical evaluation: standardised serial photographs were taken before treatment, at every visit, and 3 months after the last session. The evaluation assessments included 3 parameters: regression or cessation of growth, shrinkage or flattening of the lesion, and lightening of the surface colour. Two doctors, a paediatrician and a dermatologist blind to the treatment protocol, independently evaluated the efficacy of the 2 modes of treatment as follows: 0, no improvement; < 25%, mild improvement; 26% to 50%, moderate improvement; 51% to 75%, good improvement; and 76% to 100%, excellent improvement. • Parent satisfaction • Adverse events
Notes	• Trial registration: unclear • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: from January 2012 to March 2013 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated into two groups using a simple coin toss method." Page 370 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.

Tawfik 2015 *(Continued)*

Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that researchers were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Two independent doctors, a paediatrician and a dermatologist blind to the treatment protocol, evaluated the efficacy of the two modes of treatment as follows (...)." Page 372 Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were detected.

Tiwari 2016

Methods	• Design: 2 arms • Country: India • Method of randomisation: 64 participants were randomly divided into 2 groups using computer-generated random number table. • Blinding: double-blind • Location: Children's Hospital of Eastern Ontario • Length of follow-up: 1 year
Participants	• Diagnosis: patients with ulcerated infantile haemangiomas of head and neck region • Sex: not stated • Age: older than 1 month • Inclusion criteria: patients with ulcerated infantile haemangiomas of head and neck region, without any prior treatment and aged older than 1 month • Exclusion criteria: 4 participants of Group A and 8 participants of Group B who failed to come for follow-up on time were also excluded from the study. • Number of randomised participants: 52
Interventions	Intervention A (number of participants: 28): participants were given oral propranolol at a dose of 2 mg/kg per day in 3 divided doses as outpatients. Intervention B (number of participants: 24): participants were given oral ibuprofen at a dose of 10 mg/kg 8-hourly and paracetamol at a dose of 16.2 mg/kg 8-hourly.
Outcomes	• Primary: complete response with apparently no residual disease and requiring no adjuvant treatment • Secondary: partial response with residual disease requiring adjuvant treatment; non-responder with no response or progressive increase in lesion size even after 6 months of treatment
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated

Tiwari 2016 *(Continued)*

- A priori sample size estimation: not stated
- Conducted: March 2011 to April 2014
- Declared conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The division was performed using [a] computer-generated random number table." Page 74 Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of personnel (performance bias)	Unclear risk	It is highly probable that participants were aware of intervention group assigned, but it is unclear whether this had an impact or not on the trial results.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to assess this item as low or high.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	18.7% of participants were excluded due to insufficient follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were detected.

Xu 2006

Methods	• Design: parallel, 2 arms • Country: China • Method of randomisation: not stated • Blinding: not stated • Location: not stated • Length of follow-up: 7 days
Participants	• Diagnosis: infantile haemangioma • Sex: not stated • Age: less than 6 months • Inclusion criteria: less than 6 months of age, proliferating capillary haemangiomas • Exclusion criteria: not stated • Number of randomised children: 30
Interventions	• Intervention (N = 15 children): bleomycin (pingyangmycin), made into an emulsion and smeared on surface of tumour evenly, course lasted about 7 days, 3 times each day

Xu 2006 *(Continued)*

	• Control (no intervention) (N = 15 children): specimens were cut out by operation on day 7, then made into pathological slices and electron microscope slices.
Outcomes	• Resolution in terms of redness and size • Apoptic index
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: not stated • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "30 cases were randomly divided into A or B group (...)." Comment: There was insufficient information to assess this item as low or high.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to assess this item as low or high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported.
Selective reporting (reporting bias)	High risk	Important patient-reported outcomes, such as adverse events, were not reported.
Other bias	Low risk	No other biases were identified.

Zaher 2013

Methods	• Design: parallel, 3 arms • Country: Egypt • Method of randomisation: unclear • Blinding: not stated • Location: Cairo University Hospital and Abo El-Reesh Pediatric Hospital • Length of follow-up: 6 months
Participants	• Diagnosis: problematic infantile haemangiomas • Sex: male: 6; female: 39

Zaher 2013 *(Continued)*

	• Age: 1 to 18 months • Inclusion criteria: children with problematic IHs • Exclusion criteria: any child with a known contraindication for propranolol or with ultrasound-confirmed deeper components • Number of randomised children: 45
Interventions	• Intervention A (number of children: 15): oral propranolol was administered at dose of 2 mg/kg/day, divided into 2 daily doses. • Intervention B (number of children: 15): topical propranolol was administered at dose of 1% ointment in a hydrophilic base, applied twice daily. • Intervention C (number of children: 15): intralesional propranolol 1 mg in 1 mL of injection, administered on a weekly basis
Outcomes	• Outcome A: final response = excellent, good, fair, or poor • Outcome B: side effects, including cardiovascular follow-up • Outcome C: rebound growth
Notes	• Trial registration: not stated • Funder: no funder • Role of funder: no role • A priori sample size estimation: not stated • Conducted: not stated • Declared conflicts of interest: yes (page 651)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "(...) and those fit for inclusion were subsequently randomly divided into three groups as follows (...)." Page 647 Comment: There was insufficient information to assess this item as low or high.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to assess this item as low or high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were detected.

Zaher 2016

Methods	• Design: parallel, 2 arms • Country: Egypt • Method of randomisation: unclear • Blinding: assessors • Location: Cairo University Hospital • Length of follow-up: 4 months
Participants	• Diagnosis: problematic infantile haemangiomas • Sex: male: 12; female: 18 • Age: 1 to 14 months • Inclusion criteria: children with problematic IHs • Exclusion criteria: any child with a known contraindication for propranolol or with ultrasound-confirmed deeper components • Number of randomised children: 30
Interventions	• Intervention A (number of children: 15): oral propranolol was administered at dose of 2 mg/kg/day, divided into 2 daily doses. • Intervention B (number of children: 15): oral captopril was administered at dose of 0.5 to 1 mg/kg/day in a titrating dose.
Outcomes	• Outcome A: final response = excellent, good, fair, or poor • Outcome B: side effects, including cardiovascular follow-up
Notes	• Trial registration: not stated • Funder: no funder • Role of funder: no role • A priori sample size estimation: not stated • Conducted: not stated • Declared conflicts of interest: yes (page 499)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Only infants meeting the preset inclusion criteria were enrolled and randomly divided (using envelope concealment method) into (...)." Page 500 Comment: There was insufficient information to assess this item as low or high.
Allocation concealment (selection bias)	Low risk	Quote: "Only infants meeting the preset inclusion criteria were enrolled and randomly divided (using envelope concealment method) into (...)." Page 500 Comment: Authors reported information about adequate allocation concealment.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The final response to treatment was evaluated by 3 blinded investigators, by comparing (...)." Page 500

Zaher 2016 *(Continued)*

All outcomes		Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were detected.

Zhang 2013

Methods	• Design: parallel, 2 arms • Country: China • Method of randomisation: unclear • Blinding: not stated • Location: Ninth People's Hospital • Length of follow-up: unclear
Participants	• Diagnosis: infantile haemangiomas • Sex: male: 6; female: 6 • Age: 2 to 12 months • Inclusion criteria: written informed consent • Exclusion criteria: not stated • Number of randomised children: 12
Interventions	• Intervention A (number of children: 6): oral propranolol 1 mg/kg/day, full dose once a day • Intervention B (number of children: 6): oral propranolol 1 mg/kg/day, dose halved and given twice a day
Outcomes	Outcome A: plasma PRN concentrations at 2, 6, 10, and 24 hours
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: not stated • Declared conflicts of interest: yes (page 345)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "12 patients were randomly divided into 2 groups, qd (n=6) and bid (n=6)..." Page 343 Comment: There was insufficient information to assess this item as low or high.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.

Zhang 2013 *(Continued)*

Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to assess this item as low or high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	High risk	Patient-important outcomes were not addressed in this study.
Other bias	Low risk	No other biases were identified.

Zhong 2015

Methods	• Design: parallel, 3 arms • Country: China • Method of randomisation: random number chart • Blinding: only data analysts were blinded. • Location: Department of Dermatology, First Hospital, Jilin University, Changchun 130021, China • Length of follow-up: 6 months
Participants	• Diagnosis: infantile haemangiomas were diagnosed based on clinical history and physical examination with CT imaging. Only mixed or deep (> 8 mm on imaging) were included. • Sex: 71.7% (n = 43) were female and 28.3% (n = 17) were male. • Age: between 1 and 12 months • Inclusion criteria: those diagnosed as mixed, or deep (> 8 mm on imaging) based on clinical history and physical examination and CT imaging. No previous treatment, and no vascular malformations • Exclusion criteria: bronchitis, pneumonia, bronchial asthma, sinus bradycardia, atrioventricular block and acute heart failure, contraindications to propranolol • Number of randomised children: 60
Interventions	• YAG + propranolol (number of children: 20): YAG given once. Parameters adjusted according to lesion depth. Usual parameters are 5- to 7-millimetre laser size, at 80 to 140 J/cm^2, at 10- to 40-millisecond pulse width. Propranolol given beginning day 2 onwards, at 1.5 mg/kg/day over 3 doses for a total of 3 months. • Propranolol alone (number of children: 20): propranolol given at 1.5 mg/kg/day over 3 doses for a total of 6 months. Initiation was done while hospitalised for 1 week with daily fasting glucose measurements. Those able to tolerate it were allowed to receive the intervention on an outpatient basis under family supervision with daily pulse monitoring. • YAG laser alone (number of children: 20): similar to combined YAG + propranolol, except that given once every 2 months, for a total of 3 treatments over 6 months

Zhong 2015 *(Continued)*

Outcomes	• Primary outcome: response classified as excellent: >= 95% response; good: 60% to 94% response; fair: 30% to 59% response; poor: < 30% response, no response, or worsening. Response also categorised into: * total efficacy rate (excellent + good + dair)/(total n = 20)%; * cure rate (excellent/total n = 20)%; * efficacy rate (excellent + good/total n = 20)%. • Secondary outcomes: adverse effects, including: bradycardia, hypotension, breathing difficulties, asthma, insomnia, reduced appetite, cold skin, hypoglycaemia; skin pigmentation, thinning, peeling, or burn lesions. Adverse effects were also scored using the following points system: * 1 point = no adverse effects * 2 points = mild adverse effect, with small cosmetic impact * 3 points = moderate adverse effect, with moderate cosmetic impact * 4 points = severe adverse effect with severe cosmetic impact
Notes	• Trial registration: not stated • Funder: Science and Technology Department of Jilin Province Science and Technology Development Project funded projects (3D513U003428) • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: January 2013 to June 2014 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “60 participants were given group allocations according to a random number table.” Comment: Authors reported information about adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Two unrelated doctors not involved in the study were given the results for analysis, including all clinical, follow up, imaging and laboratory results. They were blinded to the group allocation for the participants.” Comment: Authors reported information about adequate blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were identified.

Zhu 2015

Methods	• Design: 2 arms • Country: China • Method of randomisation: the 72 infants were allocated at random into the observation or control group. • Blinding: double-blind • Location: Department of Nuclear Medicine, The First Affiliated Hospital of Nanchang University • Length of follow-up: 3 to 6 months
Participants	• Diagnosis: children with superficial haemangiomas • Sex: females: 44; males: 28 • Age: between 1 and 7 months • Inclusion criteria: a) initial manifestation between a few days and 1 month after birth, with red punctate or patchy areas visible to the naked eye and that exhibited varying degrees of growth; b) a subcutaneous haemangioma thickness of < 3 mm, with no obvious blood flow signal and no arteriovenous malformation on colour Doppler ultrasound; and c) exclusion of other skin diseases following dermatological examination • Exclusion criteria: children who exhibited serious heart, lung, liver, or kidney diseases or with other skin diseases • Number of randomised children: 72
Interventions	• Intervention A (number of children: 37): the observation group received 1 to 2 courses of ^{90}SR-^{90}Y contact therapy and local external application of 0.5% topical timolol maleate solution on the affected area for 3 to 6 months. • Intervention B (number of children: 35): the control group received an identical dosage and treatment course of ^{90}SR-^{90}Y contact therapy, combined with local topical application of normal saline for 3 to 6 months.
Outcomes	Primary: "Cure": the haemangioma subsided completely, and the skin returned to normal or exhibited barely visible decolouration.
Notes	• Trial registration: not stated • Funder: not stated • Role of funder: not stated • A priori sample size estimation: not stated • Conducted: September 2012 to December 2013 • Declared conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 72 infants were allocated at random into the observation or control group." Page 1014 Comment: There was insufficient information to assess this item as low or high.
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of participants (Performance bias)	Low risk	Quote: "Control group patients received an identical dosage and treatment course of ^{90}SR-^{90}Y contact therapy, combined with local topical application of normal saline (NS) for 3-6 months." Page 1014

Zhu 2015 *(Continued)*

		Comment: Authors reported information about adequate blinding of participants.
Blinding of personnel (performance bias)	Unclear risk	There was insufficient information to assess this item as low or high.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information to assess this item as low or high.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost at follow-up.
Selective reporting (reporting bias)	Low risk	Selective reporting bias was not detected.
Other bias	Low risk	No other biases were identified.

Abbreviations: AE: adverse events; AV block: atrioventricular block; bid: two times a day; CBC count: complete blood cell count; CIHs: complicated infantile haemangiomas; CT imaging: computed tomography imaging; HIFU: high-intensity focused ultrasound; IH: infantile haemangioma; Nd:YAG laser: neodymium-doped yttrium aluminium garnet laser; PDL: pulse dye laser; PHACE syndrome: posterior fossa malformations–haemangiomas–arterial anomalies–cardiac defects–eye abnormalities syndrome; plasma PRN concentrations: plasma propranolol concentrations; qd: one a day; rad: unit of absorbed radiation dose.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahn 2004	Study design not eligible (non-randomised trial).
Ambika 2013	Study design not eligible (case series).
Anonymous 2002	Study design not eligible (review).
Anonymous 2011	Study design not eligible (review).
Baselga 2014	Study design not eligible (review).
Bozena 2012	Comment about propranolol trials
Branco 2008	Study design not eligible (case series).
Chang 2008	Disease type not eligible (port-wine stain).
Chen 2013	Study design not eligible (case series).
Costinescu 1981	Report of clinical experience with cryotherapy
Dalby 2013	Study design not eligible (review).
Ferahbas 2008	Study design not eligible (non-randomised trial).
Frieden 2009	Study design not eligible (review).
Gajbhiye 2011	Study design not eligible (review).

Study	Reason for exclusion
Goelz 2014	Study design not eligible (non-randomised trial).
Incesoy 2011	Study design not eligible (case series).
Jalil 2006	Study design not eligible (allocated participants in sequence: every 1st to control, every 2nd to intervention 1, and every 3rd to intervention 2).
Jesitus 2011	Study design not eligible (review).
Jha 2012	Study design not eligible (case report).
Jiang 2011	Study design not eligible (self controlled trial).
Kunzi-Rapp 2012	Study design not eligible (non-randomised trial).
Liu 2009	Age of participants not eligible (aged 3 to 55 years (mean 17 years), thus likely to include adult-acquired haemangiomas).
McCuaig 2009	Study design not eligible (no comparison group, all received same treatment).
Menezes 2011	Study design not eligible (review).
Michel 1998	Study design not eligible (non-randomised trial).
Midena 2008	Disease type not eligible (internal haemangioma).
Miranda 2005	Study design not eligible (non-randomised study).
NCT01074437	Retrospective review of charts
Pancar 2011	Patient population not eligible.
Poetke 2000	Study design not eligible (non-randomised trial).
Pope 2013	Study design not eligible (non-randomised trial).
Rouvas 2009	Age of participants not eligible (aged 50+ years).
Sadan 1996	Study design not eligible (non-randomised study).
Schlosser 2009	Study design not eligible (review).
Smit 2005	Study design not eligible (review).
Song 2015	Study design not eligible (non-randomised study).
Thaivalappil 2013	Study design not eligible (non-randomised study).
Tierney 2009	Disease type not eligible (not haemangiomas).
Weienstein 2012	Study design not eligible (review).
Weissenstein 2015	Study design not eligible (case report).
Zhao 1997	Study design not eligible (non-randomised study).

Study	Reason for exclusion
Zhong 2014	Study design not eligible (non-randomised study).
Zhou 2000	Study design not eligible (non-randomised study).
Zhou 2002	Age of participants not eligible (3 months to 62 years, thus likely to include adult-acquired haemangioma).
Zhou 2015	Animal study (white rabbits)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kuang 2014

Methods	Randomised controlled trial
Participants	61 RIH patients Age: unclear Sex: unclear Country: China
Interventions	Children in Group A (sequential therapy, 30 cases) were treated with oral propranolol (1 to 2 mg/kg/d) until maximal reduction of tumour size was achieved, after which laser treatment was initiated. Children in Group B (concurrent therapy, 31 cases) were treated with oral propranolol (1 to 2 mg/kg/d) for 1 week before laser was applied concurrently.
Outcomes	Size and colour of tumours were observed and recorded to assess treatment efficacy.
Notes	Abstract

Maier 2012

Methods	Randomised trial
Participants	182 infants (55 males/127 females) with 1 (n = 124) or several (n = 58) superficial haemangiomas in the early progressive or the indifferent phase with a maximum diameter of 30 mm Age: unclear Sex: unclear Country: unclear
Interventions	Pulsed dye laser (n = 70), cryotherapy (n = 54), and observation (n = 58)
Outcomes	Authors defined the following evaluation criteria: complete remission, partial remission, stop of growth, progression; blistering, crust, scar, hypo- or hyperpigmentation. Furthermore, there was a grading of the cosmetic appearance of the vascular tumour by the children's parents: 1 (cosmetically acceptable) to 4 (cosmetically not acceptable).

Maier 2012 *(Continued)*

Notes	Abstract

NCT00004436

Methods	Parallel-group, phase III, RCT
Participants	1 month to 8 months of age, male and female. Presence of haemangioma meeting at least 1 of the following criteria: vision threatening, severe anatomic distortion, or other complications Age: 1 to 8 months Sex: all Country: USA
Interventions	All children received oral prednisone daily for 3 weeks. Children were then randomised to receive either placebo or leuprolide intramuscularly every 3 weeks, whilst continuing oral prednisone. If the tumour did not respond, the leuprolide was administered every 2 weeks.
Outcomes	Safety and efficacy: tumours were assessed at 1, 3, 6 weeks and 3 and 6 months
Notes	The study was declared completed in 2005; however, we were unable to locate a report of the findings.

NCT00555464

Methods	Cross-over design, phase II, RCT
Participants	Up to 6 months of age, male and female, infants with haemangiomas with complication that required systemic therapy to control their growth. Clinical diagnosis of infantile haemangioma confirmed by tissue biopsy positive for GLUT1. Size must be greater than or equal to 50 cm^2, adequate liver function. Age: 0.15 years (standard deviation = 0.06) Sex: 5 female, 3 male Country: USA
Interventions	Vincristine (0.05 mg/kg/dose) administered into a vein (PICC line) every week for 12 weeks, versus prednisone (3 mg/kg/day) administered by mouth for 12 weeks. If there is evidence of disease progression (larger haemangioma) at 6 weeks, then the child is switched to the other intervention.
Outcomes	*Primary outcome:* • Decrease in size of haemangioma by MRI and clinical exam (assessments at 6 and 12 weeks) *Secondary outcome:* • Toxicity to medications (assessments at 2, 4, 6, 10, and 12 weeks of therapy)
Notes	The limitations of this trial include early termination of enrolment resulting in small numbers of children analysed.

NCT00744185

Methods	Parallel-group, phase II and III, RCT
Participants	Up to 4 months of age, male and female, 1 or more haemangiomas sized more than 1 cm in diameter, social insurance, infant not threatened for vital or functional structure and for which no treatment would be proposed Age: up to 4 months Sex: all Country: France
Interventions	Propranolol (3 mg/kg for 15 days then 4 mg/kg for 15 days) versus placebo (for 30 days)
Outcomes	*Primary outcome:* • Proportion of haemangioma thickness variation, measured using ultrasonography from the basal state after 1 month *Secondary outcomes:* • Proportion of haemangioma size variation, measured clinically and with photography from the basal state after 1 month • Observance
Notes	This study has been terminated. (Study halted prematurely due to difficulties in recruitment of participants.)

NCT01072045

Methods	Parallel-group, phase II, RCT
Participants	Up to 2 years of age, male and female, absence of cardiopathy, clinically diagnosed haemangioma in proliferative or involutive phase with relative indication for clinical treatment, itemised as follows: • lesion causing alteration of regional anatomy with no systemic or functional damage and with a diameter greater than 1 cm; • lesion causing aesthetic deformity; • lesion causing local repetitive complications such as ulceration, bleeding, or local irritation; • lesion causing partial damage of orifices; • lesion causing psychological compromise. Age: up to 2 years Sex: all Country: Brazil
Interventions	Propranolol (2 mg/kg/day) given orally, divided into 2 doses for initial 60 days, versus prednisone (2 mg/kg/day) given orally, divided into 2 doses for initial 60 days
Outcomes	*Primary outcome:* • Reduction in tumour volume based on direct measurement and photographic analysis (weekly in first 2 months and twice a week in following months)

NCT01072045 *(Continued)*

	Secondary outcome: • Evidence of collateral effects (weekly in first 2 weeks and twice a week in the following months)
Notes	This study has been completed. Study completion date: December 2014

Pandey 2010

Methods	Parallel RCT
Participants	Fewer than 2 superficial haemangiomas less than 5 cm Age: unclear Sex: unclear Country: unclear
Interventions	Topical steroid (mometasone furoate) given twice daily versus intralesional steroid (triamcinolone acetonide), injected at monthly intervals using 24-gauge needle at doses of 1 to 2 mg/kg
Outcomes	*Primary outcome:* • Excellent response *Secondary outcome:* • Good response Complications (including irritation, hypopigmentation, pain, bleeding, infection, cutaneous atrophy, Cushingoid facies, and growth retardation)
Notes	

GLUT1: glucose transporter 1; MRI: magnetic resonance imaging; PHACE syndrome: posterior fossa malformations–haemangiomas–arterial anomalies–cardiac defects–eye abnormalities syndrome; PICC line: peripherally inserted central catheter; RCT: randomised controlled trial; RIH: refractory infantile haemangiomas.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01147601

Trial name or title	Topical timolol maleate 0.5% solution for proliferating infantile hemangiomas: a prospective double blinded placebo controlled study
Methods	Parallel randomised controlled trial
Participants	Boys and girls, aged 1 to 8 months with haemangiomas 3 cm or less on the scalp, trunk, or extremities Exclusion: facial, genital, hand, finger, feet, or toe haemangiomas; proven or suspected PHACE syndrome; ulcerated haemangiomas; hypersensitivity to beta blockers; history of asthma; known renal impairment; cardiac conditions that may predispose to heart block; hypoglycaemia; medication that could interact with beta blockers
Interventions	Topical 0.5% timolol maleate versus placebo, 2 to 3 drops to cover the haemangioma, twice daily
Outcomes	*Primary outcome:*

NCT01147601 *(Continued)*

	• Proportion of children with at least 75% improvement in the extent of the haemangioma as compared to baseline photos using a visual analogue scale *Secondary outcomes:* • Proportion of children with at least 50% improvement in the extent of the haemangioma as compared to baseline photos using a visual analogue scale • Difference between extent/size of haemangioma as an outcome measure versus colour changes • Frequency of adverse events (hypotension, behavioural changes, etc.) collected by investigators and reported by parents Assessments: 6 months
Starting date	March 2010
Contact information	Alfons L Krol (503-494-9993, krola@ohsu.edu) and Lindsay K Severson (503-494-6009, seversol@ohsu.edu)
Notes	The recruitment status of this study is unknown because the information has not been recently verified.

NCT02913612

Trial name or title	Efficacy, safety and pharmacokinetics of topical timolol in infants with infantile hemangioma (IH) (TIM01)
Methods	Multicentre, double-masked randomised, efficacy, safety, and pharmacokinetic study
Participants	110 children up to 60 days
Interventions	Drug: 0.25% timolol maleate gel forming solution Drug: 0.5% timolol maleate gel forming solution Wait-and-see
Outcomes	*Primary outcomes:* • Comparison of partial response of haemangioma colour within the treatment arm compared to the untreated controls • Partial response of haemangioma colour from baseline to 180 days within each treatment arm and compared with untreated controls
Starting date	12 August 2016
Contact information	Chiara Melloni, Principal Investigator, Duke University Medical Center
Notes	This study is not yet open for participant recruitment.

PHACE syndrome: posterior fossa malformations–haemangiomas–arterial anomalies–cardiac defects–eye abnormalities syndrome.

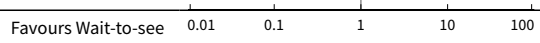
DATA AND ANALYSES

Comparison 1. Pulsed dye laser versus wait-and-see

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	121	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.62, 1.42]
2 Adverse events: skin atrophy	1	121	Risk Ratio (M-H, Random, 95% CI)	3.46 [1.36, 8.77]
3 Adverse events: skin hypopigmentation	1	121	Risk Ratio (M-H, Random, 95% CI)	3.05 [1.57, 5.93]
4 Adverse events: minimal crusting	1	22	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.27, 93.55]
5 Adverse events: pain	1	22	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.27, 93.55]
6 Other measures of resolution: no redness	1	121	Risk Ratio (M-H, Random, 95% CI)	4.83 [1.75, 13.36]
7 Parents who consider that their child still has a problem	1	121	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.56, 2.78]
8 Aesthetic appearance: better cosmetic outcome	1	22	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.71, 4.31]
9 Requirement for surgical correction	1	121	Risk Ratio (M-H, Random, 95% CI)	2.37 [0.64, 8.75]

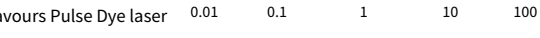
Analysis 1.1. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 1 Clearance.

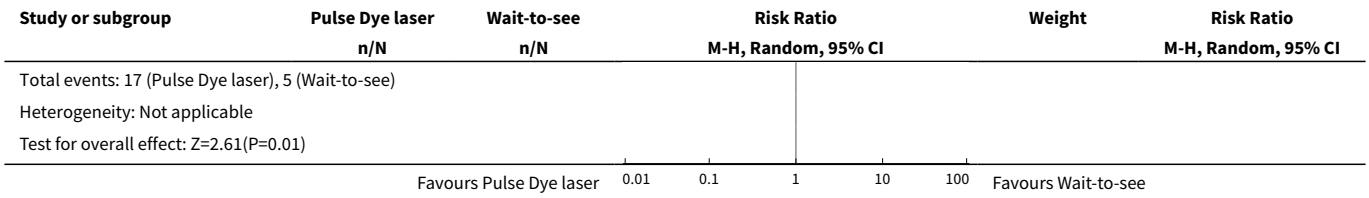
Study or subgroup	Pulse Dye laser n/N	Wait-to-see n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batta 2002	25/60	27/61		100%	0.94[0.62,1.42]
Total (95% CI)	**60**	**61**		**100%**	**0.94[0.62,1.42]**
Total events: 25 (Pulse Dye laser), 27 (Wait-to-see)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.29(P=0.77)					



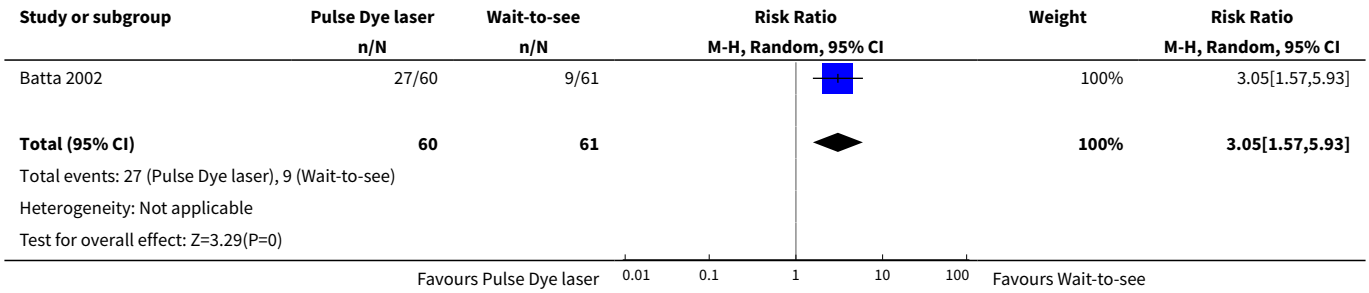
Analysis 1.2. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 2 Adverse events: skin atrophy.

Study or subgroup	Pulse Dye laser n/N	Wait-to-see n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batta 2002	17/60	5/61		100%	3.46[1.36,8.77]
Total (95% CI)	**60**	**61**		**100%**	**3.46[1.36,8.77]**

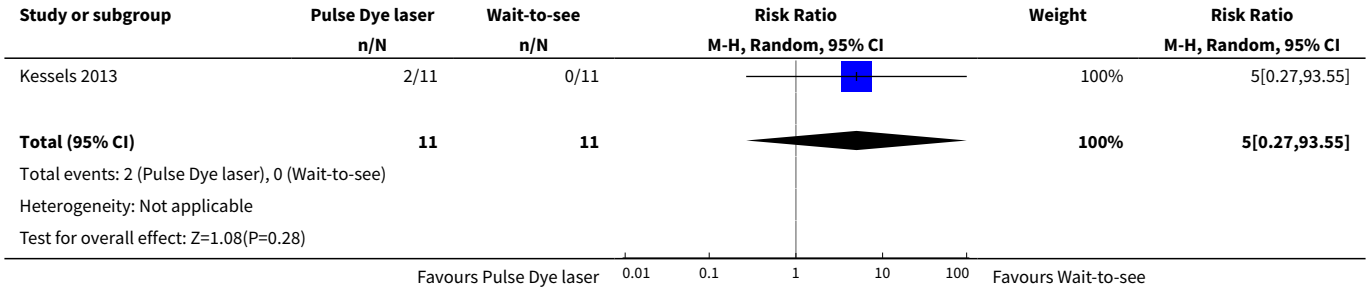




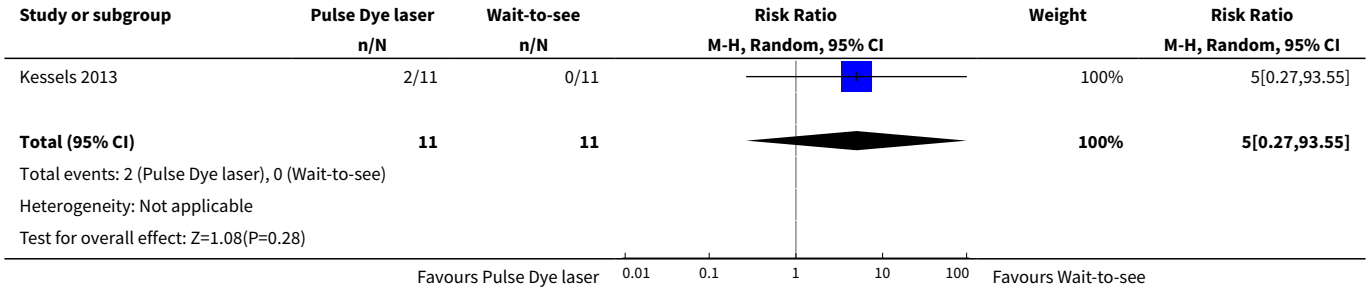
Analysis 1.3. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 3 Adverse events: skin hypopigmentation.



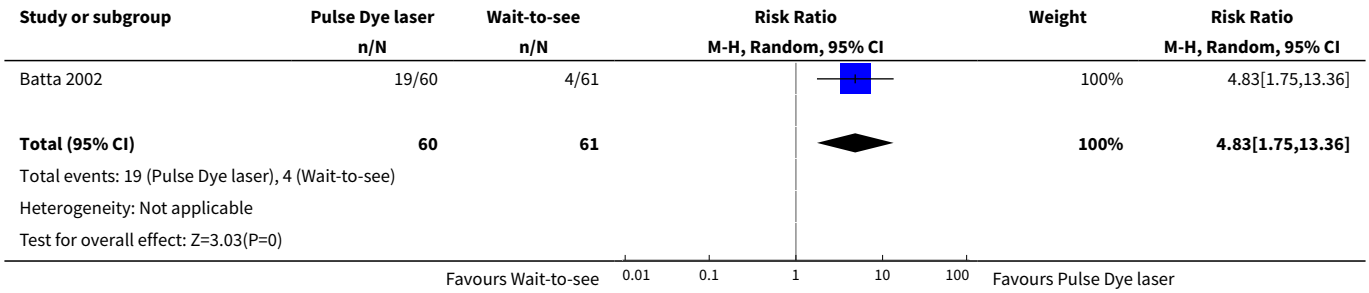
Analysis 1.4. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 4 Adverse events: minimal crusting.



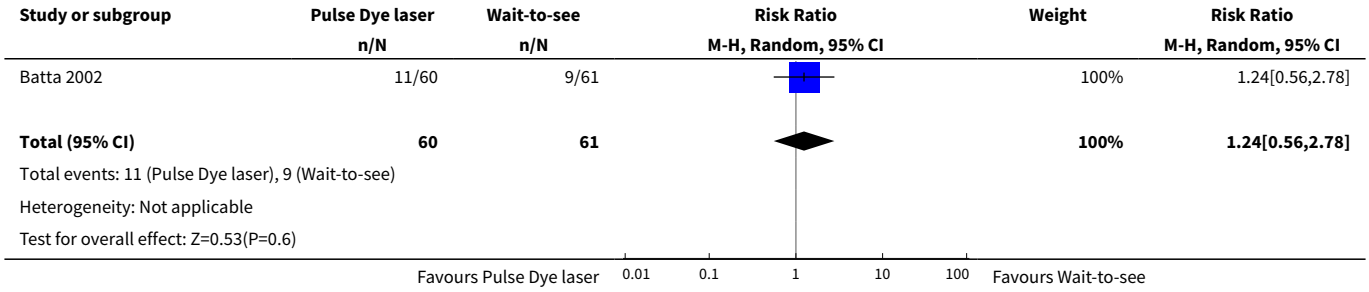
Analysis 1.5. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 5 Adverse events: pain.



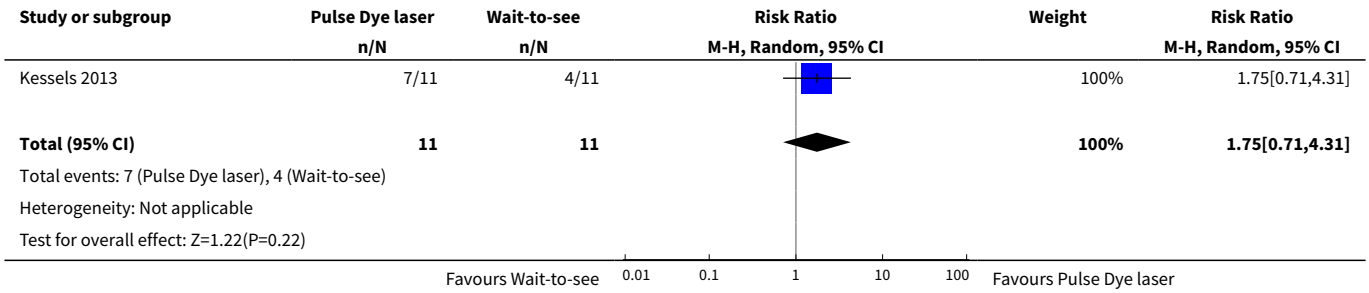
Analysis 1.6. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 6 Other measures of resolution: no redness.



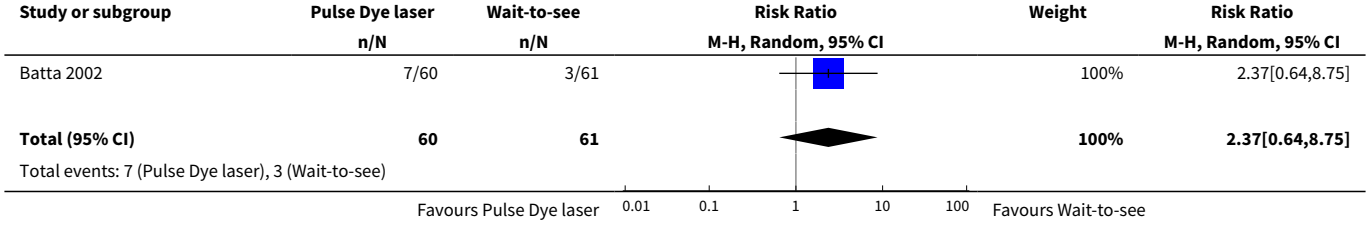
Analysis 1.7. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 7 Parents who consider that their child still has a problem.

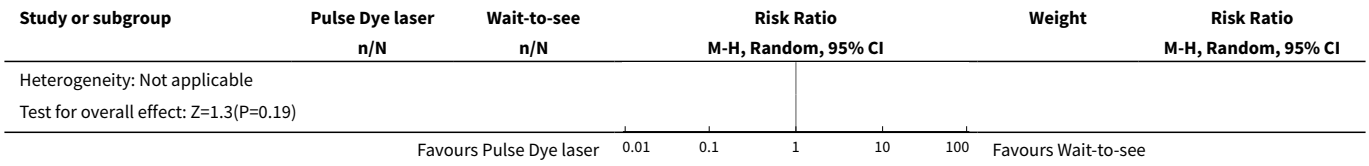


Analysis 1.8. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 8 Aesthetic appearance: better cosmetic outcome.



Analysis 1.9. Comparison 1 Pulsed dye laser versus wait-and-see, Outcome 9 Requirement for surgical correction.

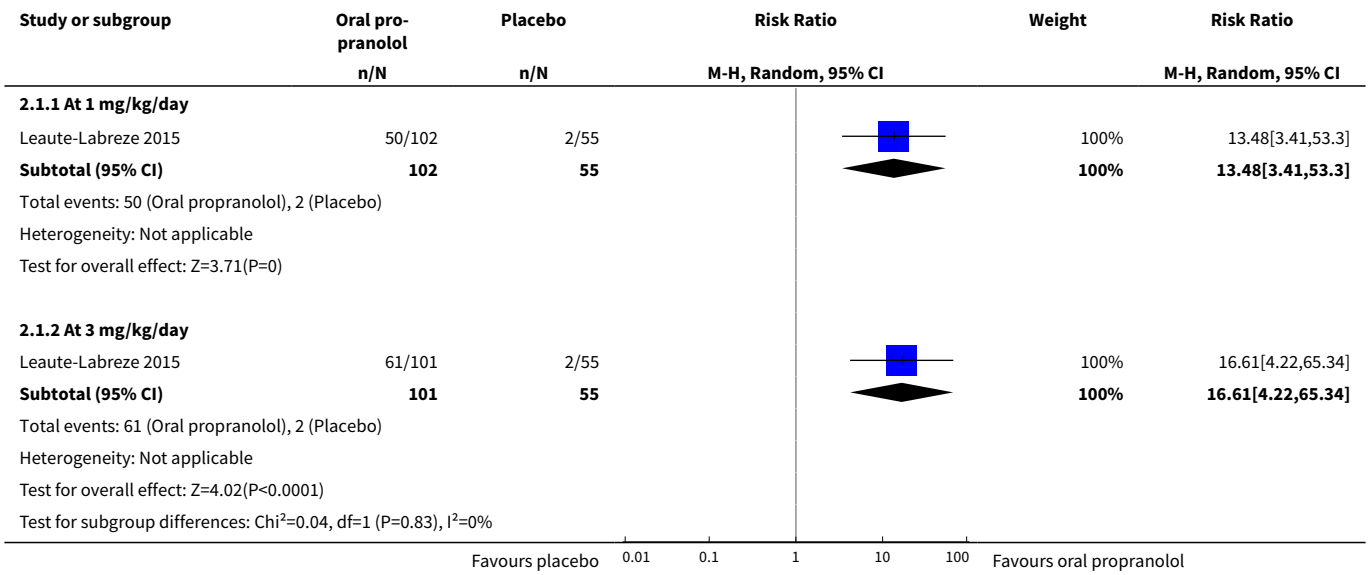




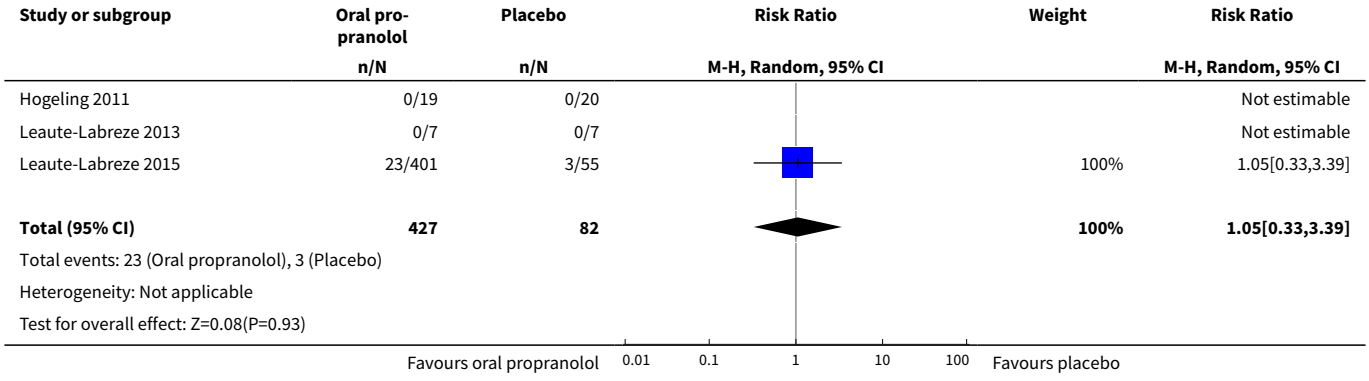
Comparison 2. Oral propranolol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance, as assessed by a clinician	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At 1 mg/kg/day	1	157	Risk Ratio (M-H, Random, 95% CI)	13.48 [3.41, 53.30]
1.2 At 3 mg/kg/day	1	156	Risk Ratio (M-H, Random, 95% CI)	16.61 [4.22, 65.34]
2 Serious adverse events	3	509	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.33, 3.39]
3 Serious cardiovascular adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Bradycardia	3	509	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.03, 14.32]
3.2 Hypotension	3	509	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.10, 6.71]
4 Other adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Bronchospasm	1	456	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.04, 3.89]
4.2 Bronchitis	1	456	Risk Ratio (M-H, Random, 95% CI)	5.62 [0.79, 40.07]
4.3 Bronchiolitis	1	456	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.42, 4.21]
4.4 Hypoglycaemia	1	456	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.03, 14.32]
4.5 Sleep disturbance	2	495	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.79, 3.00]
5 Other measures of resolution: change in volume	1		Mean Difference (Random, 95% CI)	-45.9 [-80.20, -11.60]
6 Other measures of resolution: no improvement in redness	1	40	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]

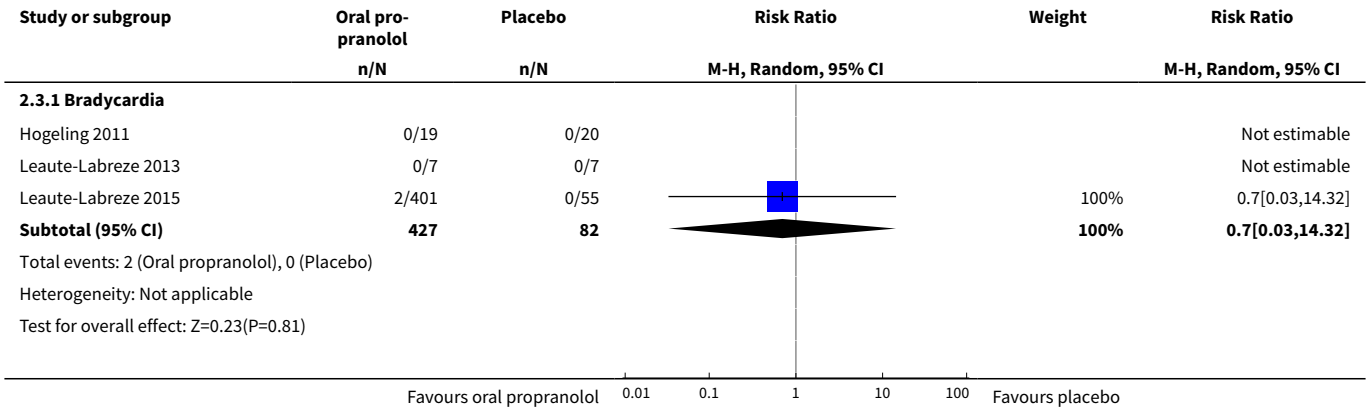
Analysis 2.1. Comparison 2 Oral propranolol versus placebo, Outcome 1 Clearance, as assessed by a clinician.

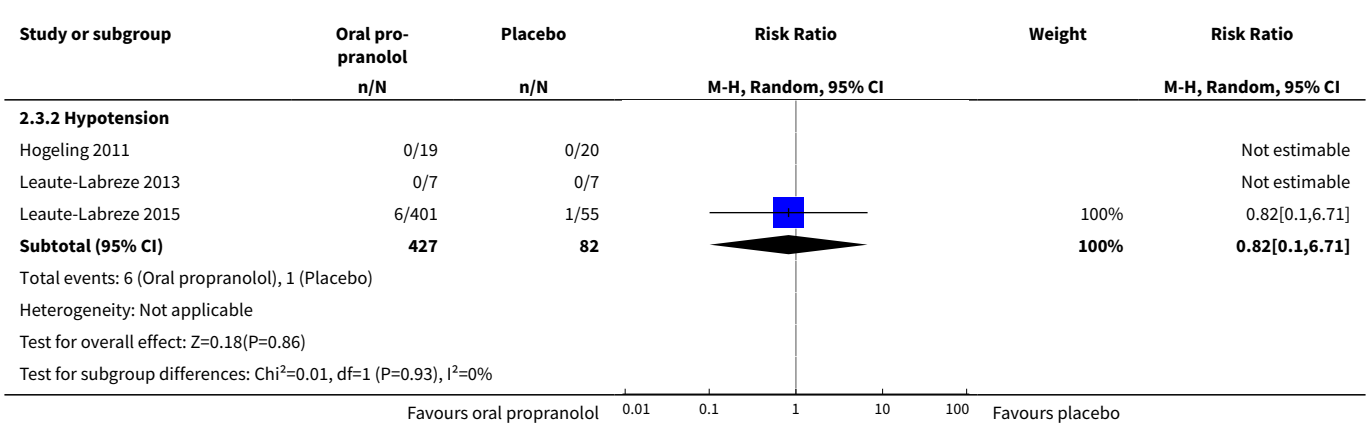


Analysis 2.2. Comparison 2 Oral propranolol versus placebo, Outcome 2 Serious adverse events.

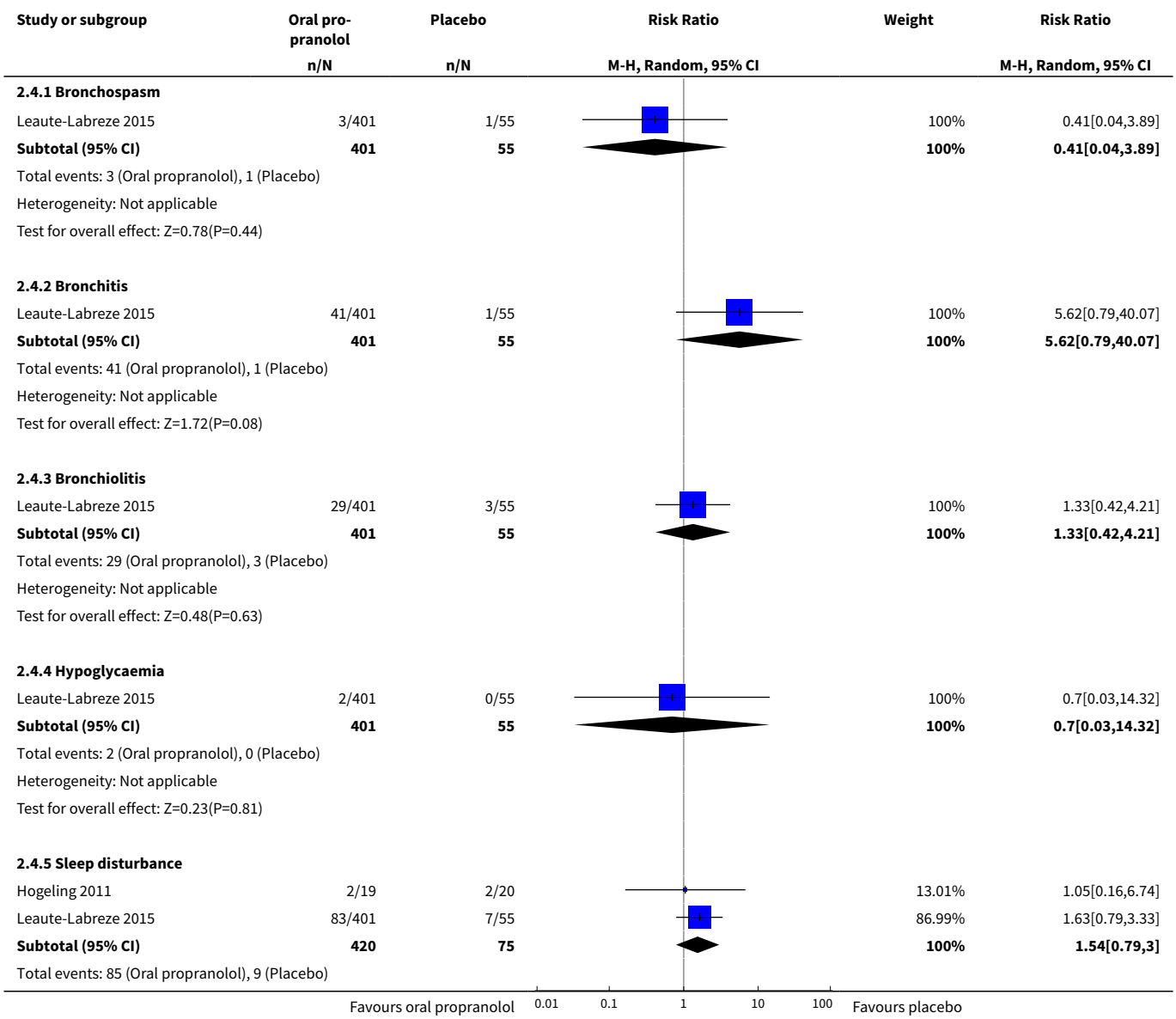


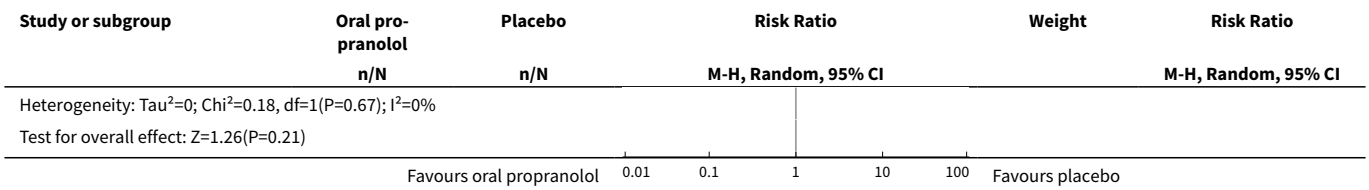
Analysis 2.3. Comparison 2 Oral propranolol versus placebo, Outcome 3 Serious cardiovascular adverse events.



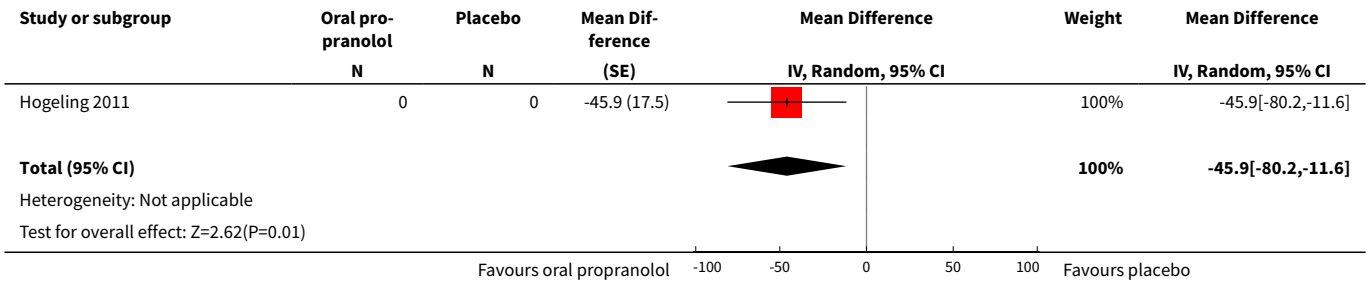


Analysis 2.4. Comparison 2 Oral propranolol versus placebo, Outcome 4 Other adverse events.

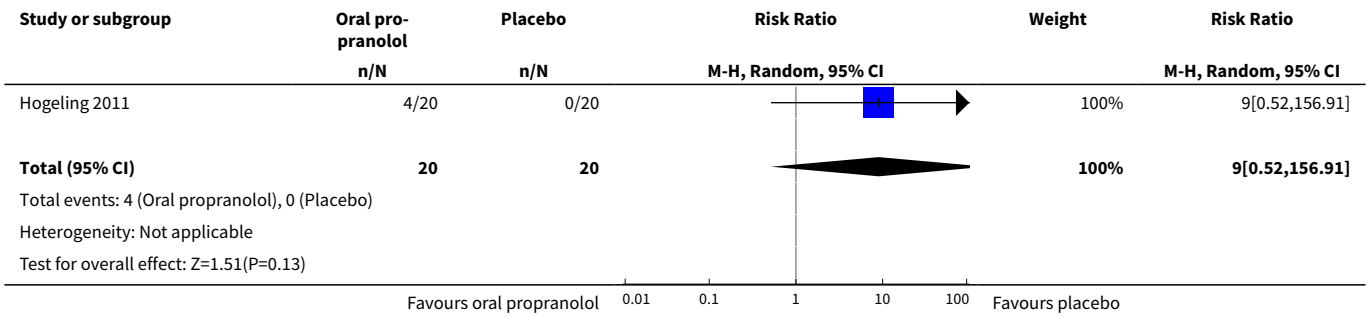




Analysis 2.5. Comparison 2 Oral propranolol versus placebo, Outcome 5 Other measures of resolution: change in volume.



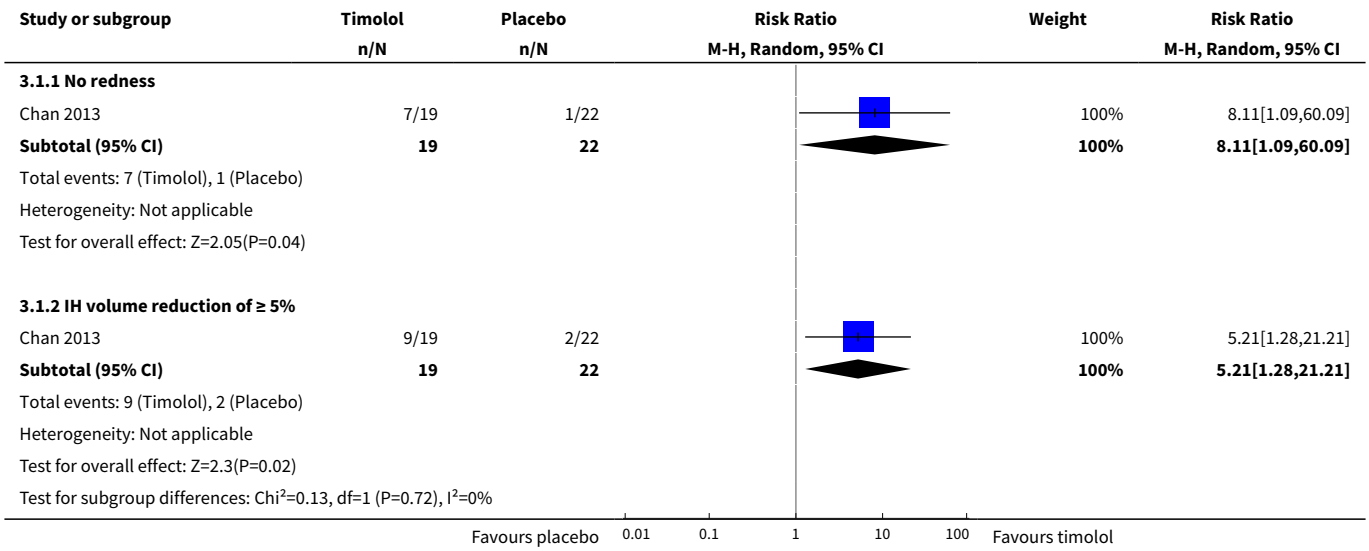
Analysis 2.6. Comparison 2 Oral propranolol versus placebo, Outcome 6 Other measures of resolution: no improvement in redness.



Comparison 3. Topical timolol maleate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other measures of resolution (6 months)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 No redness	1	41	Risk Ratio (M-H, Random, 95% CI)	8.11 [1.09, 60.09]
1.2 IH volume reduction of ≥ 5%	1	41	Risk Ratio (M-H, Random, 95% CI)	5.21 [1.28, 21.21]

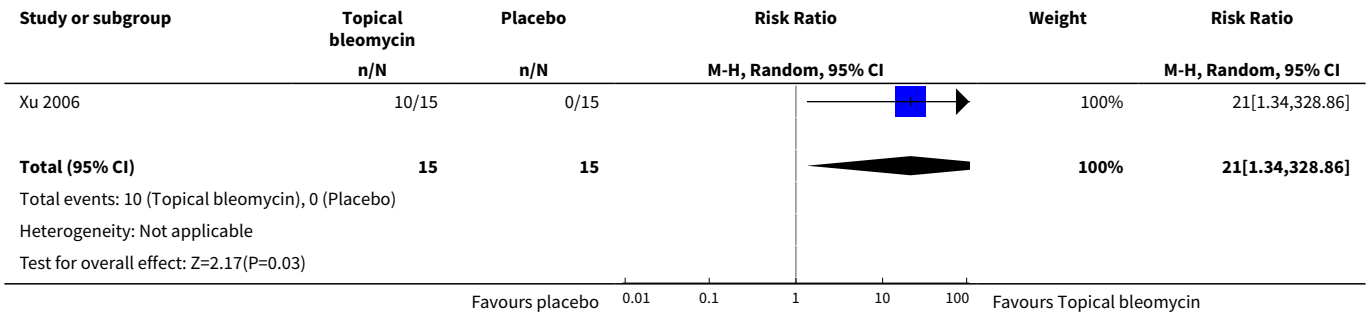
Analysis 3.1. Comparison 3 Topical timolol maleate versus placebo, Outcome 1 Other measures of resolution (6 months).



Comparison 4. Topical bleomycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other measures of resolution: reduction in size at day 7	1	30	Risk Ratio (M-H, Random, 95% CI)	21.0 [1.34, 328.86]

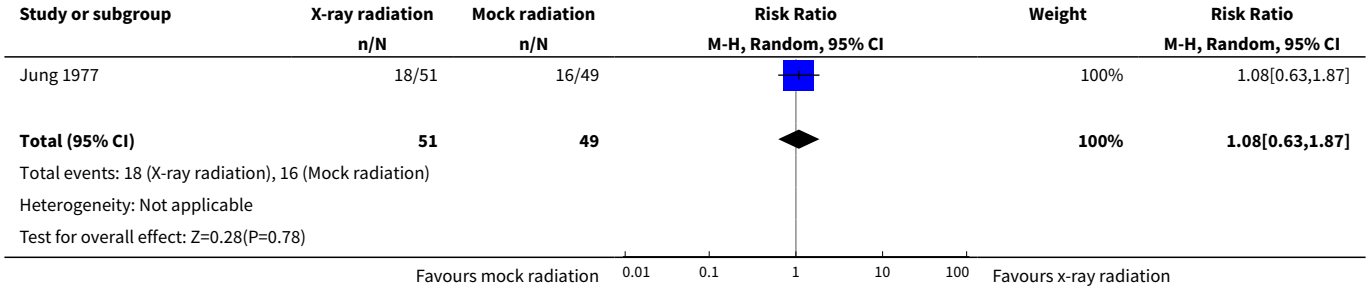
Analysis 4.1. Comparison 4 Topical bleomycin versus placebo, Outcome 1 Other measures of resolution: reduction in size at day 7.



Comparison 5. X-ray radiation versus sham radiation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	100	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.63, 1.87]

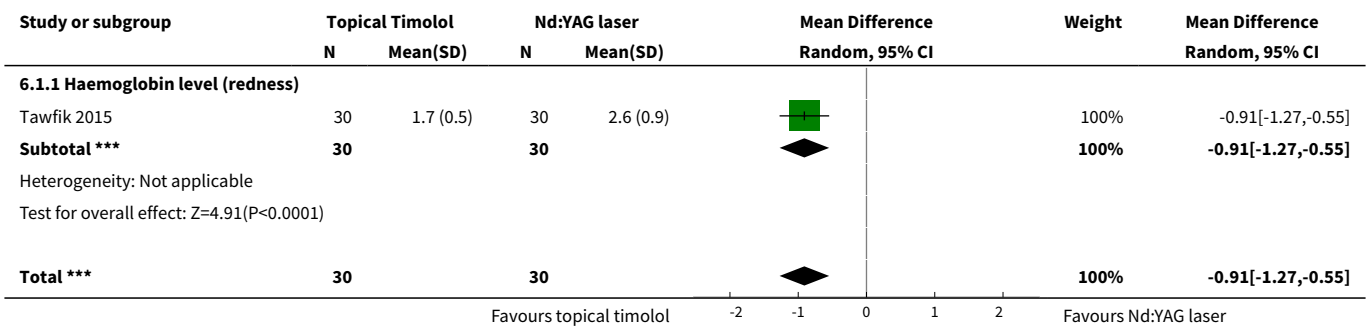
Analysis 5.1. Comparison 5 X-ray radiation versus sham radiation, Outcome 1 Clearance.

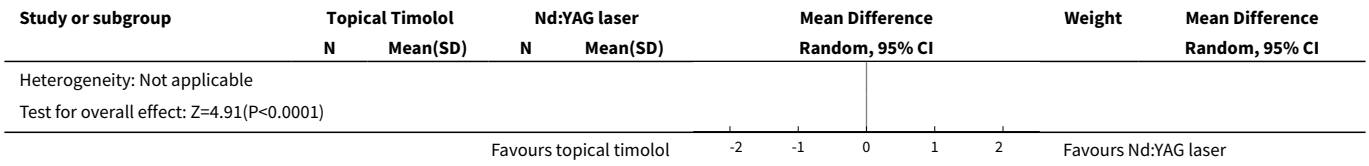


Comparison 6. Topical timolol maleate versus Nd:YAG laser

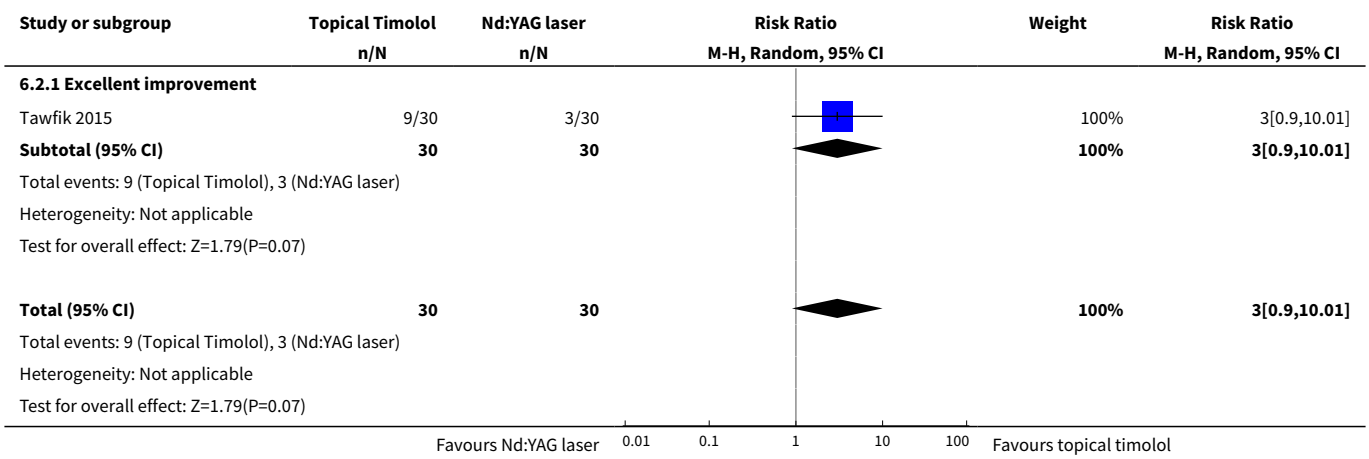
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other measures of resolution (continuous)	1	60	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.27, -0.55]
1.1 Haemoglobin level (redness)	1	60	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.27, -0.55]
2 Other measures of resolution (dichotomous)	1	60	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.90, 10.01]
2.1 Excellent improvement	1	60	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.90, 10.01]

Analysis 6.1. Comparison 6 Topical timolol maleate versus Nd:YAG laser, Outcome 1 Other measures of resolution (continuous).





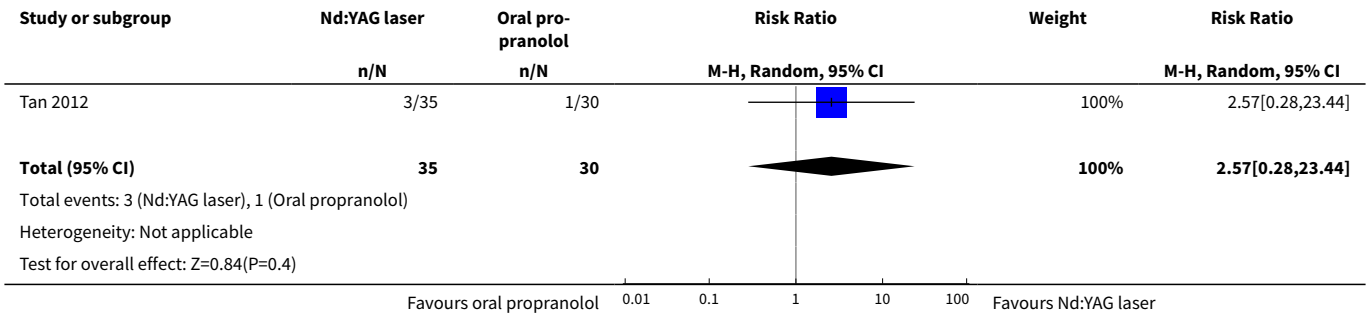
Analysis 6.2. Comparison 6 Topical timolol maleate versus Nd:YAG laser, Outcome 2 Other measures of resolution (dichotomous).



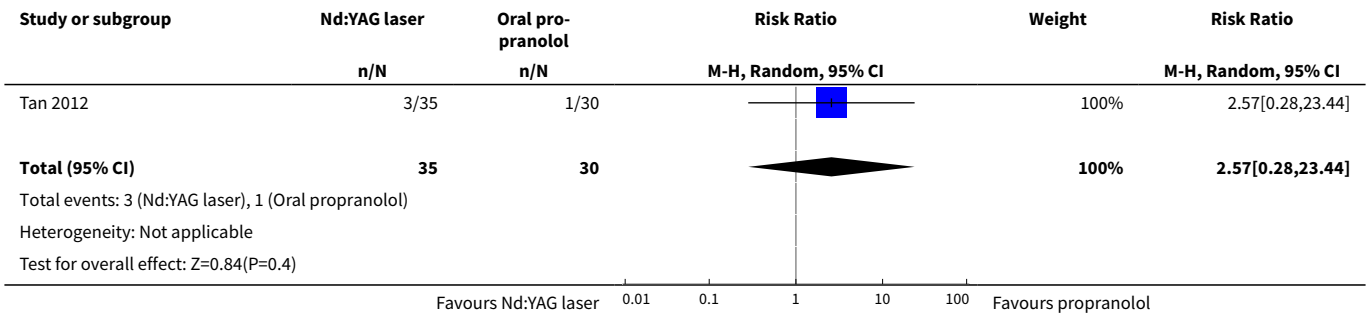
Comparison 7. Nd:YAG laser versus oral propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	65	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.28, 23.44]
2 Adverse events: hyperpigmentation	1	65	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.28, 23.44]
3 Adverse event: pigmentation and thinning	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 1.05]
4 Adverse events: superficial scar	2	105	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.24, 9.58]
5 Other measures of resolution: excellent response	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.46]

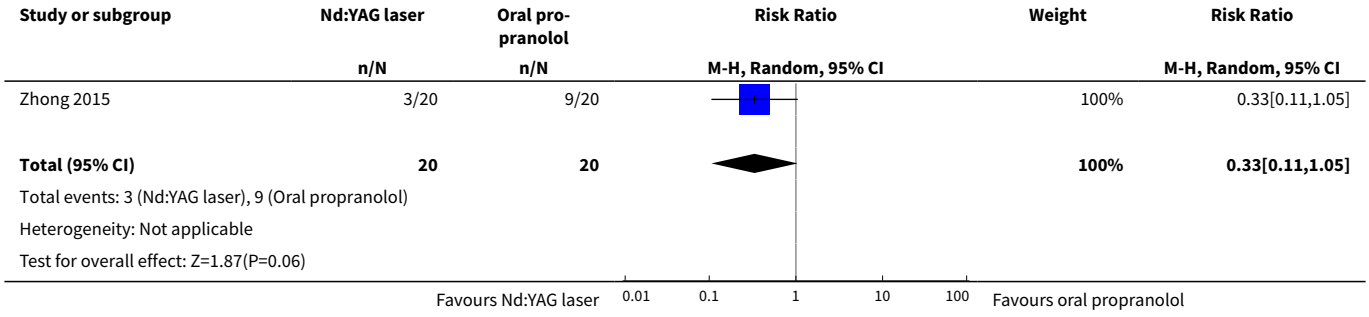
Analysis 7.1. Comparison 7 Nd:YAG laser versus oral propranolol, Outcome 1 Clearance.



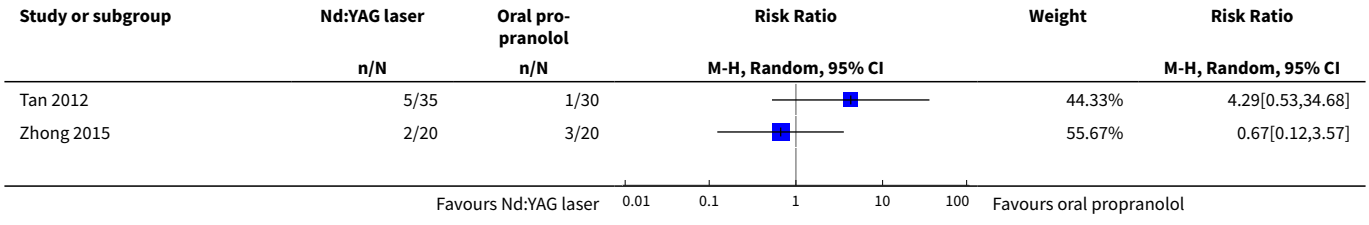
Analysis 7.2. Comparison 7 Nd:YAG laser versus oral propranolol, Outcome 2 Adverse events: hyperpigmentation.

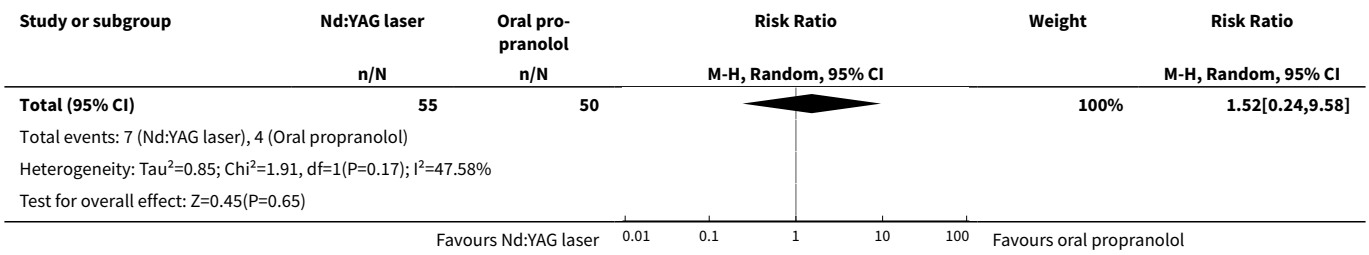


Analysis 7.3. Comparison 7 Nd:YAG laser versus oral propranolol, Outcome 3 Adverse event: pigmentation and thinning.

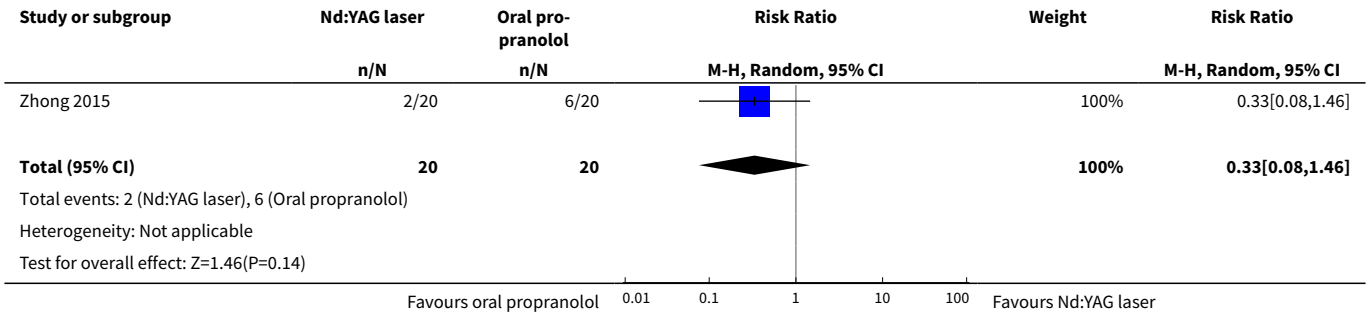


Analysis 7.4. Comparison 7 Nd:YAG laser versus oral propranolol, Outcome 4 Adverse events: superficial scar.





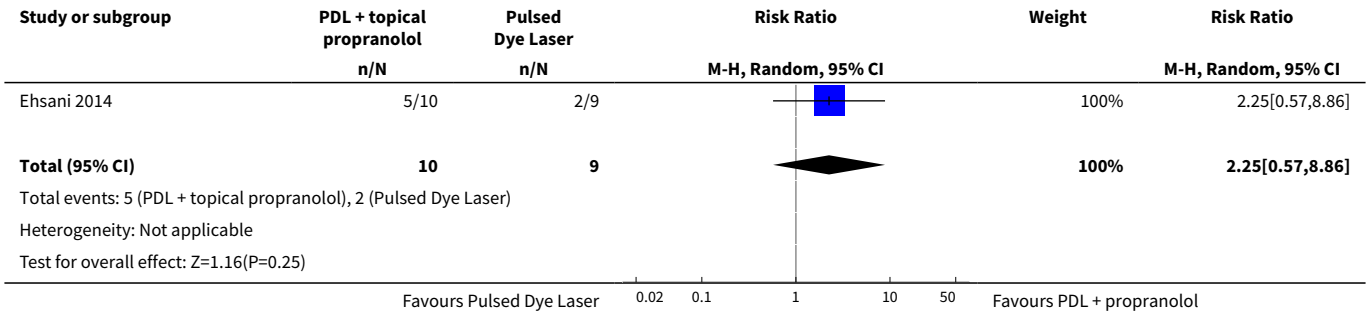
Analysis 7.5. Comparison 7 Nd:YAG laser versus oral propranolol, Outcome 5 Other measures of resolution: excellent response.



Comparison 8. Pulsed dye laser + topical propranolol versus pulsed dye laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance, as assessed by a clinician	1	19	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.57, 8.86]

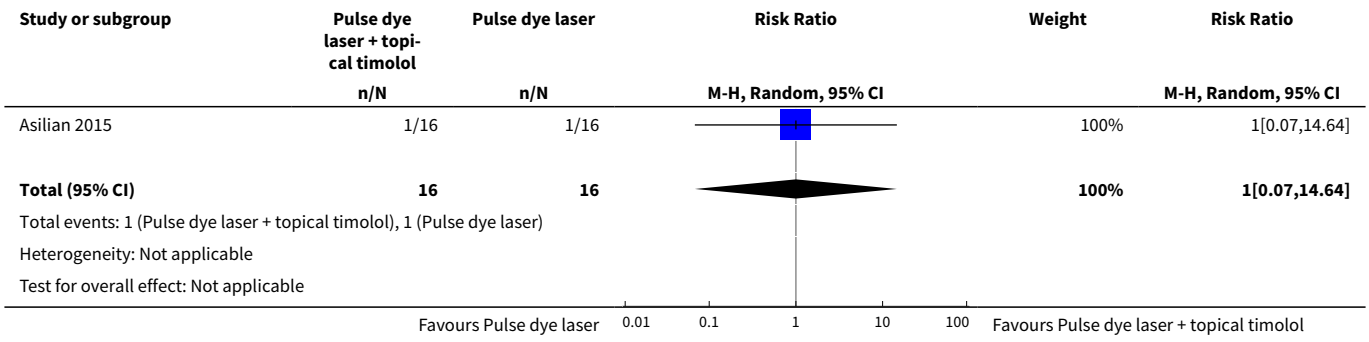
Analysis 8.1. Comparison 8 Pulsed dye laser + topical propranolol versus pulsed dye laser, Outcome 1 Clearance, as assessed by a clinician.



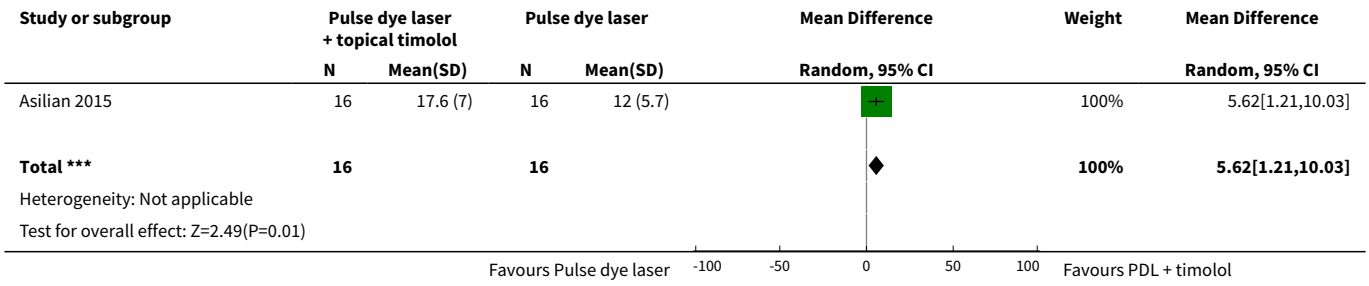
Comparison 9. Pulsed dye laser + topical timolol maleate versus pulsed dye laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	32	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.64]
2 Other measures of resolution: mean size reduction	1	32	Mean Difference (IV, Random, 95% CI)	5.62 [1.21, 10.03]

Analysis 9.1. Comparison 9 Pulsed dye laser + topical timolol maleate versus pulsed dye laser, Outcome 1 Clearance.



Analysis 9.2. Comparison 9 Pulsed dye laser + topical timolol maleate versus pulsed dye laser, Outcome 2 Other measures of resolution: mean size reduction.

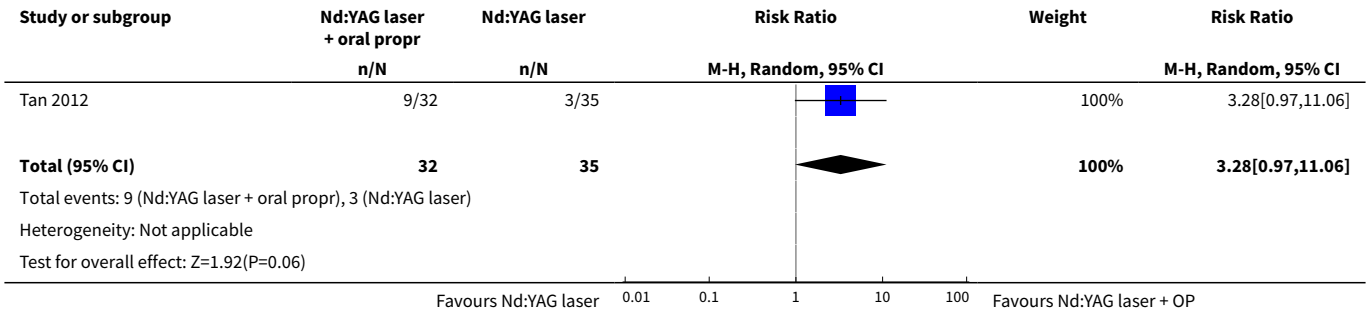


Comparison 10. Nd:YAG laser + oral propranolol versus Nd:YAG laser

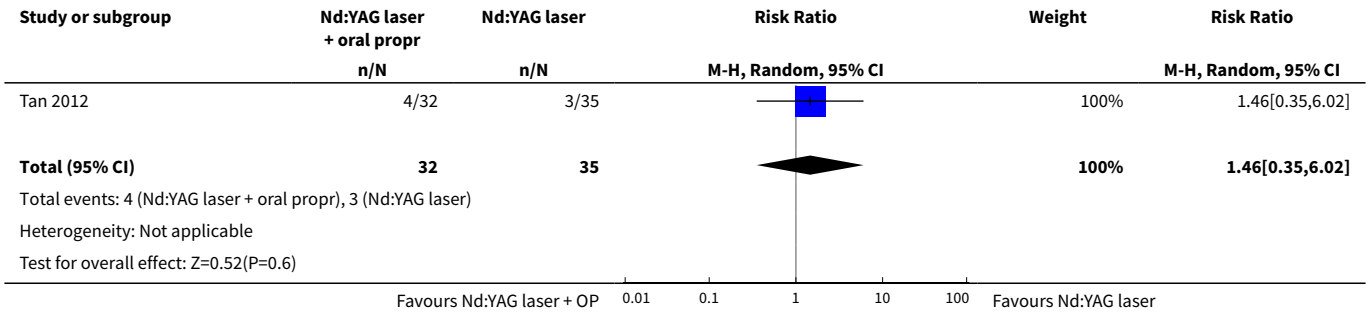
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	67	Risk Ratio (M-H, Random, 95% CI)	3.28 [0.97, 11.06]
2 Adverse events: hyperpigmentation	1	67	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.35, 6.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse events: pigmentation and thinning	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.57]
4 Adverse events: superficial scar	2	107	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.09, 1.48]
5 Other measures of resolution: excellent response	1	40	Risk Ratio (M-H, Random, 95% CI)	8.5 [2.25, 32.06]

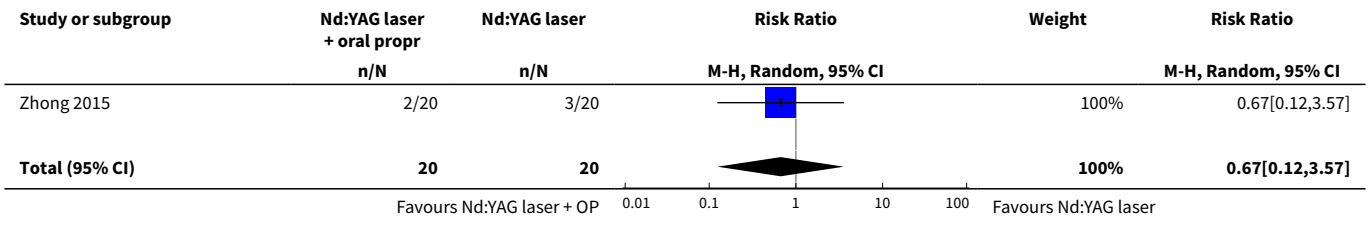
Analysis 10.1. Comparison 10 Nd:YAG laser + oral propranolol versus Nd:YAG laser, Outcome 1 Clearance.

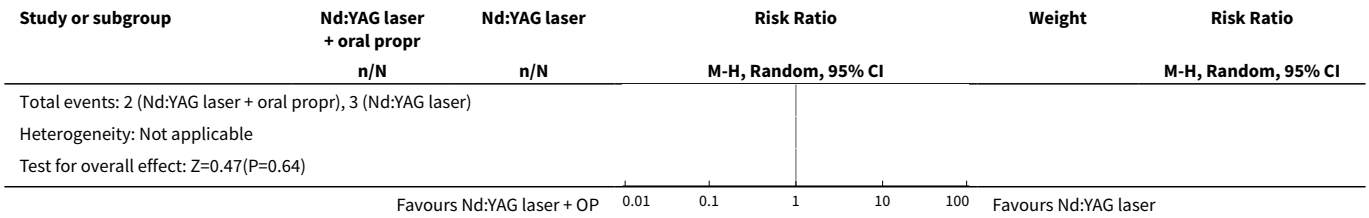


Analysis 10.2. Comparison 10 Nd:YAG laser + oral propranolol versus Nd:YAG laser, Outcome 2 Adverse events: hyperpigmentation.

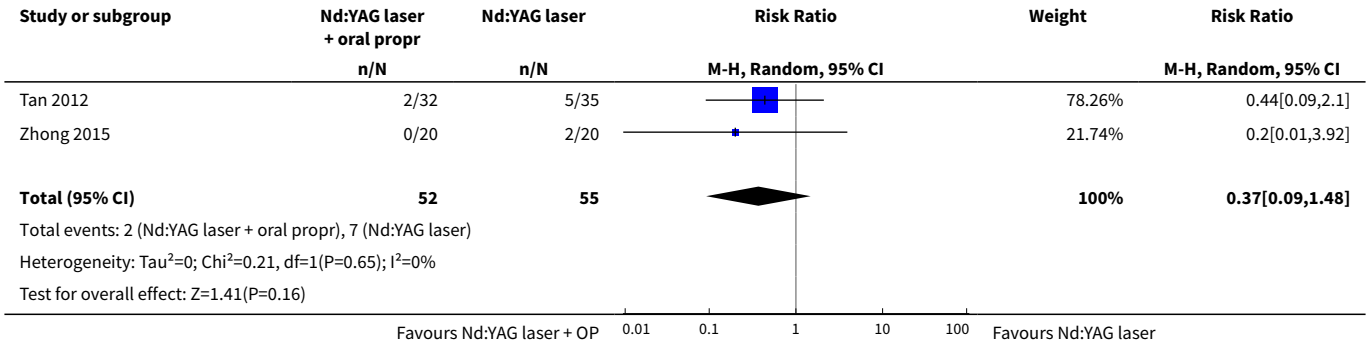


Analysis 10.3. Comparison 10 Nd:YAG laser + oral propranolol versus Nd:YAG laser, Outcome 3 Adverse events: pigmentation and thinning.

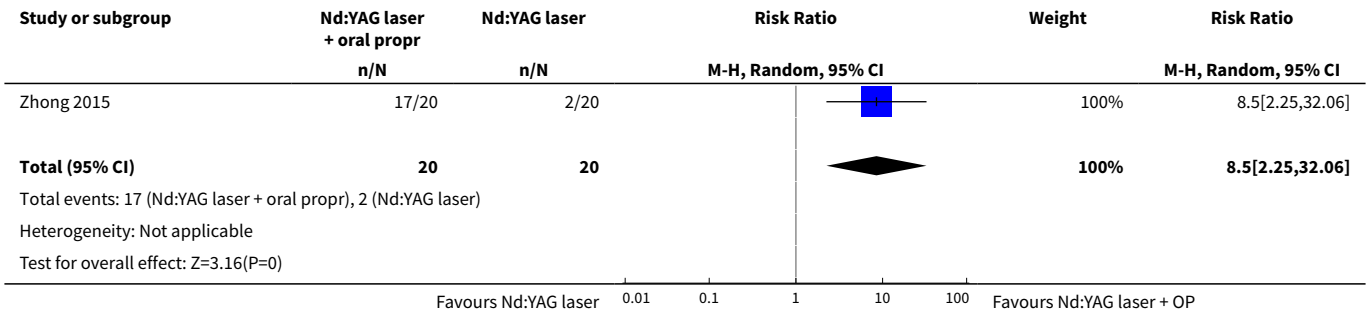




Analysis 10.4. Comparison 10 Nd:YAG laser + oral propranolol versus Nd:YAG laser, Outcome 4 Adverse events: superficial scar.



Analysis 10.5. Comparison 10 Nd:YAG laser + oral propranolol versus Nd:YAG laser, Outcome 5 Other measures of resolution: excellent response.

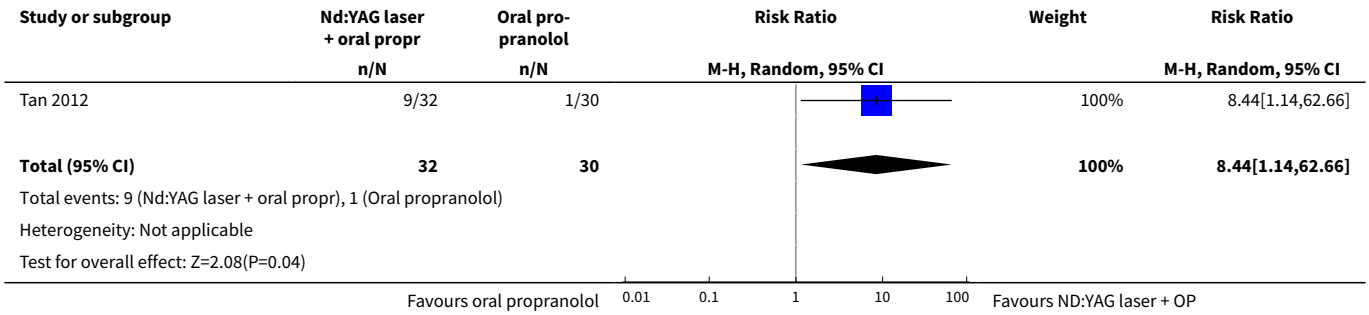


Comparison 11. Nd:YAG laser + oral propranolol versus oral propranolol

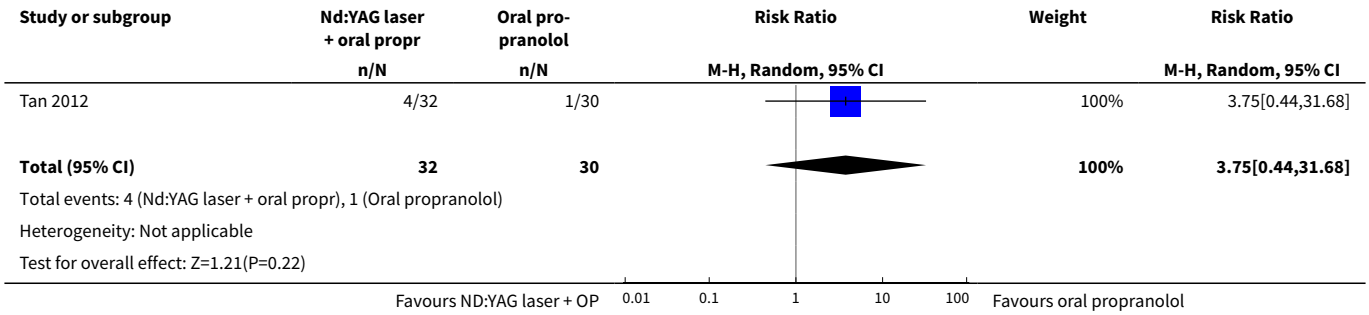
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	62	Risk Ratio (M-H, Random, 95% CI)	8.44 [1.14, 62.66]
2 Adverse events: hyperpigmentation	1	62	Risk Ratio (M-H, Random, 95% CI)	3.75 [0.44, 31.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse events: pigmentation and thinning	1	40	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.90]
4 Adverse events: superficial scar	2	102	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.05, 7.63]
5 Other measures of resolution: excellent response	1	40	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.42, 5.67]

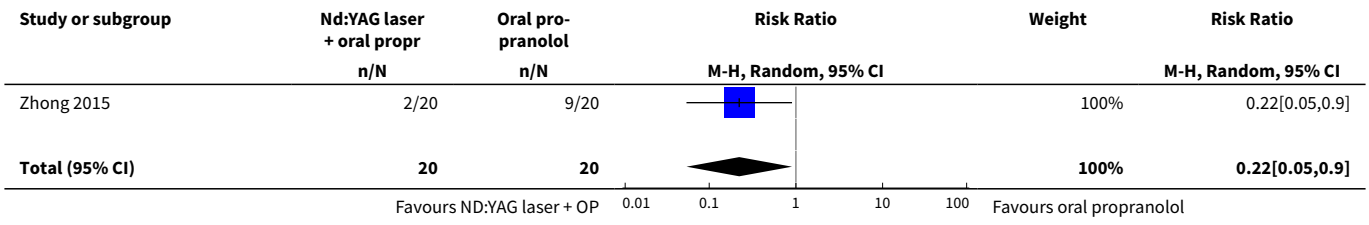
Analysis 11.1. Comparison 11 Nd:YAG laser + oral propranolol versus oral propranolol, Outcome 1 Clearance.

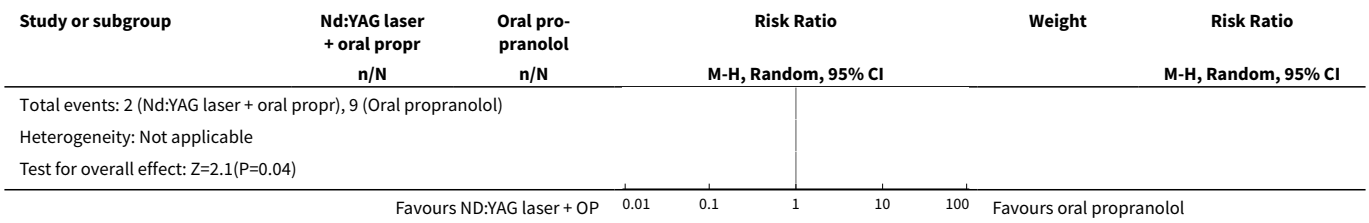


Analysis 11.2. Comparison 11 Nd:YAG laser + oral propranolol versus oral propranolol, Outcome 2 Adverse events: hyperpigmentation.

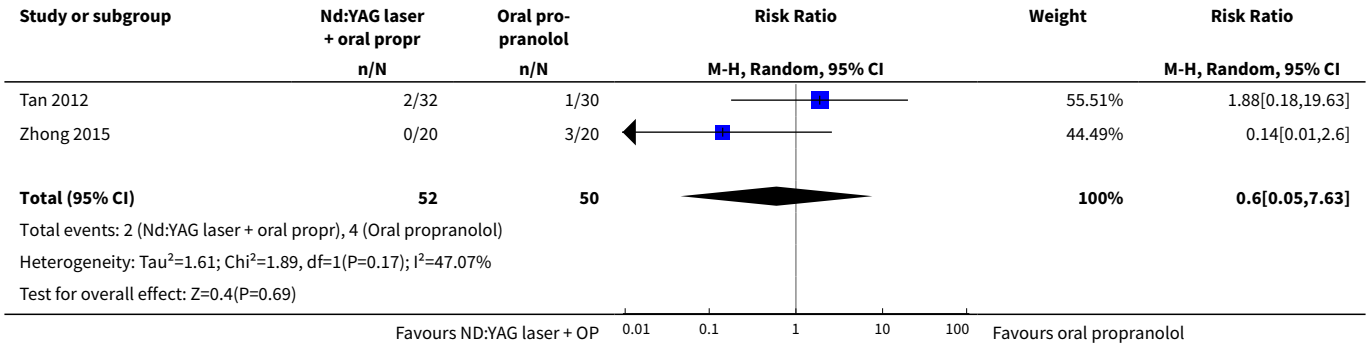


Analysis 11.3. Comparison 11 Nd:YAG laser + oral propranolol versus oral propranolol, Outcome 3 Adverse events: pigmentation and thinning.

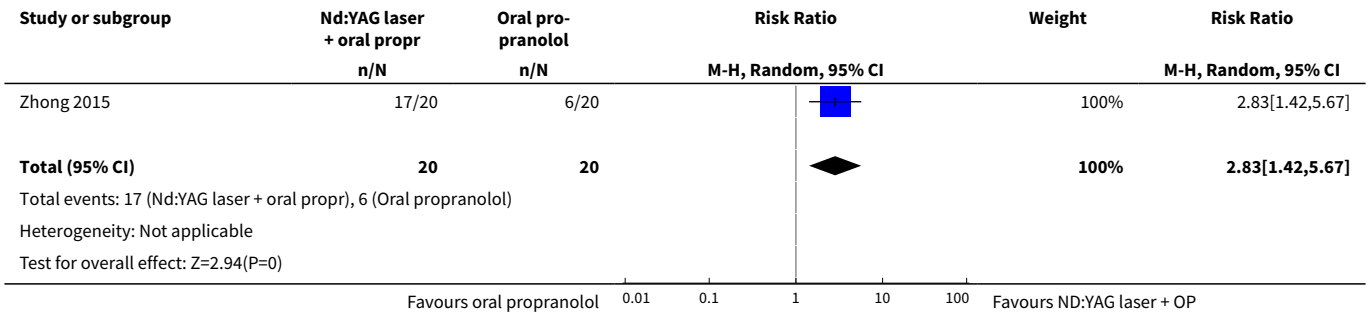




Analysis 11.4. Comparison 11 Nd:YAG laser + oral propranolol versus oral propranolol, Outcome 4 Adverse events: superficial scar.



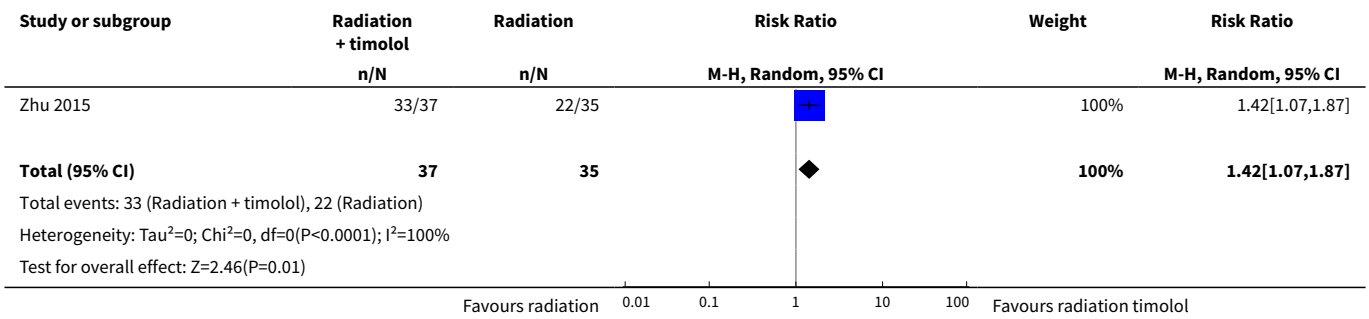
Analysis 11.5. Comparison 11 Nd:YAG laser + oral propranolol versus oral propranolol, Outcome 5 Other measures of resolution: excellent response.



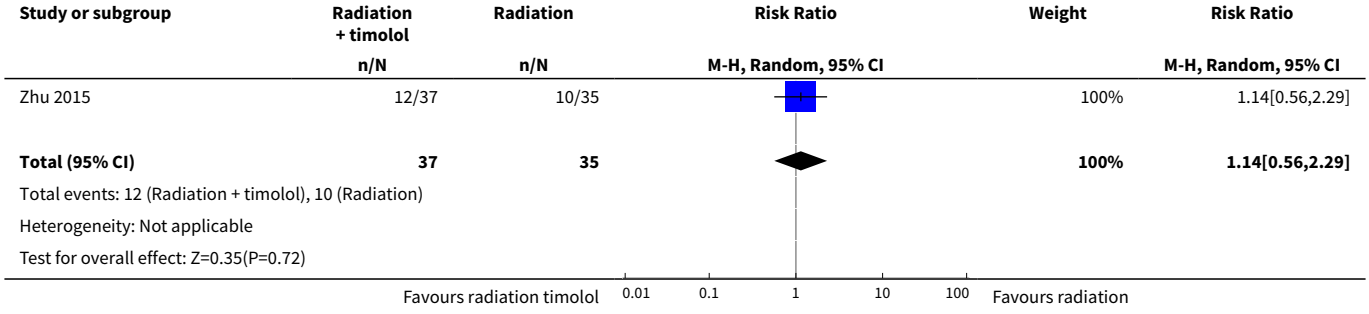
Comparison 12. ^{90}SR-^{90}Y radiation + topical timolol maleate versus ^{90}SR-^{90}Y radiation

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clearance	1	72	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.07, 1.87]
2 Adverse events	1	72	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.56, 2.29]

Analysis 12.1. Comparison 12 ^{90}SR-^{90}Y radiation + topical timolol maleate versus ^{90}SR-^{90}Y radiation, Outcome 1 Clearance.



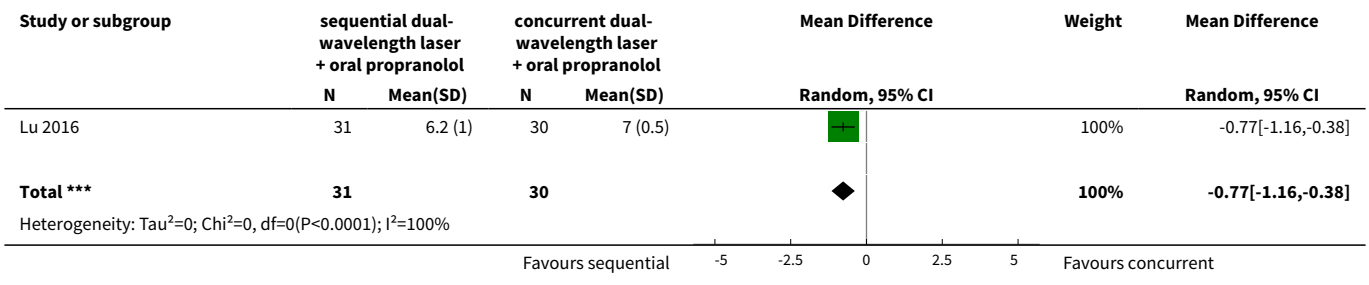
Analysis 12.2. Comparison 12 ^{90}SR-^{90}Y radiation + topical timolol maleate versus ^{90}SR-^{90}Y radiation, Outcome 2 Adverse events.



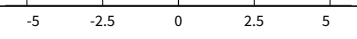
Comparison 13. Sequential dual-wavelength laser + oral propranolol versus concurrent dual-wavelength laser + oral propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other outcomes of resolution: mean efficacy rating	1	61	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.16, -0.38]

Analysis 13.1. Comparison 13 Sequential dual-wavelength laser + oral propranolol versus concurrent dual-wavelength laser + oral propranolol, Outcome 1 Other outcomes of resolution: mean efficacy rating.



Study or subgroup	sequential dual-wavelength laser + oral propranolol N	Mean(SD)	concurrent dual-wavelength laser + oral propranolol N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=3.92(P<0.0001)							



Favours sequential

Favours concurrent

Comparison 14. Oral propranolol versus topical propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	30	Risk Ratio (M-H, Random, 95% CI)	3.0 [1.01, 8.95]
2 Adverse events: syncopal attack	1	30	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.39, 124.83]

Analysis 14.1. Comparison 14 Oral propranolol versus topical propranolol, Outcome 1 Clearance.

Study or subgroup	Oral propranolol n/N	Topical propranolol n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zaher 2013	9/15	3/15		100%	3[1.01,8.95]
Total (95% CI)	**15**	**15**		**100%**	**3[1.01,8.95]**
Total events: 9 (Oral propranolol), 3 (Topical propranolol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.97(P=0.05)					

Favours topical propranolol

Favours oral propranolol

Analysis 14.2. Comparison 14 Oral propranolol versus topical propranolol, Outcome 2 Adverse events: syncopal attack.

Study or subgroup	Oral propranolol n/N	Topical propranolol n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zaher 2013	3/15	0/15		100%	7[0.39,124.83]
Total (95% CI)	**15**	**15**		**100%**	**7[0.39,124.83]**
Total events: 3 (Oral propranolol), 0 (Topical propranolol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.32(P=0.19)					

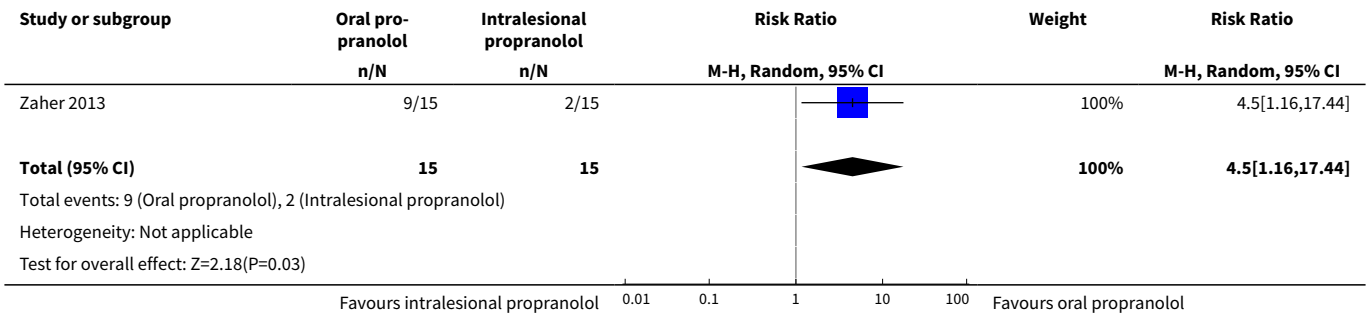
Favours oral

Favours topical

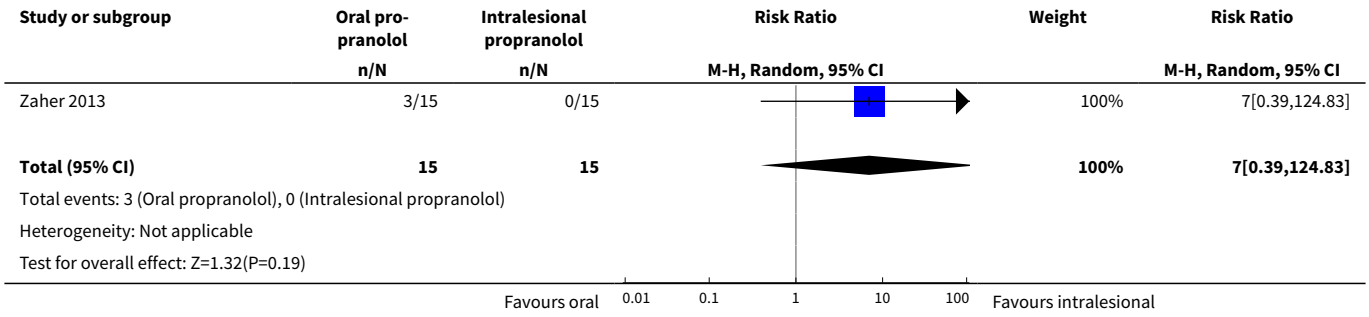
Comparison 15. Oral propranolol versus intralesional propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	30	Risk Ratio (M-H, Random, 95% CI)	4.5 [1.16, 17.44]
2 Adverse events: syncopal attack	1	30	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.39, 124.83]

Analysis 15.1. Comparison 15 Oral propranolol versus intralesional propranolol, Outcome 1 Clearance.



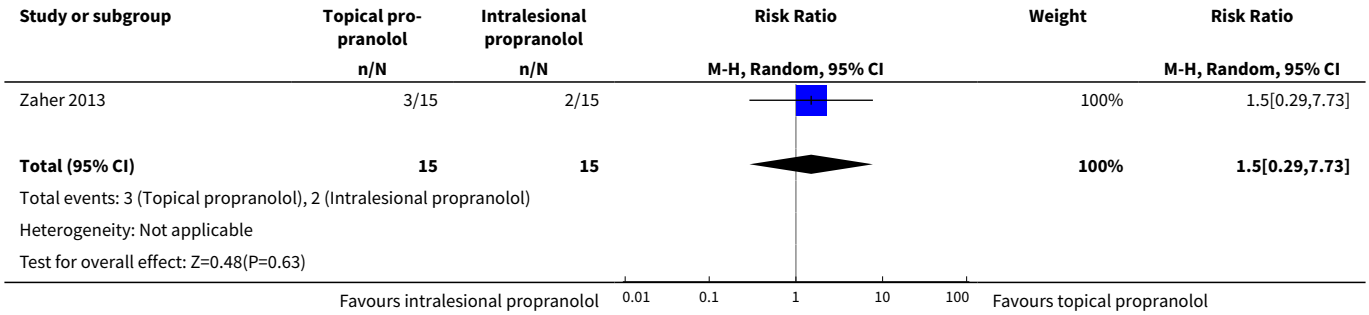
Analysis 15.2. Comparison 15 Oral propranolol versus intralesional propranolol, Outcome 2 Adverse events: syncopal attack.



Comparison 16. Topical propranolol versus intralesional propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	30	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.29, 7.73]

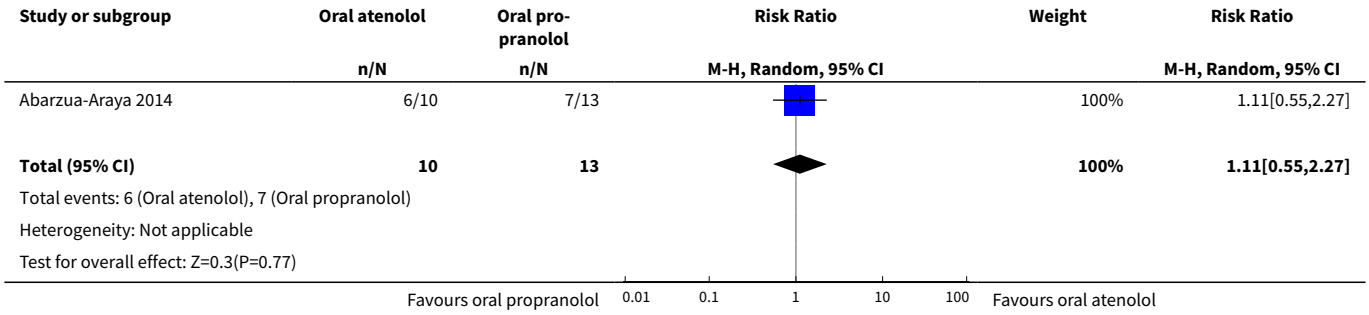
Analysis 16.1. Comparison 16 Topical propranolol versus intralesional propranolol, Outcome 1 Clearance.



Comparison 17. Oral atenolol versus oral propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	23	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.27]

Analysis 17.1. Comparison 17 Oral atenolol versus oral propranolol, Outcome 1 Clearance.

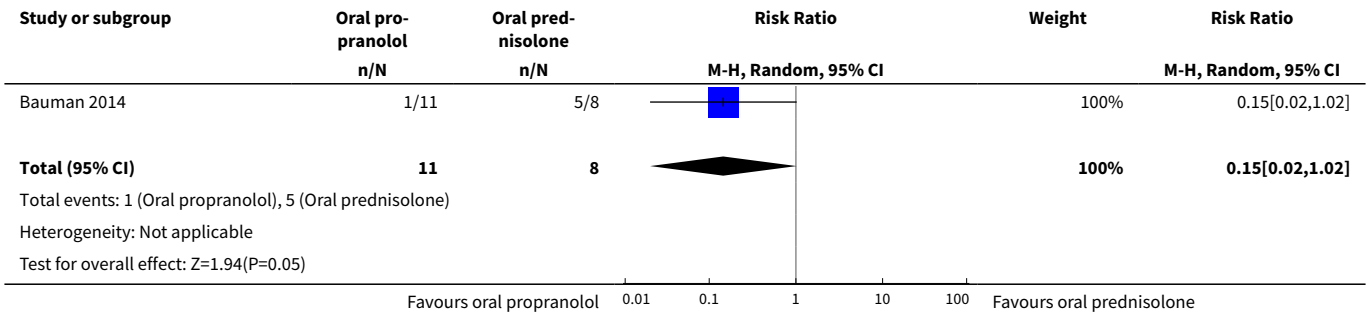


Comparison 18. Oral propranolol versus oral prednisolone

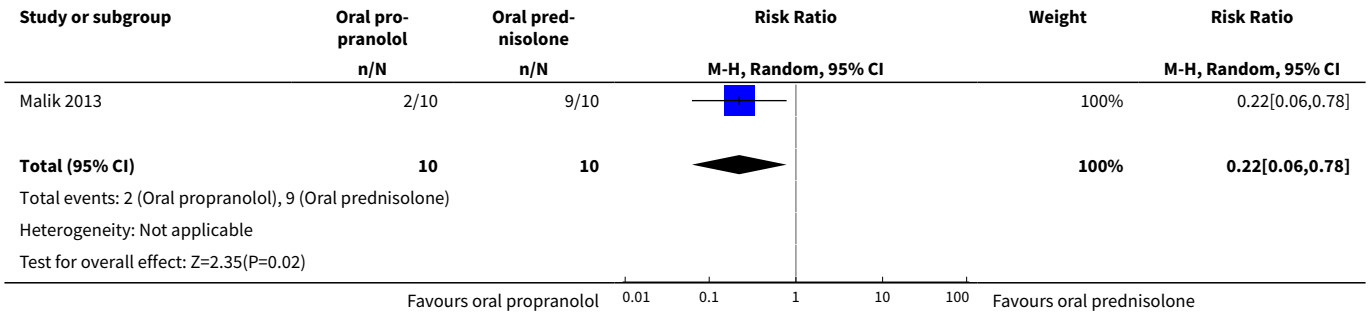
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe adverse events	1	19	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.02]
2 Adverse events: complications in general	1	20	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.78]
3 Other measures of resolution: colour fading	1	20	Mean Difference (IV, Random, 95% CI)	-1.0 [-3.08, 1.08]
4 Other measures of resolution: mean size reduction	1	20	Mean Difference (IV, Random, 95% CI)	23.20 [-3.36, 49.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Other measures of resolution: proportional change in the total surface area	1	19	Mean Difference (IV, Random, 95% CI)	0.23 [-0.08, 0.54]

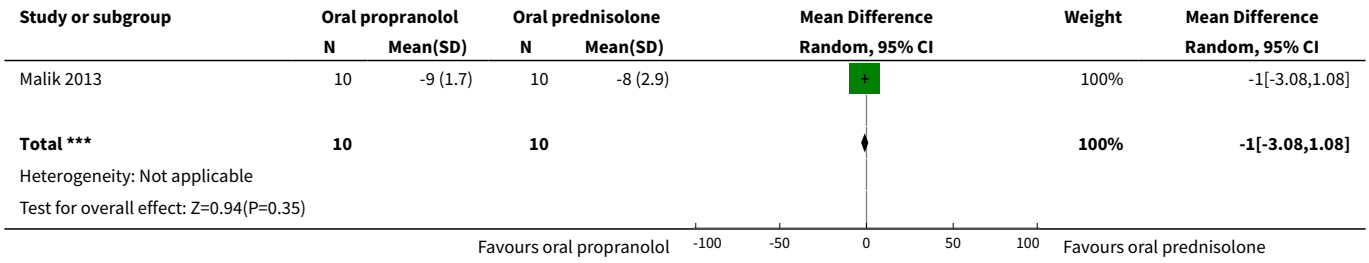
Analysis 18.1. Comparison 18 Oral propranolol versus oral prednisolone, Outcome 1 Severe adverse events.



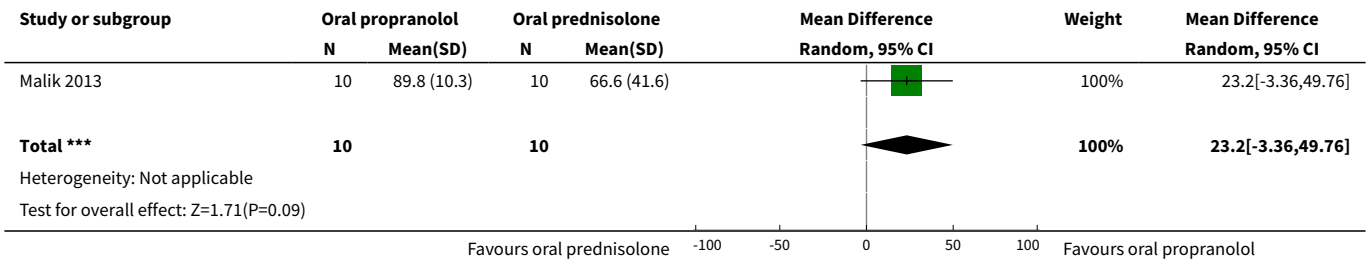
Analysis 18.2. Comparison 18 Oral propranolol versus oral prednisolone, Outcome 2 Adverse events: complications in general.



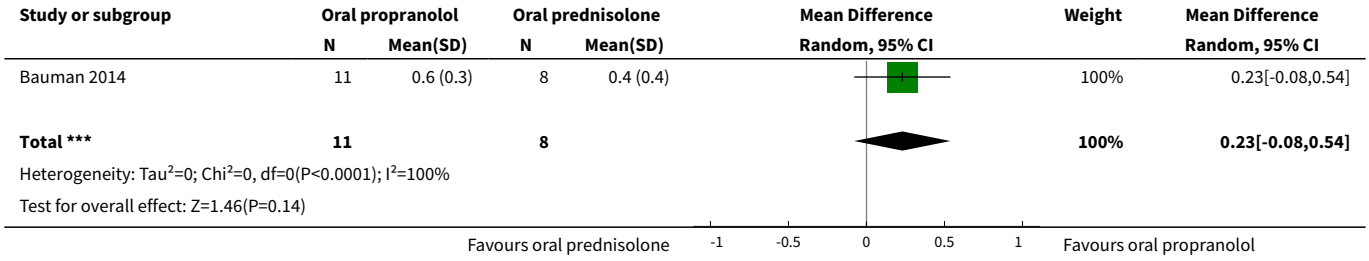
Analysis 18.3. Comparison 18 Oral propranolol versus oral prednisolone, Outcome 3 Other measures of resolution: colour fading.



Analysis 18.4. Comparison 18 Oral propranolol versus oral prednisolone, Outcome 4 Other measures of resolution: mean size reduction.



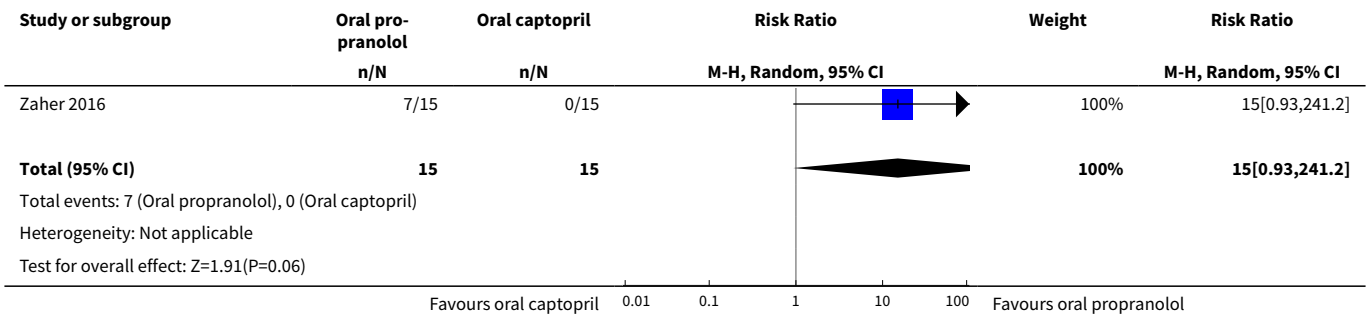
Analysis 18.5. Comparison 18 Oral propranolol versus oral prednisolone, Outcome 5 Other measures of resolution: proportional change in the total surface area.



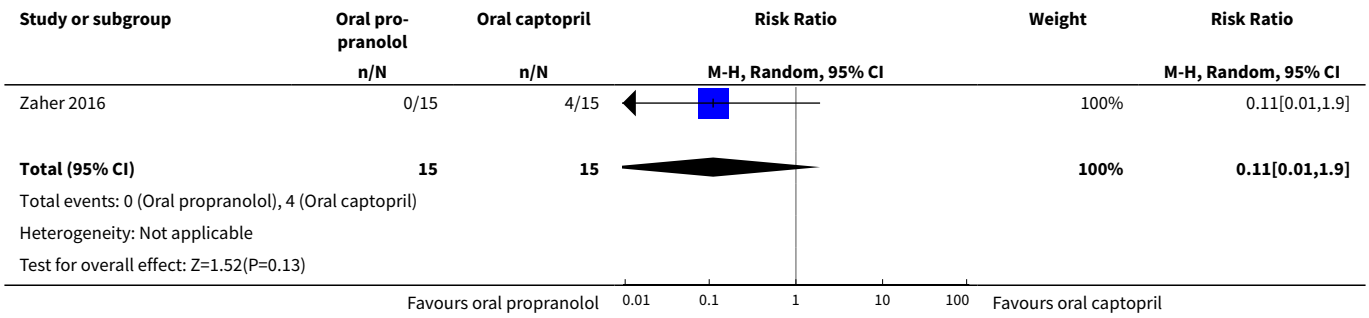
Comparison 19. Oral propranolol versus oral captopril

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	30	Risk Ratio (M-H, Random, 95% CI)	15.0 [0.93, 241.20]
2 Adverse events: cardiac side effects	1	30	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.90]

Analysis 19.1. Comparison 19 Oral propranolol versus oral captopril, Outcome 1 Clearance.



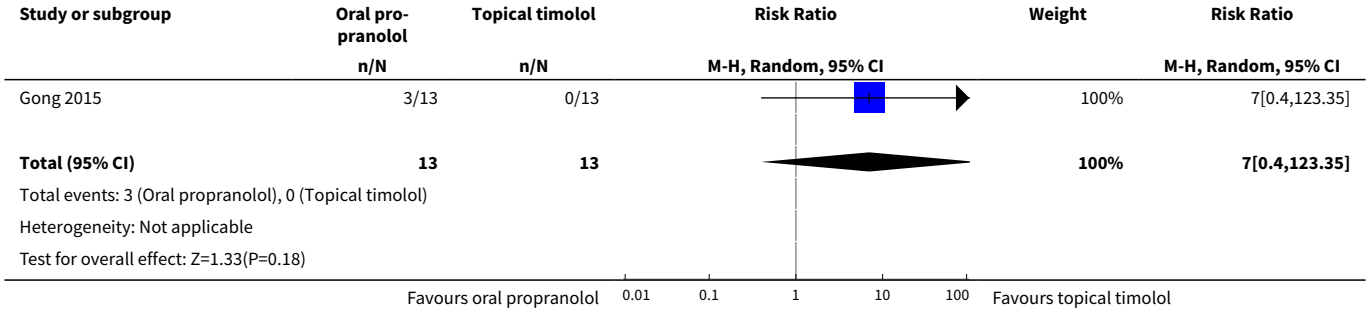
Analysis 19.2. Comparison 19 Oral propranolol versus oral captopril, Outcome 2 Adverse events: cardiac side effects.



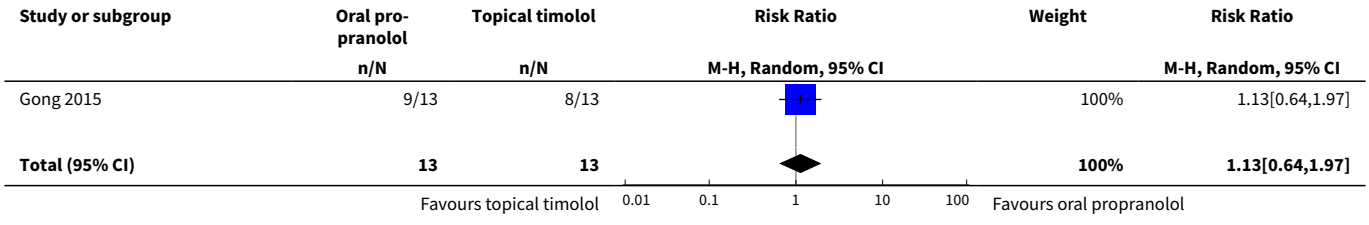
Comparison 20. Oral propranolol versus topical timolol maleate

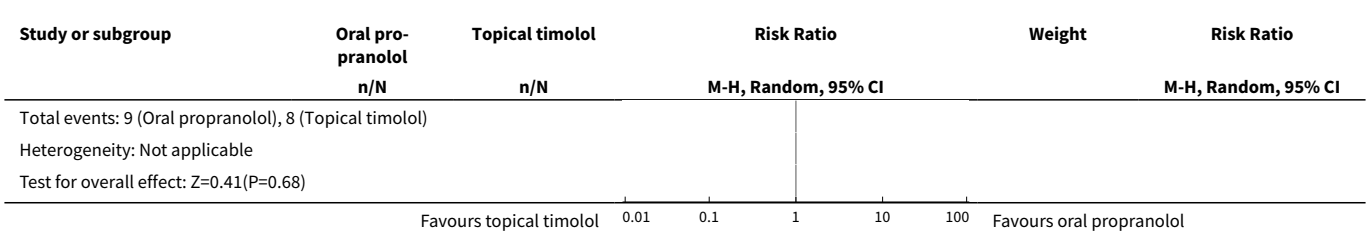
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1	26	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.40, 123.35]
2 Other measures of resolution: size reduction > 50%	1	26	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.64, 1.97]

Analysis 20.1. Comparison 20 Oral propranolol versus topical timolol maleate, Outcome 1 Adverse events.



Analysis 20.2. Comparison 20 Oral propranolol versus topical timolol maleate, Outcome 2 Other measures of resolution: size reduction > 50%.

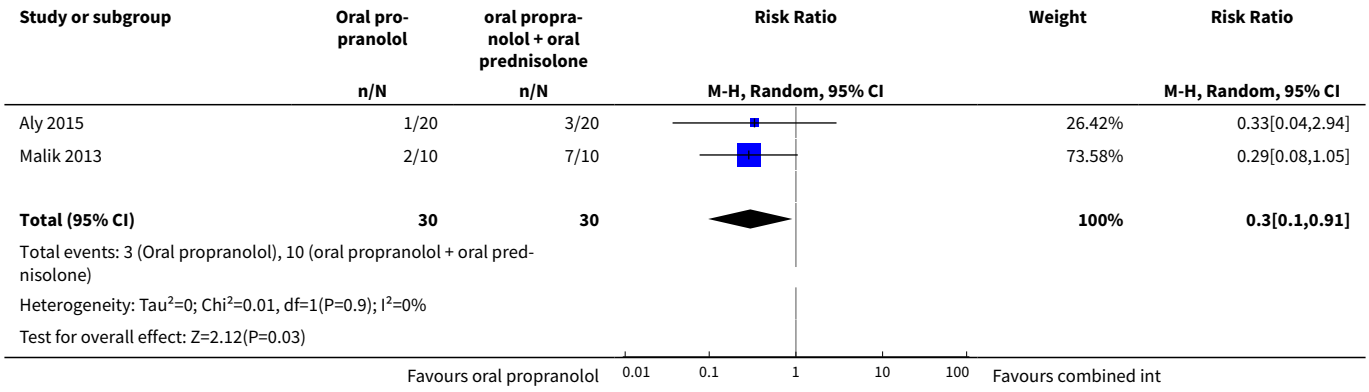




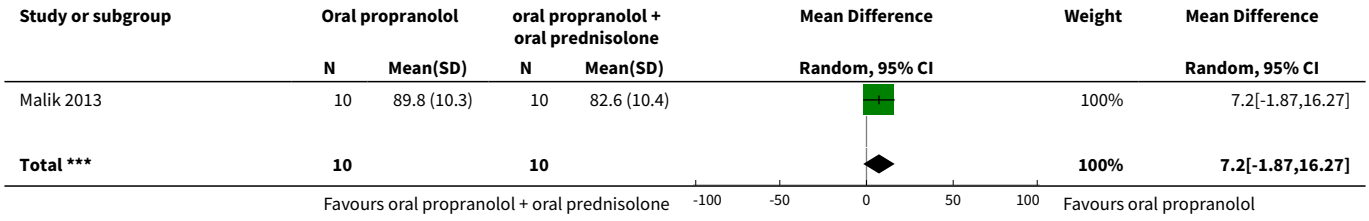
Comparison 21. Oral propranolol versus oral propranolol + oral prednisolone

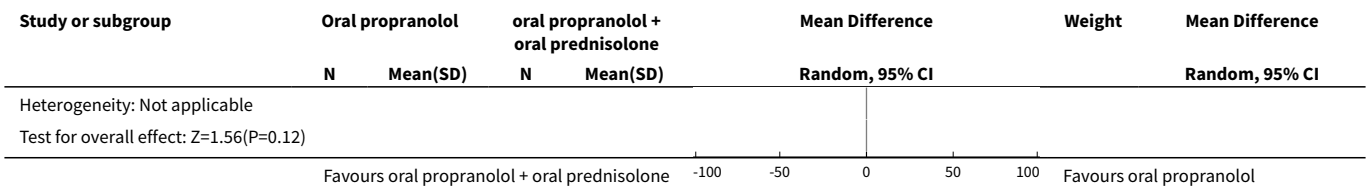
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events in general	2	60	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.10, 0.91]
2 Other measures of resolution: mean size reduction	1	20	Mean Difference (IV, Random, 95% CI)	7.20 [-1.87, 16.27]
3 Other measures of resolution: decrease in redness	1	40	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.32]

Analysis 21.1. Comparison 21 Oral propranolol versus oral propranolol + oral prednisolone, Outcome 1 Adverse events in general.

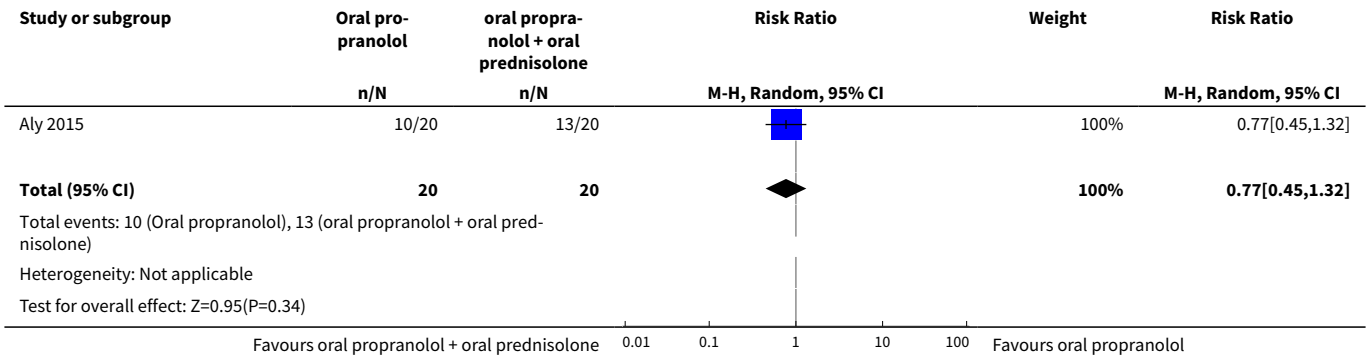


Analysis 21.2. Comparison 21 Oral propranolol versus oral propranolol + oral prednisolone, Outcome 2 Other measures of resolution: mean size reduction.





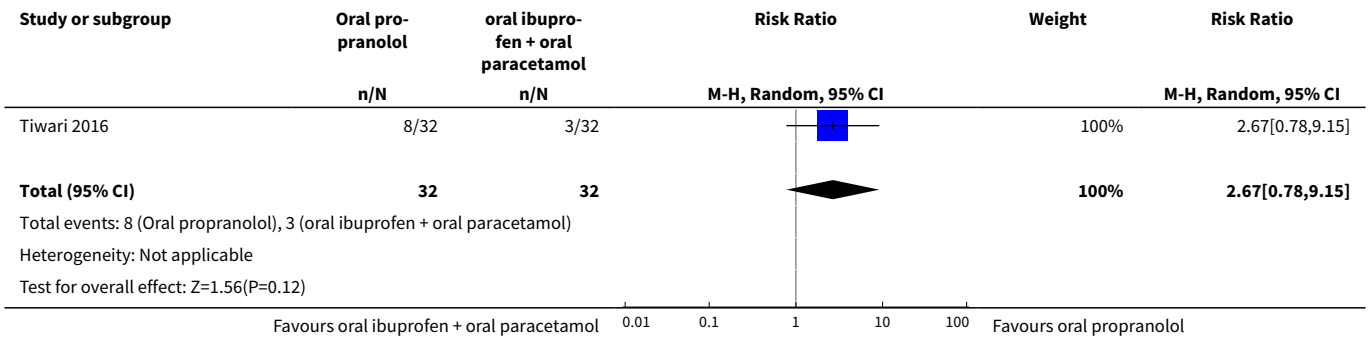
Analysis 21.3. Comparison 21 Oral propranolol versus oral propranolol + oral prednisolone, Outcome 3 Other measures of resolution: decrease in redness.



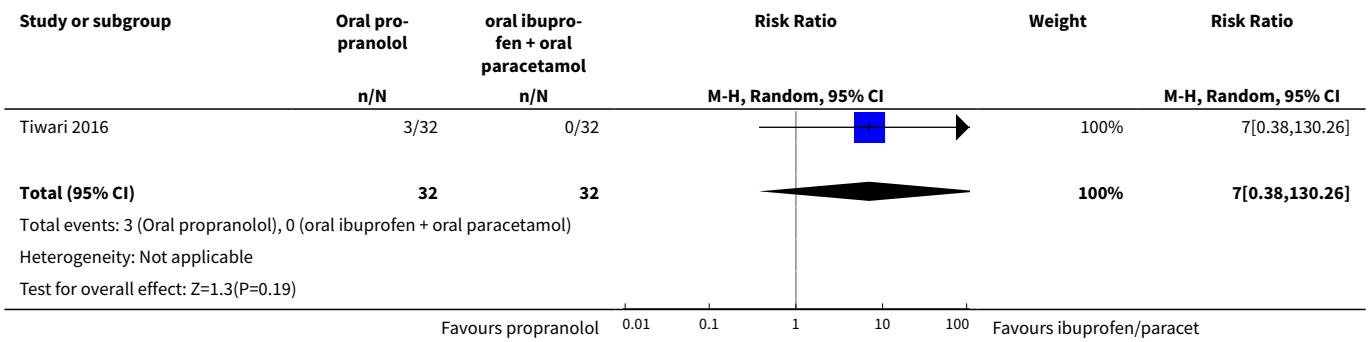
Comparison 22. Oral propranolol versus oral ibuprofen + oral paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	64	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.78, 9.15]
2 Adverse events	1	64	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.38, 130.26]
3 Other measures of resolution: mean size of ulceration	1	64	Mean Difference (IV, Random, 95% CI)	0.31 [0.01, 0.61]

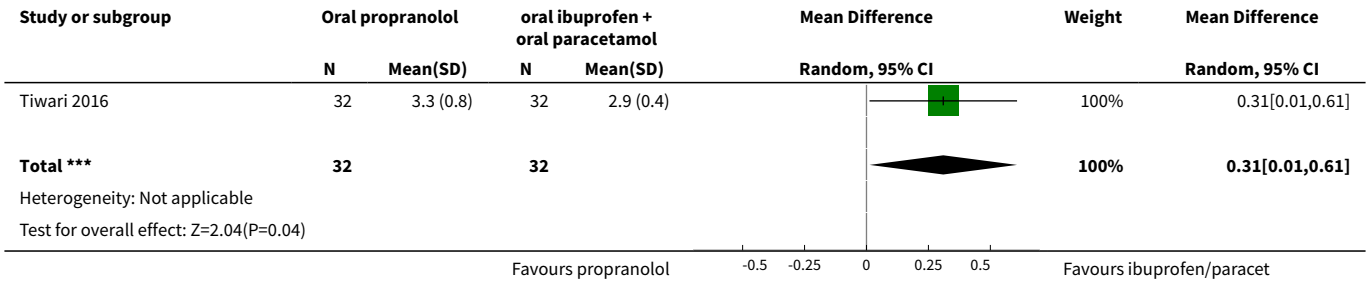
Analysis 22.1. Comparison 22 Oral propranolol versus oral ibuprofen + oral paracetamol, Outcome 1 Clearance.



Analysis 22.2. Comparison 22 Oral propranolol versus oral ibuprofen + oral paracetamol, Outcome 2 Adverse events.



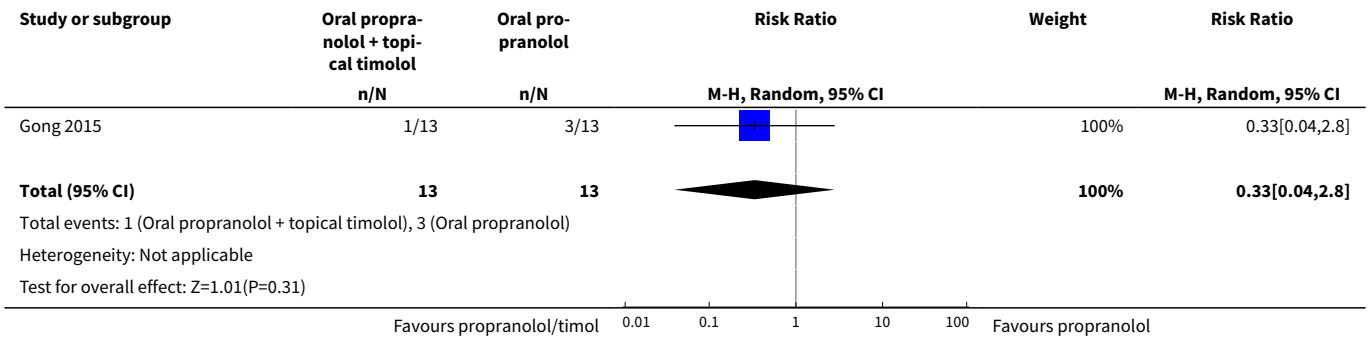
Analysis 22.3. Comparison 22 Oral propranolol versus oral ibuprofen + oral paracetamol, Outcome 3 Other measures of resolution: mean size of ulceration.



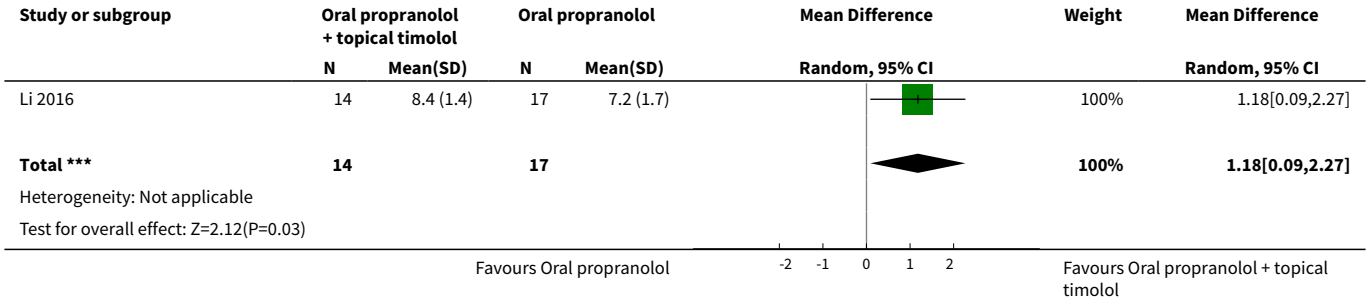
Comparison 23. Oral propranolol + topical timolol maleate versus oral propranolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events in general	1	26	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.80]
2 Other measures of resolution: colour fading/visual analogue scale score	1	31	Mean Difference (IV, Random, 95% CI)	1.18 [0.09, 2.27]
3 Other measures of resolution: size reduction/visual analogue scale score	1	31	Mean Difference (IV, Random, 95% CI)	0.41 [-0.84, 1.66]
4 Other measures of resolution: size reduction > 50%	1	26	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.79, 1.88]

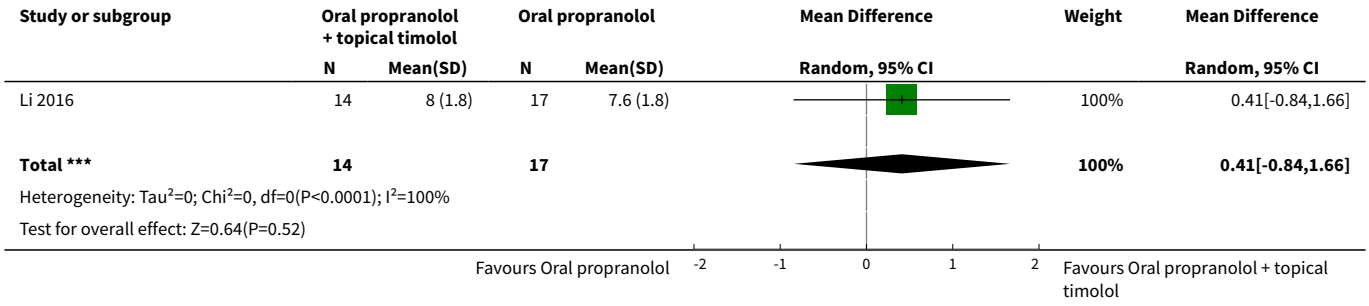
Analysis 23.1. Comparison 23 Oral propranolol + topical timolol maleate versus oral propranolol, Outcome 1 Adverse events in general.



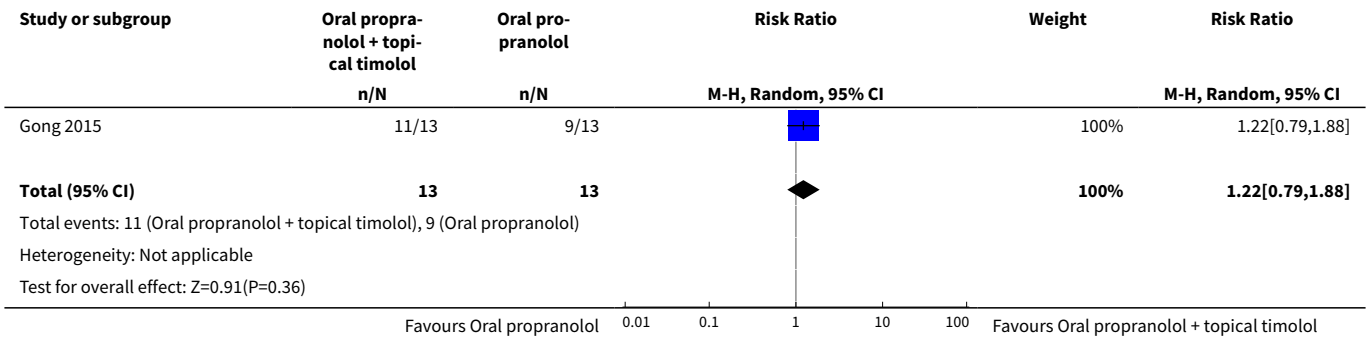
Analysis 23.2. Comparison 23 Oral propranolol + topical timolol maleate versus oral propranolol, Outcome 2 Other measures of resolution: colour fading/visual analogue scale score.



Analysis 23.3. Comparison 23 Oral propranolol + topical timolol maleate versus oral propranolol, Outcome 3 Other measures of resolution: size reduction/visual analogue scale score.



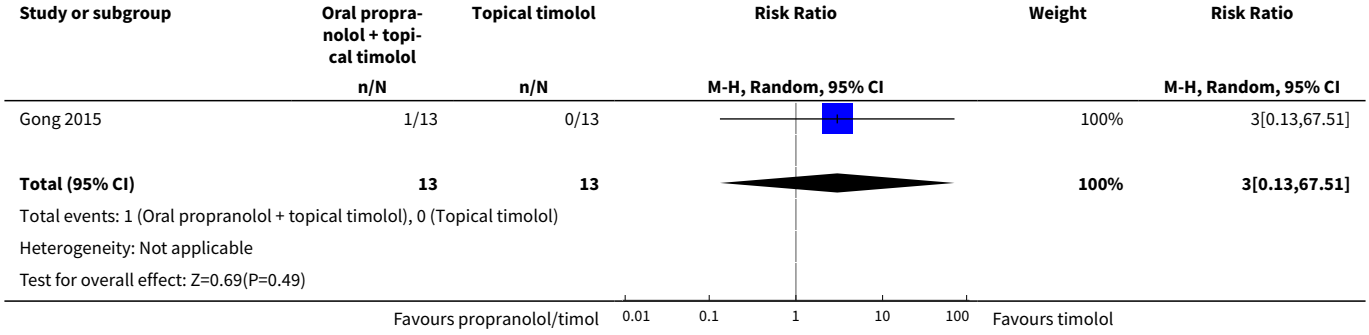
Analysis 23.4. Comparison 23 Oral propranolol + topical timolol maleate versus oral propranolol, Outcome 4 Other measures of resolution: size reduction > 50%.



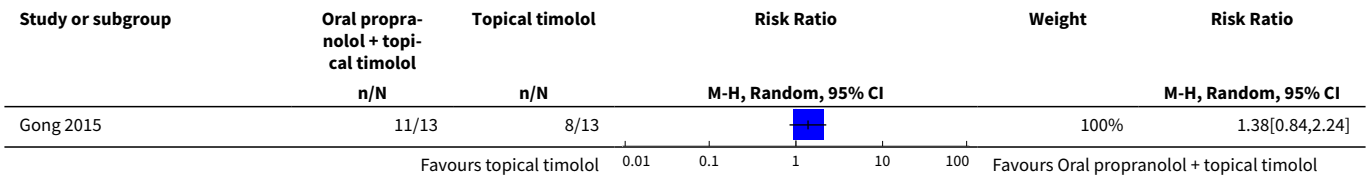
Comparison 24. Oral propranolol + topical timolol maleate versus topical timolol maleate

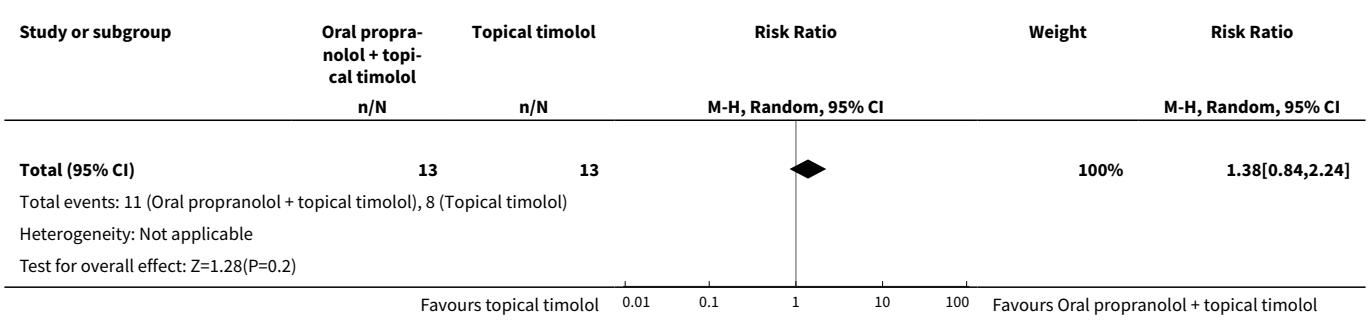
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1	26	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 67.51]
2 Other measures of resolution: size reduction > 50%	1	26	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.84, 2.24]

Analysis 24.1. Comparison 24 Oral propranolol + topical timolol maleate versus topical timolol maleate, Outcome 1 Adverse events.



Analysis 24.2. Comparison 24 Oral propranolol + topical timolol maleate versus topical timolol maleate, Outcome 2 Other measures of resolution: size reduction > 50%.

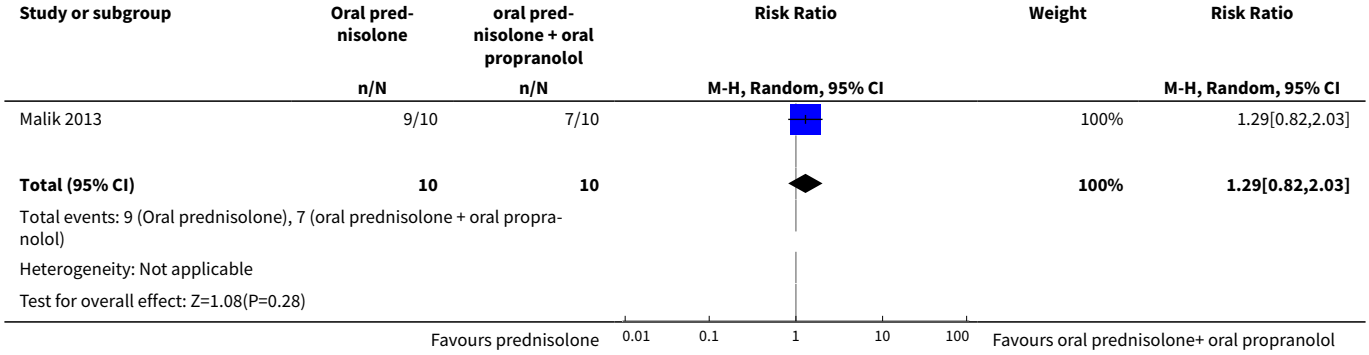




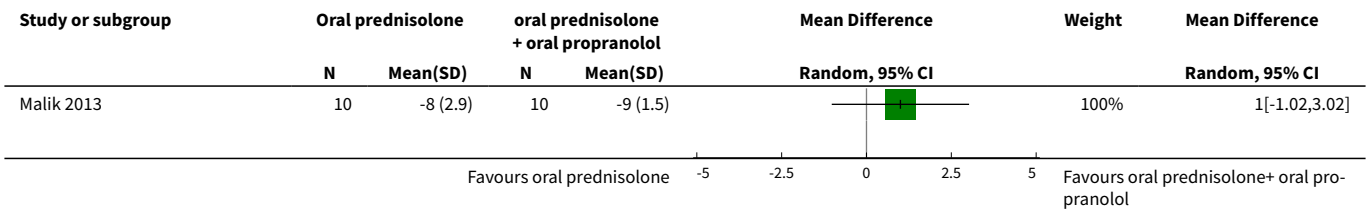
Comparison 25. Oral prednisolone versus oral prednisolone + oral propranolol

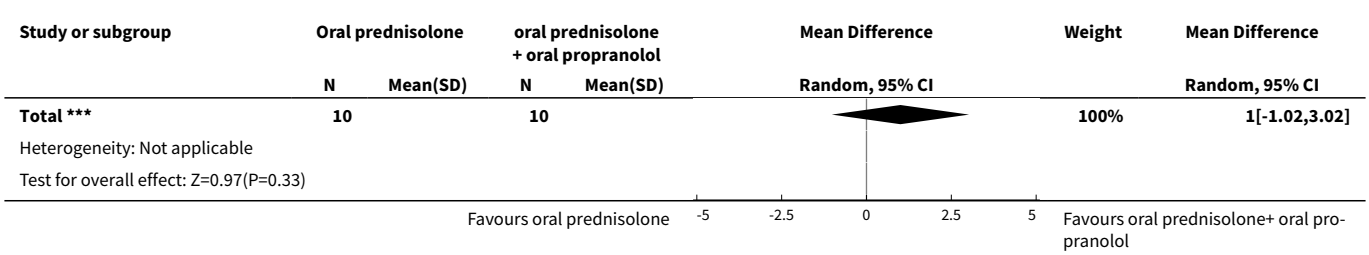
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events: complications	1	20	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.82, 2.03]
2 Other measures of resolution: colour fading	1	20	Mean Difference (IV, Random, 95% CI)	1.0 [-1.02, 3.02]
3 Other measures of resolution: mean size reduction	1	20	Mean Difference (IV, Random, 95% CI)	-16.0 [-42.58, 10.58]

Analysis 25.1. Comparison 25 Oral prednisolone versus oral prednisolone + oral propranolol, Outcome 1 Adverse events: complications.

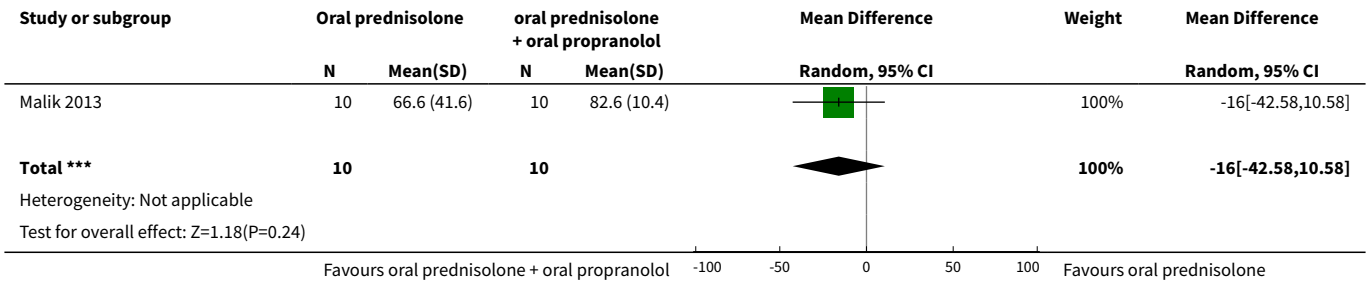


Analysis 25.2. Comparison 25 Oral prednisolone versus oral prednisolone + oral propranolol, Outcome 2 Other measures of resolution: colour fading.





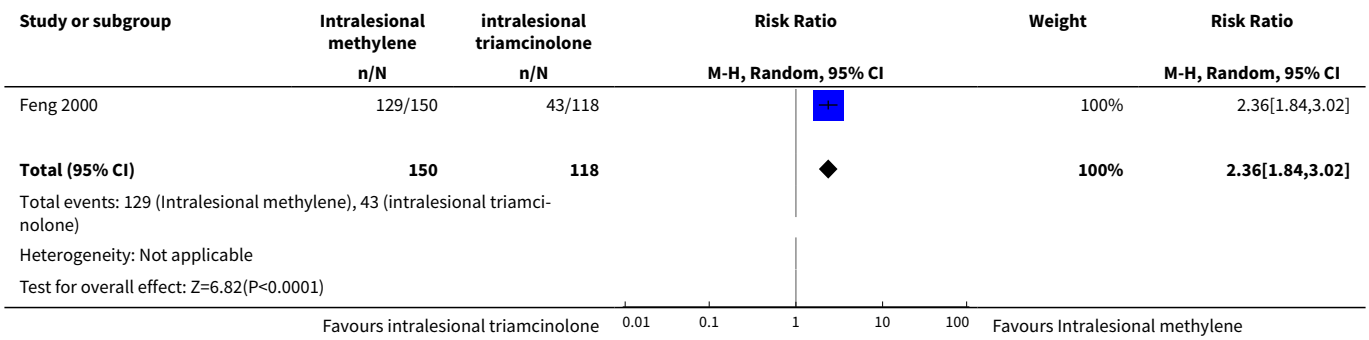
Analysis 25.3. Comparison 25 Oral prednisolone versus oral prednisolone + oral propranolol, Outcome 3 Other measures of resolution: mean size reduction.



Comparison 26. Intralesional methylene blue versus intralesional triamcinolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	268	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.84, 3.02]

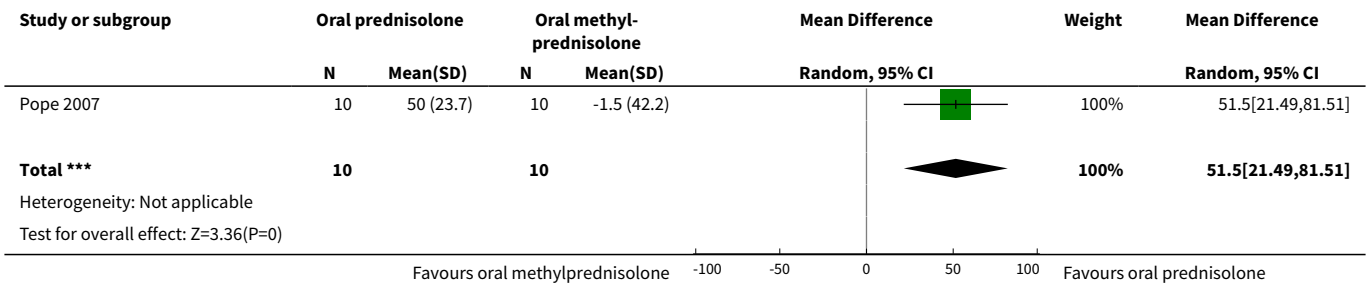
Analysis 26.1. Comparison 26 Intralesional methylene blue versus intralesional triamcinolone, Outcome 1 Clearance.



Comparison 27. Oral prednisolone versus intravenous methylprednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other measures of resolution: haemangioma size	1	20	Mean Difference (IV, Random, 95% CI)	51.5 [21.49, 81.51]

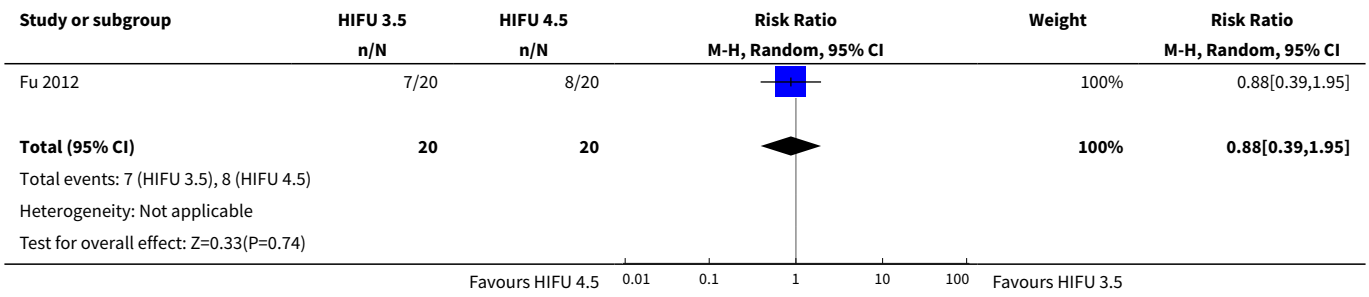
Analysis 27.1. Comparison 27 Oral prednisolone versus intravenous methylprednisolone, Outcome 1 Other measures of resolution: haemangioma size.



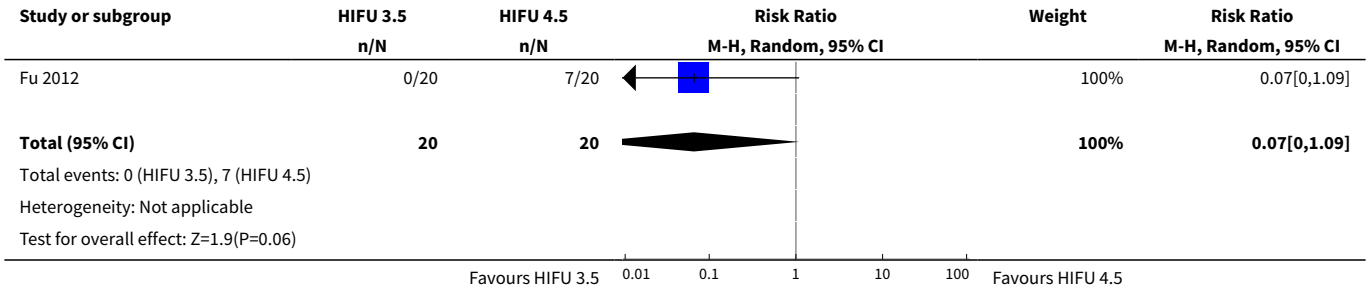
Comparison 28. HIFU 3.5 W versus HIFU 4.5 W

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	40	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.39, 1.95]
2 Adverse events: ulceration or scars	1	40	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.09]

Analysis 28.1. Comparison 28 HIFU 3.5 W versus HIFU 4.5 W, Outcome 1 Clearance.



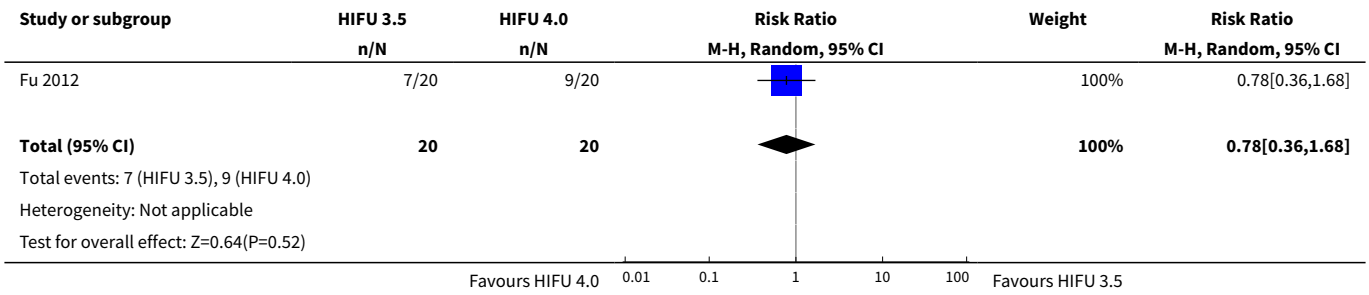
Analysis 28.2. Comparison 28 HIFU 3.5 W versus HIFU 4.5 W, Outcome 2 Adverse events: ulceration or scars.



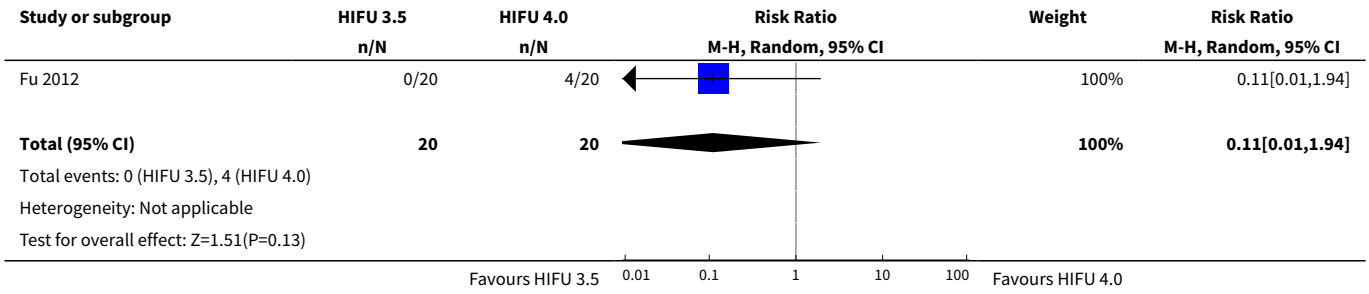
Comparison 29. HIFU 3.5 W versus HIFU 4.0 W

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	40	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.36, 1.68]
2 Adverse events: ulceration or scars	1	40	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.94]

Analysis 29.1. Comparison 29 HIFU 3.5 W versus HIFU 4.0 W, Outcome 1 Clearance.



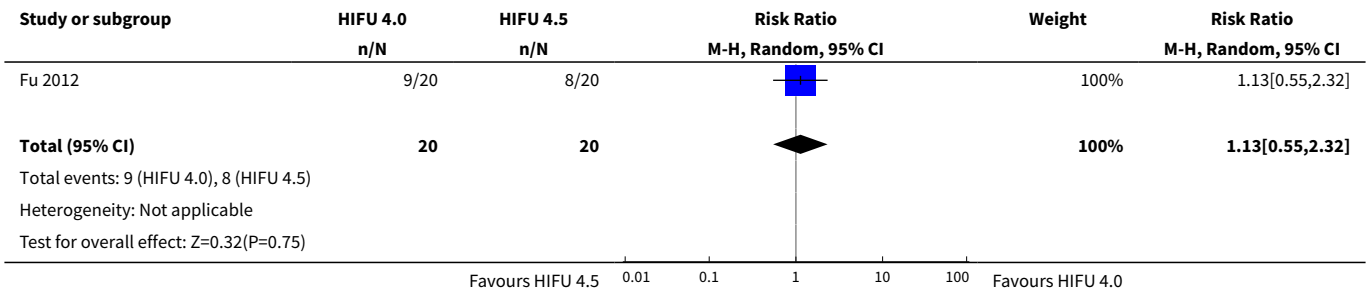
Analysis 29.2. Comparison 29 HIFU 3.5 W versus HIFU 4.0 W, Outcome 2 Adverse events: ulceration or scars.



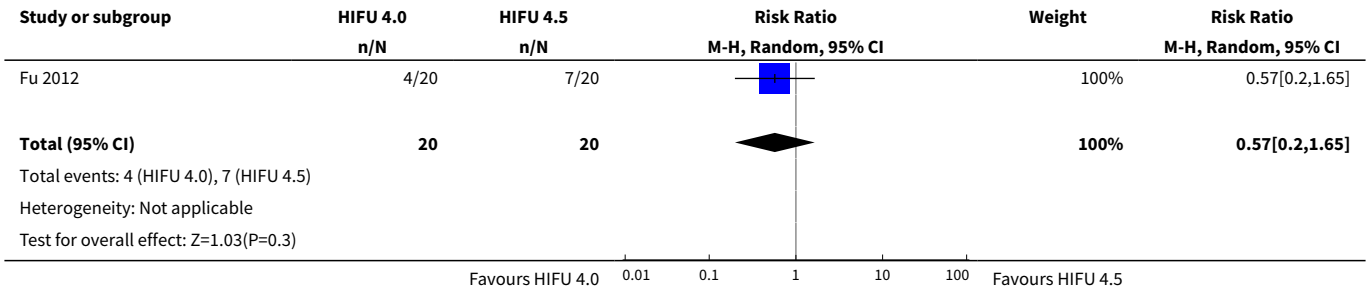
Comparison 30. HIFU 4.0 W versus HIFU 4.5 W

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clearance	1	40	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.55, 2.32]
2 Adverse events: ulceration or scars	1	40	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.20, 1.65]

Analysis 30.1. Comparison 30 HIFU 4.0 W versus HIFU 4.5 W, Outcome 1 Clearance.



Analysis 30.2. Comparison 30 HIFU 4.0 W versus HIFU 4.5 W, Outcome 2 Adverse events: ulceration or scars.



APPENDICES

Appendix 1. Skin Group Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Hemangioma
#2 MeSH DESCRIPTOR Hemangioma, Capillary
#3 MeSH DESCRIPTOR Hemangioma, Cavernous
#4 (hemangioma* or haemangioma*)
#5 (capillary and (naev* or nev*))
#6 (strawberry and (naev* or nev*))
#7 (strawberry birthmark*)
#8 (strawberry mark*)
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 hemangioma* or haemangioma*:ti,ab,kw
#2 MeSH descriptor: [Hemangioma] explode all trees
#3 MeSH descriptor: [Hemangioma, Capillary] explode all trees
#4 capillary and (naev* or nev*):ti,ab,kw
#5 strawberry and (naev* or nev*):ti,ab,kw
#6 strawberry birthmark*:ti,ab,kw
#7 MeSH descriptor: [Hemangioma, Cavernous] explode all trees
#8 strawberry mark*:ti,ab,kw
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Hemangioma, Capillary/ or exp Hemangioma/ or exp Hemangioma, Cavernous/
2. (haemangioma$ or hemangioma$).mp.
3. (strawberry naev$ or strawberry nev$).mp.
4. (capillary naev$ or capillary nev$).mp.
5. (superficial angiomatous naev$ or superficial angiomatous nev$).mp.
6. strawberry birthmark$.mp.
7. strawberry mark$.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. clinical trials as topic.sh.
14. randomly.ab.
15. trial.ti.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp animals/ not humans.sh.
18. 16 not 17
19. 8 and 18

Lines 9-18: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision).

Appendix 4. Embase (Ovid) search strategy

1. exp skin hemangioma/ or exp capillary hemangioma/ or exp hemangioma/ or exp cavernous hemangioma/
2. (haemangioma$ or hemangioma$).mp.
3. (strawberry naev$ or strawberry nev$).mp.
4. (capillary naev$ or capillary nev$).mp.
5. (superficial angiomatous naev$ or superficial angiomatous nev$).mp.
6. strawberry birthmark$.mp.
7. strawberry mark$.mp.
8. or/1-7
9. crossover procedure.sh.
10. double-blind procedure.sh.
11. single-blind procedure.sh.
12. (crossover$ or cross over$).tw.
13. placebo$.tw.
14. (doubl$ adj blind$).tw.
15. allocat$.tw.
16. trial.ti.
17. randomized controlled trial.sh.
18. random$.tw.
19. or/9-18
20. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
21. human/ or normal human/
22. 20 and 21
23. 20 not 22
24. 19 not 23

25. 8 and 24

Appendix 5. AMED (Ovid) search strategy

1. (haemangioma$ or hemangioma$).mp.
2. strawberry birthmark$.mp.
3. strawberry mark$.mp.
4. or/1-3
5. randomized controlled trial$/
6. random allocation/
7. double blind method/
8. single blind method.mp.
9. exp Clinical trials/
10. (clin$ adj25 trial$).mp.
11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp.
12. (placebo$ or random$).mp.
13. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
14. prospective studies.mp.
15. cross over studies.mp.
16. Follow up studies/
17. control$.mp.
18. (multicent$ or multi-cent$).mp.
19. ((stud or design$) adj25 (factorial or prospective or intervention or crossver or cross-over or quasi-experiment$)).mp.
20. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 4 and 20

Appendix 6. PsycINFO (Ovid) search strategy

1. (haemangioma$ or hemangioma$).mp.
2. strawberry birthmark$.mp.
3. strawberry mark$.mp.
4. or/1-3
5. double-blind.tw.
6. random$ assigned.tw.
7. control.tw.
8. 5 or 6 or 7
9. 4 and 8

Lines 5-8: therapy filter for PsycINFO (Ovid) created by the Health Information Research Unit at McMaster University.

Appendix 7. LILACS search strategy

In LILACS we searched using the Controlled clinical trials topic-specific query filter and the following terms: hemangioma$ or haemangioma$ or nevi or nevus

Appendix 8. CINAHL (EBSCO) search strategy

S1 TX strawberry birthmark*
S2 TX strawberry mark*
S3 (MM "Hemangioma+") OR (MM "Hemangioma, Cavernous")
S4 (MH "Clinical Trials+")
S5 PT clinical trial
S6 TX (clinic* n1 trial*)
S7 (MH "Random Assignment")
S8 TX random* allocat*
S9 TX placebo*
S10 (MH "Placebos")
S11 (MH "Quantitative Studies")
S12 TX allocat* random*
S13 "randomi#ed control* trial*"
S14 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S15 S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S16 TI (haemangioma* or hemangioma*) OR AB (haemangioma* or hemangioma*)

S17 S1 OR S2 OR S3 OR S16
S18 S15 AND S17

Lines S4 to S15: based on the SIGN filter for RCTs in CINAHL via EBSCO.

WHAT'S NEW

Date	Event	Description
4 April 2018	New citation required and conclusions have changed	This update included studies of many more interventions, including beta blockers, which are currently the standard treatment for infantile haemangiomas.
4 April 2018	New search has been performed	A new search led to the addition of 24 new included studies, and we updated the review in line with MECIR standards.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 5, 2011

Date	Event	Description
15 March 2012	Amended	Corrected a 'What's new' event on a previous version of the review
1 August 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

IAR was the contact person with the editorial base.
IAR and MN co-ordinated the contributions from the coauthors and wrote the final draft of the protocol.
IAR, MN, SB, and LG worked on the methods sections.
MN, EB, SB, AS, and LG drafted the clinical sections of the Background and responded to the clinical comments of the referees.
MN and IAR responded to the methodology and statistics comments of the referees.
HPH was the consumer coauthor and checked the protocol for readability and clarity. He also ensured that the outcomes are relevant to consumers.
IAR is the guarantor of the final review.

Disclaimer

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Skin Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

DECLARATIONS OF INTEREST

Monica Novoa: nothing to declare.
Eulalia Baselga: I have been the principal investigator for propranolol trials in infantile haemangioma, which included reviewing the final data, and for this I received honorarium/a consulting fee from Pierre Fabre Dermatology. I have received financial support for travel to meetings from Pierre Fabre Dermatology. I have received consultancy fees from the following: Pierre Fabre Dermatology and Sanofi-Regeneron. I have received payment for lectures from the following: Ordesa, Meda, Cantabria, and Almirall. I have given paid educational presentations for the following companies: Pierre Fabre Dermatology, Almirall, ISDIN, Novartis, Ferrer, Leo, IFC (Cantabria), and Ordesa. I have received travel/accommodation funding to attend the European Academy of Dermatology & Venereology and Spanish Academy of Dermatology meeting from the following: Novartis, Almirall, Ferrer, ISDIN, Cantabria, and Lao.
Sandra Beltrán: nothing to declare.

Lucia Giraldo: nothing to declare.
Ali Shahbaz: nothing to declare.
Hector Pardo-Hernandez: nothing to declare.
Ingrid Arevalo-Rodriguez: nothing to declare.

Dr Baselga was involved in the development of Leaute-Labreze 2015. She did not participate in the 'Risk of bias' assessment and data extraction for this study.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

External sources

- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is an update of the review published by Leonardi-Bee 2011. We made the following modifications to the original version.

- Background: We incorporated additional information about current findings about infantile haemangiomas (IH), as well as the current treatment for this condition.
- Methods/Types of participants: We decided we would exclude internal haemangiomas due to the fact that most of them are not symptomatic and are usually treated in the presence of other IH.
- Methods/Types of participants: We clarified that we excluded studies with a mixture of populations that did not provide separate information for children, due to our review focusing on children only.
- Methods/Types of interventions: We updated the list of interventions used to manage infantile haemangiomas in line with current practice. We also included studies comparing combinations of interventions, as interventions may be used in combination for complicated IH or in special circumstances.
- Methods/Types of outcome measures: We modified the list of primary and secondary outcomes, including making adverse events a primary outcome in line with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) conduct standard 14. We reported outcome data at any follow-up, but still considered six months or less to be short term. Finally, we considered 'economic data' as additional information and removed it from this list.
- Methods/Types of outcome measures/adverse events: Due to some studies reporting adverse events in general (i.e. not specifying which were the serious adverse events), we presented total number of adverse events along with information about single adverse events related to each intervention. In addition, we included information about what we defined as short-term adverse events (those presented until 48 hours after treatment) and long-term adverse events (those presented after 48 hours following treatment).
- Methods/Search methods: We updated the search strategies in line with current Cochrane Skin practices and searched currently recommended trials registers.
- Methods/Search methods: We did not handsearch conference proceedings, as many are now available online in Embase.
- Methods/Search methods: We did not correspond with pharmaceutical companies that manufacture specific treatments, or companies that produce laser-based therapies, in order to identify relevant trials, since it is probable that these randomised controlled trials would be registered with one of the databases of ongoing trials already included in the search methods.
- Methods/Data collection and analysis: We updated the methods according to the current guidelines to develop systematic reviews of interventions (Higgins 2011). We used the Cochrane 'Risk of bias' tool for each study, including those identified in the first version of this review.
- Methods/Measures of treatment effect: We omitted the estimation of the number needed to treat, as we believe this figure is mostly helpful in the presence of high-quality evidence, and there were a scarcity of data to calculate these numbers.
- Methods/Assessment of heterogeneity: We updated this section according to the current Cochrane guidelines (Higgins 2011).
- Methods/Data synthesis: We added information about the software employed to perform the statistical analysis (Review Manager 5.3).
- Methods/Data collection and analysis: We included the assessment of the quality/certainty of evidence, following the principles of the GRADE system, including the development of 'Summary of findings' tables (Guyatt 2008).
- Methods/'Summary of findings' tables: For the outcome 'adverse events', we presented in the corresponding table the most frequent or the most important adverse event, or both, related to each intervention. When information about adverse events in general (including serious/severe adverse events) was available, we presented these results instead of individual findings.
- We checked all ongoing studies and classified them as 'included' or 'excluded' when the full publication was available.

- We selected information about the most currently used treatments to report as main findings in the abstract, summary of main results, and 'Summary of findings' tables. This included oral propranolol and topical timolol maleate.

Due to scarcity of data in all comparisons, we were unable to perform a full analysis of reporting bias, subgroup analysis, sensitivity analysis, or investigation of heterogeneity.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects] [therapeutic use]; Adrenergic beta-Antagonists [administration & dosage]; Antineoplastic Agents [therapeutic use]; Bleomycin [therapeutic use]; Hemangioma, Capillary [*therapy]; Lasers, Dye [therapeutic use]; Methylprednisolone [adverse effects] [therapeutic use]; Photochemotherapy [methods]; Prednisolone [adverse effects] [therapeutic use]; Propranolol [administration & dosage]; Radiotherapy [methods]; Randomized Controlled Trials as Topic; Remission Induction [methods]; Skin Neoplasms [*therapy]; Timolol [administration & dosage]

MeSH check words

Child, Preschool; Humans; Infant