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Integrated versus non-integrated orbital implants for treating anophthalmic sockets (Review)

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[Intervention Review]

Integrated versus non-integrated orbital implants for treating anophthalmic sockets

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ABSTRACT

Background

Anophthalmia is the absence of one or both eyes, and it can be congenital (i.e. a birth defect) or acquired later in life. There are two main types of orbital implant: integrated, whereby the implant receives a blood supply from the body that allows for the integration of the prosthesis within the tissue; and non-integrated, where the implant remains separate. Despite the remarkable progress in anophthalmic socket reconstruction and in the development of various types of implants, there are still uncertainties about the real roles of integrated (hydroxyapatite (HA), porous polyethylene (PP), composites) and non-integrated (polymethylmethacrylate (PMMA)/acrylic and silicone) orbital implants in anophthalmic socket treatment.

Objectives

To assess the effects of integrated versus non-integrated orbital implants for treating anophthalmic sockets.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2016), Embase (January 1980 to August 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to August 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 8 August 2016.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs of integrated and non-integrated orbital implants for treating anophthalmic sockets.

Data collection and analysis

Two authors independently selected relevant trials, assessed methodological quality and extracted data.

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Main results

We included three studies with a total of 284 participants (250 included in analysis). The studies were conducted in India, Iran and the Netherlands. The three studies were clinically heterogenous, comparing different materials and using different surgical techniques. None of the included studies used a peg (i.e. a fixing pin used to connect the implant to the prosthesis). In general the trials were poorly reported, and we judged them to be at unclear risk of bias.

One trial compared HA using traditional enucleation versus alloplastic implantation using evisceration (N = 100). This trial was probably not masked. The second trial compared PP with scleral cap enucleation versus PMMA with either myoconjunctival or traditional enucleation (N = 150). Although participants were not masked, outcome assessors were. The last trial compared HA and acrylic using the enucleation technique (N = 34) but did not report comparative effectiveness data.

In the trial comparing HA versus alloplastic implantation, there was no evidence of any difference between the two groups with respect to the proportion of successful procedures at one year (risk ratio (RR) 1.02, 95% confidence interval (CI) 0.95 to 1.09, N = 100, low-certainty evidence). People receiving HA had slightly worse horizontal implant mobility compared to the alloplastic group (mean difference (MD) −3.35 mm, 95% CI −4.08 to −2.62, very low-certainty evidence) and slightly worse vertical implant motility (MD −2.76 mm, 95% CI −3.45 to −2.07, very low-certainty evidence). As different techniques were used – enucleation versus evisceration – it is not clear whether these differences in implant motility can be attributed solely to the type of material. Investigators did not report adverse events.

In the trial comparing PP versus PMMA, there was no evidence of any difference between the two groups with respect to the proportion of successful procedures at one year (RR 0.92, 95% CI 0.84 to 1.01, N = 150, low-certainty evidence). There was very low-certainty evidence of a difference in horizontal implant motility depending on whether PP was compared to PMMA with traditional enucleation (MD 1.96 mm, 95% CI 1.01 to 2.91) or PMMA with myoconjunctival enucleation (−0.57 mm, 95% CI −1.63 to 0.49). Similarly, for vertical implant motility, there was very low-certainty evidence of a difference in the comparison of PP to PMMA traditional (MD 3.12 mm 95% CI 2.36 to 3.88) but no evidence of a difference when comparing PP to PMMA myoconjunctival (MD −0.20 mm 95% CI −1.28 to 0.88). Four people in the PP group (total N = 50) experienced adverse events (i.e. exposures) compared to 6/100 in the PMMA groups (RR 17.82, 95% CI 0.98 to 324.67, N = 150, very low-certainty evidence).

None of the studies reported socket sphere size, cosmetic effect or quality of life measures.

Authors' conclusions

Current very low-certainty evidence from three small published randomised controlled trials did not provide sufficient evidence to assess the effect of integrated and non-integrated material orbital implants for treating anophthalmic sockets. This review underlines the need to conduct further well-designed trials in this field.

PLAIN LANGUAGE SUMMARY

Integrated compared with non-integrated orbital implants for treating anophthalmic sockets

What is the aim of this review?
The aim of this Cochrane Review was to find out if integrated orbital implants are better than non-integrated orbital implants for treating anophthalmic sockets. Cochrane researchers collected and analysed all relevant studies to answer this question and found three studies.

Key messages
There is uncertainty as to the benefits and harms of integrated compared with non-integrated orbital implants.

What was studied in the review?
'Anophthalmia' is the absence of the eye in the orbit. This can occur in childhood (because of problems with development) or it can happen during the course of life (due to an accident or other eye disease).

Doctors can put an implant in the orbit to fill the void left by the removal of the eye and this together with an external prosthesis can improve the patient's appearance. This orbital implant can be made of two types of materials – integrated or non-integrated material. If the material is integrated, then new blood vessels can grow into the implant material. If the material is non-integrated, then the orbital implant remains separate from the rest of the orbit's tissue.

The review authors looked to see if the type of implant material affected the success of the surgery or, in other words, if integrated implants can provide better results than non-integrated implants. They were also interested in how much the external prosthesis could move better after surgery – using integrated or non-integrated orbital implants. Also, the authors wanted to know if the type of orbital implant material can affect people's quality of life. Were there any adverse (harmful) effects of using integrated or non-integrated orbital implants?

What are the main results of the review?
The type of material used for the orbital implant may not affect the success of the surgery (low-certainty evidence). The review authors judged the evidence on prosthesis movement and adverse effects as providing very little certainty about the true effects. There was no information on quality of life.

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How up-to-date is this review?
The Cochrane researchers searched for studies that had been published up to 8 August 2016.

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SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Integrated versus non-integrated orbital implants for treating anophthalmic sockets

Patient or population: people with anophthalmic sockets

Intervention: integrated implants

Comparison: non-integrated implants

Outcomes	Comparison	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty (quality) of the evidence (GRADE)	Comment
		Risk with non-integrated material	Risk with integrated material				
Proportion of successful procedures at 1 year and up to 5 years after surgery (no exposure/extrusion)	PP (scleral cap enucleation) versus PMMA (traditional and myoconjunctival enucleation)	960 per 1000	883 per 1000 (806 to 1000)	**RR** 0.92 (0.84 to 1.01)	150 (1)	⊕⊕⊙⊙ **Low** [a]	—
	HA (traditional enucleation) versus alloplastic (evisceration)	960 per 1000	980 per 1000 (912 to 1000)	**RR** 1.02 (0.95 to 1.09)	100 (1)	⊕⊕⊙⊙ **Low** [b]	—
Socket and prosthesis motility (horizontal)	PP (scleral cap enucleation) versus PMMA (traditional enucleation)	The mean socket and prosthesis motility (horizontal) score was 5.14 mm	The mean socket and prosthesis motility (horizontal) score in the intervention group was on average **1.96 mm more** (1.01 mm more to 2.91 mm more)	—	100 (1)	⊕⊙⊙⊙ **Very low** [a,c]	—
	PP (scleral cap enucleation) versus PMMA (myoconjunctival enucleation)	The mean socket and prosthesis motility (horizontal) score was 7.67 mm	The mean socket and prosthesis motility (horizontal) score in the intervention group was on average **0.57 mm less** (1.63 mm less to 0.49 mm more)	—	100 (1)	⊕⊙⊙⊙ **Very low** [a,c]	—
	HA (traditional enucleation) versus alloplastic (evisceration)	The mean socket and prosthesis motility (horizontal) score was 10.25 mm	The mean socket and prosthesis motility (horizontal) score in the intervention group was on average **3.35 mm less** (4.08 mm less to 2.62 mm less)	—	100 (1)	⊕⊙⊙⊙ **Very low** [b,c]	—

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Socket and prosthesis motility (vertical)	PP (scleral cap enucleation) versus PMMA (traditional enucleation)	The mean socket and prosthesis motility (vertical) score was 2.68 mm	The mean socket and prosthesis motility (vertical) score in the intervention group was on average **3.12 mm more** (2.36 mm more to 3.88 mm more)	—	100 (1)	⊕⊖⊖⊖ **Very low** [a,c]	—
	PP (scleral cap enucleation) versus PMMA (myoconjunctival enucleation)	The mean socket and prosthesis motility (vertical) score was 6 mm	The mean socket and prosthesis motility (vertical) score in the intervention group was on average **0.20 mm less** (1.28 mm less to 0.88 mm more)	—	100 (1)	⊕⊖⊖⊖ **Very low** [a,c]	—
	HA (traditional enucleation) versus alloplastic (evisceration)	The mean socket and prosthesis motility (vertical) score was 8.45 mm	The mean socket and prosthesis motility (vertical) score in the intervention group was on average **2.76 mm less** (3.45 mm less to 2.07 mm less)	—	100 (1)	⊕⊖⊖⊖ **Very low** [b,c]	—
Any adverse outcomes (e.g. extrusions or migration, infections, ectropion)	PP (scleral cap enucleation) versus PMMA (traditional or myoconjunctival enucleation)	1 per 1000	18 per 1000 (1 to 325 per 1000)	**RR** 17.82 (0.98 to 324.67)	150 (1)	⊕⊖⊖⊖ **Very low** [a,c]	Adverse outcomes not reported for HA versus alloplastic comparison

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HA**: hydroxyapatite; **PMMA**: polymethylmethacrylate; **PP**: porous polyethylene; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded for risk of bias (−1) and indirectness (−1). The trial was poorly reported, and it was difficult to judge risk of bias for many domains. It was conducted in one specific setting, and it is unclear if the findings are generalisable to other settings.
[b]Downgraded for risk of bias (−1) and indirectness (−1). The trial was poorly reported, and it was difficult to judge risk of bias for most domains. It was a quasi-randomised study and probably not masked. It was conducted in one specific setting, and it is unclear if the findings are generalisable to other settings.
[c]Downgraded for imprecision (−1): confidence intervals include clinically unimportant effect.

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BACKGROUND

Description of the condition

Anophthalmia is the absence of one or both eyes, and it can be congenital (i.e. a birth defect) or acquired later in life (such as by trauma, tumour, glaucoma, etc.).

Description of the intervention

History

The development of techniques for enucleation (the surgical removal of the eyeball leaving the eye muscles and orbital contents intact) and evisceration (the removal of the eye's contents) occurred almost concurrently with the development of the materials used in the manufacture of prostheses and implants for aesthetic and functional repair of the anophthalmic socket. The first implants were very light and made of a type of very thin glass (Tonkelaar 1991). Since the destruction of glass implant manufacturing plants during World War II, other types of non-integrated (non-porous) materials, such as silicone and polymethylmethacrylate (PMMA), have emerged and gained popularity. These types of implants still dominate the world market in anophthalmic socket repair.

Since 1987, the landscape of eye socket reconstruction has changed substantially, with integrated (porous) implants made of natural hydroxyapatite becoming widely available (Perry 1990). The BioEye (Hydroxyapatite Orbital Implant; Integrated Orbital Implants Inc., San Diego, CA, USA) is an implant built using natural hydroxyapatite and composed of calcium carbonate, the same mineral that forms the hard parts of bones. A hydrothermal reaction converts calcium carbonate into calcium phosphate during BioEye manufacture (Massry 1995). This material is extremely porous, allowing for vascular and fibrovascular ingrowth; thus, it can become "part of the patient's body" as an integrated implant (Flanagan 1990). Synthetic hydroxyapatites were introduced soon after natural hydroxyapatite in several countries (Jordan 1998), including Brazil (Jordan 2000; Schellini 2000).

Other biomaterials, such as porous polyethylene (Medpor; Porex Technologies Corporation, Fairburn, GA, USA), became available for the repair of anophthalmic sockets in mid-1991 (Karesh 1994). Experimental research in Brazil also made use of similar materials, showing good results (Schellini 2000).

Different types of implants are used to reconstruct the anophthalmic cavity. These implants can be classified according to their shape (spherical, oval or conical), the material used (integrated or non-integrated) and the surface type (smooth/non-porous or porous). Non-porous (non-integrated) implants are most often composed of PMMA or silicone, while porous (integrated) implants are made of hydroxyapatite, porous polyethylene and composites (including bioceramics).

In 1995, a study from the USA reported that most American surgeons were using spheres made of natural hydroxyapatite (Hornblass 1995). By 2004, this preference had changed, with American surgeons preferring to use porous polyethylene implants without coupling pegs between the implant and the external prosthesis (Su 2004). A Canadian study in 2006 revealed that porous polyethylene implants were the most widely used prostheses in Canada (Jordan 2006). In Brazil, despite a lack of studies on anophthalmic socket implants, integrated implants are rarely used, most likely due to their higher cost; however, actually PMMA is still the preferred choice among 62.75% of Brazilian ophthalmologists (Schellini 2015; Sousa 2012).

Physicians originally considered that the use of pegs conferred advantages for integrated implants, enabling the anchoring of implants to the external prothesis. Nowadays, pegs have fallen out of use, as there have been observational reports of complications, although the evidence for this is scarce.

With the increased use of integrated implants, studies have observed complications in 10% to 22% of patients, including conjunctival dehiscence, implant exposure or extrusion, and the necessity to remove the implant (Buettner 1992; Goldberg 1994; Nunery 1993; Rubin 1994; Shields 1992; Shields 1994). These complication rates are based on the longest periods of observation in the individuals who received the implants. Several reports have been published on the lack of success of integrated implants, and these failures have been related to the failure of the surgical technique, the use of external prostheses that create too much pressure against the surface of the implant (Shields 1994), and the use of uncoated spheres (Rubin 1994). This research led to the conclusion that hydroxyapatite spheres had a higher risk of failure than spheres made of silicone (Nunery 1993).

Thus, despite the remarkable progress in anophthalmic socket reconstruction and the development of various types of implants, there are still uncertainties about the real roles of integrated and non-integrated orbital implants in anophthalmic socket treatment.

Enucleation surgery

Enucleation surgery refers to removing the entire eyeball, that is, without cutting into or dissecting the globe. It consists of the following steps.

1. Determination of general or local anaesthesia.
2. A 360° conjunctival peritomy (the conjunctiva is separated from the sclera with scissors close to the limbus).
3. Identification and sectioning of the extrinsic ocular rectus muscle and sectioning of the optic nerve.
4. Removal of the entire eye and the inspection of Tenon's capsule.
5. Determination of the implant size.
6. Insertion of the orbital implant.
7. If necessary, wrapping of the implant to be attached to the extrinsic ocular rectus muscles.
8. Suturing of Tenon's fascia.
9. Suturing of the conjunctiva (attaching the upper conjunctiva to the lower conjunctiva).

Evisceration surgery

Evisceration surgery removes the eye's contents but leaves the scleral shell, Tenon's capsule, the orbital fat and the extraocular muscles intact. The operation consists of the following steps.

1. Determination of general or local anaesthesia.
2. A 360° peritomy (the conjunctiva is separated from the sclera using scissors).

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3. Penetration into the anterior chamber using a no. 11 scalpel blade and enlargement of the corneo-scleral opening with scissors.
4. Removal of the eye contents using an ocular evisceration spoon.
5. Evaluating the size of the implant to be placed into the scleral shell.
6. Suturing of the sclera and Tenon's fascia.
7. Suturing of the conjunctiva (attaching the upper conjunctiva to the lower conjunctiva).

How the intervention might work

The main factors that favour the use of integrated implants are the mobility of the external prosthesis and the presence of immune cells within implants that receive a blood supply from the host, allowing for the integration of the prosthesis with the host's tissue, which in turn results in a lower risk of migration and implant extrusion (Flanagan 1990; Rubin 1994). In contrast, the non-integrated implants contain no unique apparatus for attachments to the extraocular muscles and do not allow in-growth of organic tissue into their inorganic substance.

Enucleation surgery is used in cases of intraocular tumours, in patients at risk of sympathetic ophthalmia and in cases of severe atrophy of the scleral layer (phthisis bulbi). Evisceration surgery is used in cases of virulent endophthalmitis. However, both enucleation and evisceration surgeries are used for painful and blind eyes, and there are different arguments as to whether these techniques should be the procedure of choice. Both procedures should include implant placement to replace the lost volume and to restore the facial aesthetics. The implants can be non-integrated (PMMA, silicone) or integrated (i.e. hydroxyapatite, polyethylene or composites).

Why it is important to do this review

Various autologous tissues, such as bone, fat and dermis, have been used to restore anophthalmic sockets, as have organic and alloplastic materials, including acrylics, silicone, hydroxyapatite and porous polyethylene. The high incidence of complications has prompted new research aiming to identify the gold standard material. However, the best technique in the management of anophthalmic sockets is currently unclear, and there is variation in trends around the world. A systematic review of integrated and non-integrated orbital implants would be useful to patients, ophthalmologists and other professionals involved in providing eye care to evaluate the efficacy of procedures and to reduce complications.

OBJECTIVES

To assess the effects of integrated versus non-integrated orbital implants for treating anophthalmic sockets.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which investigators determined allocation to treatment by alternation, use of alternate medical records, date of birth, or other predictable methods). This decision was due to our anticipation of not finding many trials in this area.

Types of participants

Participants were people affected by anophthalmia, regardless of age or sex. We also considered patients who had an implant rejection.

Types of interventions

We included the following interventions in this review.

- Intervention group: porous/integrated materials (hydroxyapatite, porous polyethylene, composites).
- Comparator: non-porous/non-integrated materials (polymethylmethacrylate (PMMA)/acrylic and silicone).

We also planned to investigate composite integrated/non-integrated implants such as the Gutthoff implant as per our published protocol (Schellini 2013).

We considered both the enucleation and evisceration reconstruction of the anophthalmic socket.

Types of outcome measures

Primary outcomes

The primary outcomes for this review were:

1. the proportion of successful procedures at one year and up to five years after surgery; and
2. the proportion of successful procedures after five years.

We considered a successful procedure as involving no need for secondary reconstruction of the anophthalmic socket or implant extrusion. We also considered implant removal and implant exposure needing implant removal as an implant extrusion.

Secondary outcomes

Secondary outcomes for this review were:

1. Horizontal and vertical socket and prosthesis motility measured by evaluating the prosthesis excursion in different eye gaze positions or any validated measurement aiming to measure the impact of motility function loss;
2. degree of vascularisation measured by magnetic resonance imaging (MRI);
3. sphere size before and after surgery;
4. cosmetic effect (self-reported);
5. quality of life measures: any validated measurement scale aiming to measure the impact of visual function loss on quality of life of participants;
6. economic data: we planned to perform comparative cost analysis if data were available; and
7. adverse events: any adverse outcomes as reported in trials, particularly extrusions or migration, infections, ectropion, ptosis, significant inflammatory responses or exposures.

We wanted to measure the secondary outcome measures at one year or more after surgery.

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Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2016), Embase (January 1980 to August 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to August 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 8 August 2016.

See appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), LILACS (Appendix 4), ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We handsearched the reference lists of the identified relevant studies for additional citations. We also contacted specialists in the area and the main authors of included trials about unpublished data as well as pharmaceutical companies for further details of published and unpublished trials.

Data collection and analysis

Selection of studies

Two authors (RED and EJC) independently screened the trials identified by the literature search. We obtained full copies of all potentially or definitely relevant articles. We resolved disagreements by discussion and consulted each other for quality assurance of the processes. We documented reasons for exclusion for any study we rejected after viewing full copies in the 'Characteristics of excluded studies' table.

Data extraction and management

Two authors (RED and EJC) independently extracted data. We resolved any discrepancies by discussion. We used a standard data extraction form to record the following information: characteristics of the study (design, methods of randomisation), participants, interventions and outcomes (types of outcome measures, adverse events). One author (ECJ) entered all data into RevMan 5 (RevMan 2014). The second author (RED) independently checked the data entered.

Assessment of risk of bias in included studies

We assessed risk of bias using the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the following six separate criteria: random sequence generation, allocation concealment, masking (blinding), incomplete outcome data, selective reporting and other types of bias. See Table 1 for further information on each parameter.

Firstly, we copied information that was relevant for making a judgment on a criterion from the original publication into an assessment table. If study authors provided additional information, we entered it in the table along with an indication that this was unpublished information. Two review authors (RED and ECJ) independently made a judgment as to whether the risk of bias for each criterion was low, uncertain, or high. We resolved disagreements by discussion.

When we classified trials as being at low risk of bias in sequence generation, allocation concealment, masking, incomplete data and selective outcome reporting, we considered them to be trials at low risk of bias. If the protocol was available, we compared the pre-specified outcomes with the outcomes reported in the Results to assess selective reporting bias. Otherwise, we used the primary trial report to compare outcomes listed in the Methods section with those in the Results.

We recorded this information for each included trial in 'Risk of bias' tables in RevMan 5 (RevMan 2014) and summarised the risk of bias for each study in a summary 'Risk of bias' figure and graph.

Measures of treatment effect

Binary outcomes

For dichotomous data (proportion of successful procedures and adverse outcomes), we used the risk ratio (RR) as the effect measure with 95% confidence intervals (CIs).

Continuous outcomes

For continuous data (socket motility and prosthesis motility, degree of vascularisation, sphere size, cosmetic effect, and quality of life), we presented the results as mean differences (MDs) with 95% CIs. When pooling data across studies we would have estimated the MD if different trials measured the outcomes in the same way. We would have used the standardised mean difference (SMD) to combine trials that measure the same outcome but used different methods.

Unit of analysis issues

The unit of analysis was each participant, as only a minority would be anophthalmic in both eyes.

Dealing with missing data

An intention-to-treat analysis (ITT) considers data from all trial participants allocated to an intervention whether they received the intervention or not. We planned to impute an outcome for a dropout rate of 5%. For each trial we planned to report whether or not the investigators stated if the analysis was performed according to the ITT principle. If participants were excluded after allocation, we planned to report any details provided in full.

Furthermore, we planned to perform the analysis on an ITT basis whenever possible (Newell 1992). Otherwise, we adopted the available case analysis.

We attempted to contact study authors for missing data if necessary.

Assessment of heterogeneity

We quantified inconsistency among the pooled estimates using the Chi^2 test for heterogeneity. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error (Higgins 2003). I^2 = [(Q - df)/Q] x 100% test, where Q is the Chi^2 statistic and df its degrees of freedom. We

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assessed heterogeneity between the trials by visual examination of the forest plot to check for overlapping CIs, using the Chi^2 test for heterogeneity with a 10% level of significance, and the I^2 statistic. We classified heterogeneity using the following I^2 values.

- 0 to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting (see Assessment of risk of bias in included studies), we would have assessed the likelihood of potential publication bias using funnel plots had there been at least 10 trials. If small studies in a meta-analysis showed larger treatment effects, we would have considered other causes including selection biases, poor methodological quality, heterogeneity, artefactual causes and chance.

Data synthesis

We ana lysed data as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If three or more studies had been included in a meta-analysis, we would have used the random-effects model, and if there were substantial heterogeneity, we would have investigated the source of heterogeneity by conducting a subgroup analysis. As there were fewer than three studies, we described the clinical characteristics of the included studies in tables.

Subgroup analysis and investigation of heterogeneity

In the case of excessive clinical heterogeneity (I^2 > 50%), we would have used subgroup analyses to pool the results. Subgroup analyses are secondary analyses in which the participants are divided into groups according to shared characteristics, and outcome analyses are conducted to determine if any significant treatment effect occurs according to that characteristic. If data had permitted, we would have carried out the following subgroup analyses, as we hypothesised that the effect of the interventions might be different due to variations in the surgical techniques, type or size of material used, and age.

1. Types of anophthalmic reconstructions (enucleation and evisceration).
2. Different implant sizes (small, medium, and large, approximating the volume of a 16 mm, 18 mm and 20 mm sphere).
3. Different types of non-integrated and integrated materials.
4. Different ages: adults (aged 18 to 65 years) versus older adults (66 to 70 years) versus children and adolescents (17 years old or younger).

Sensitivity analysis

Had there been an adequate number of studies, we would have performed a sensitivity analysis to assess methodological decisions and the robustness of the results. We would have included the following factors in the sensitivity analysis, separating studies according to:

1. trials with low risk of bias versus those with high risk of bias; and
2. rates of withdrawal for each outcome (greater than 5%).

Summary of findings and assessment of the certainty of the evidence

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes (the proportion of successful procedures at one year or more after surgery; the proportion of successful procedures after five years and; socket and prosthesis motility; cosmetic effect; any adverse outcomes and quality of life) in our review and construct a 'Summary of findings' table using the GRADE software (GRADEpro 2015). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The assessment of the quality of a body of evidence considers within-study risk of bias (methodologic quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 407 references (Figure 1). The Cochrane Information Specialist removed 69 duplicate records, and we screened the remaining 338 reports. We rejected 259 records after reading the abstracts and obtained the full-text reports of 79 references for further assessment. We identified three studies that met the inclusion criteria (Colen 2000; Shome 2010; Tari 2009). We assessed and excluded a further 76 references; see Characteristics of excluded studies for details.

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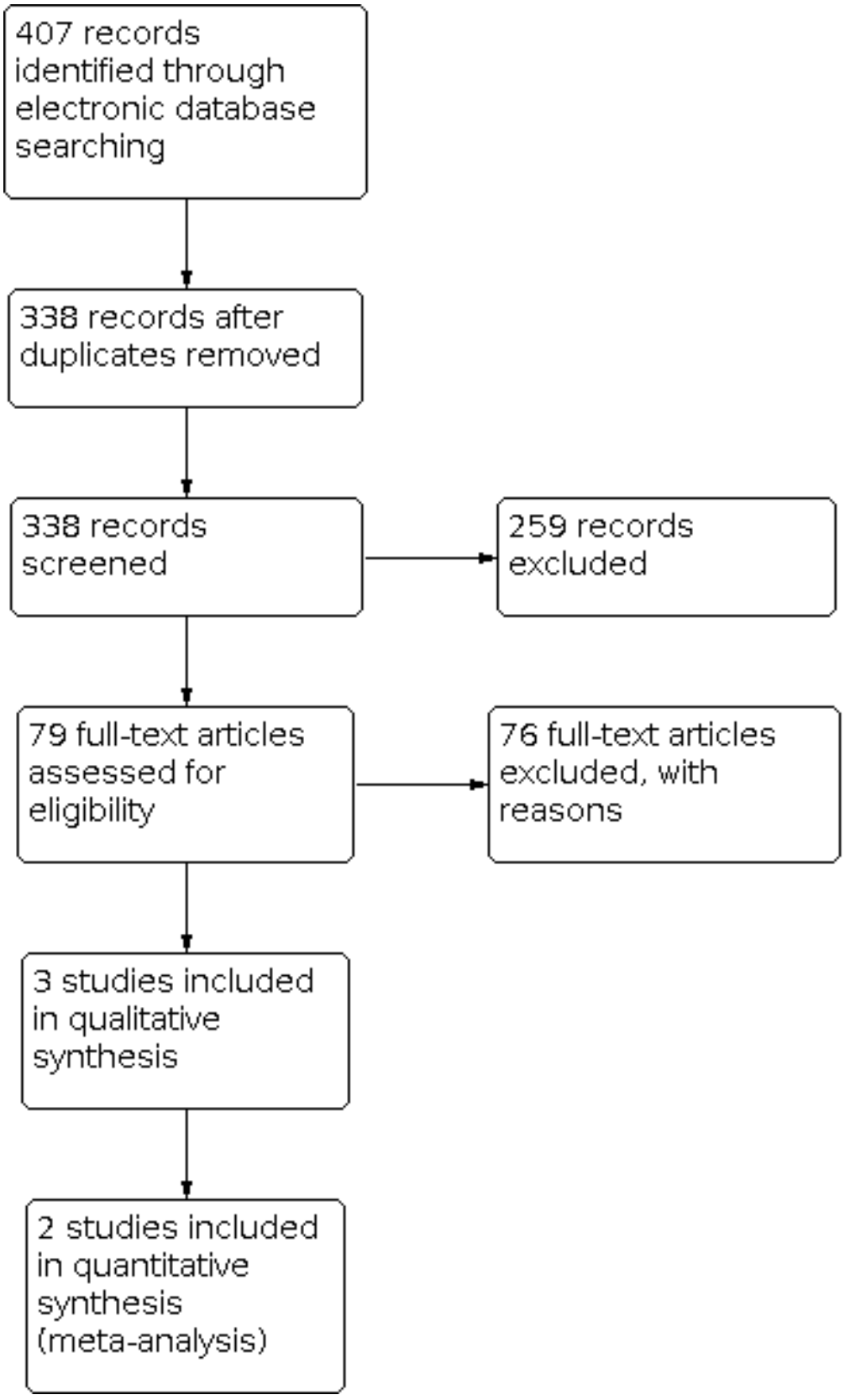
Figure 1. Study flow diagram.



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Included studies

See Characteristics of included studies and Table 2.

We included three trials with a total of 284 participants (Colen 2000; Shome 2010; Tari 2009).

Design

Colen 2000 was a multicentre randomised clinical trial, while Tari 2009 was a single-centre randomised clinical trial, and Shome 2010, a randomised trial did not report whether it took place in one or more centres.

Participants

Tari 2009 took place in Tehran University Eye Research Center, Tehran, Iran. The quadrisection group consisted of 50 participants: 35 men and 15 women with a mean age of 42.32 years. The HA group consisted of 50 participants: 41 men and 9 women with a mean age of 39.56 years. The reason(s) for operation in the quadrisection group were: a painful blind eye (n = 36), cosmetic unacceptability (n = 9) and endophthalmitis (n = 8). In the other group, there were 36 participants who had a painful blind eye; 6 cited cosmetic unacceptability; 5, acute trauma; and three were attributed to the other group.

Shome 2010 took place in Hyderabad, India; however, authors did not specify the institution, nor did they report the age, sex or health status details of the 150 participants.

Colen 2000 was a multicentre trial in the Rotterdam Eye Hospital, Rotterdam, and in the University Medical Center, Utrecht, Netherlands. The hydroxyapatite group consisted of 14 participants: seven men and seven women with a mean age of 64.0 years. In this group, six participants had the implant on the right side and eight on the left side. The acrylic group consisted of 16 participants: nine men and seven women with a mean age of 57.8 years. In this group, nine participants had the implant on the right side and seven on the left side. Thirty-four participants were eligible for the study, and 30 were ana lysed. All participants had intraocular melanoma.

Interventions

Colen 2000 studied hydroxyapatite (integrated group) (n = 14) and acrylic implants (non-integrated group) (n = 16). All participants underwent the enucleation technique. The follow-up was three months.

Shome 2010 compared PMMA (non-integrated group) (n = 50) versus PMMA myoconjunctival (non-integrated group) (n = 50) versus integrated porous polyethylene (integrated group) (n = 50). The mean follow-up of the participants was 16.4 months in the traditional PMMA group, 17.3 in the myoconjunctival PMMA group, and 15.6 in the porous polyethylene group.

Tari 2009 compared evisceration plus quadrisection of sclera with alloplastic implantation (non-integrated group) (n = 50) versus enucleation with HA (integrated group) (n = 50). The mean follow-up was 11.6 months for quadrisection and 13.2 months for HA.

Outcomes

Colen 2000 evaluated motility, saccadic gain and saccadic symmetry.

Shome 2010 measured implant and prosthesis movement as well as implant displacement and exposure.

Tari 2009 evaluated the presence or absence of exposure or extrusion and deep superior sulcus deformity along with implant motility.

Excluded studies

We excluded 76 studies after obtaining full-text reports, as they did not meet the inclusion criteria. See the Characteristics of excluded studies for study names and the reasons for exclusion.

Risk of bias in included studies

See: Figure 2; Figure 3.

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

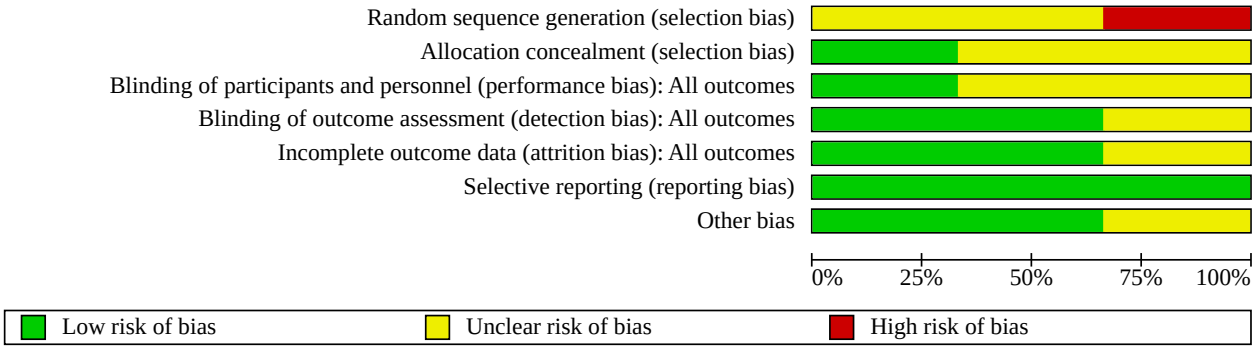

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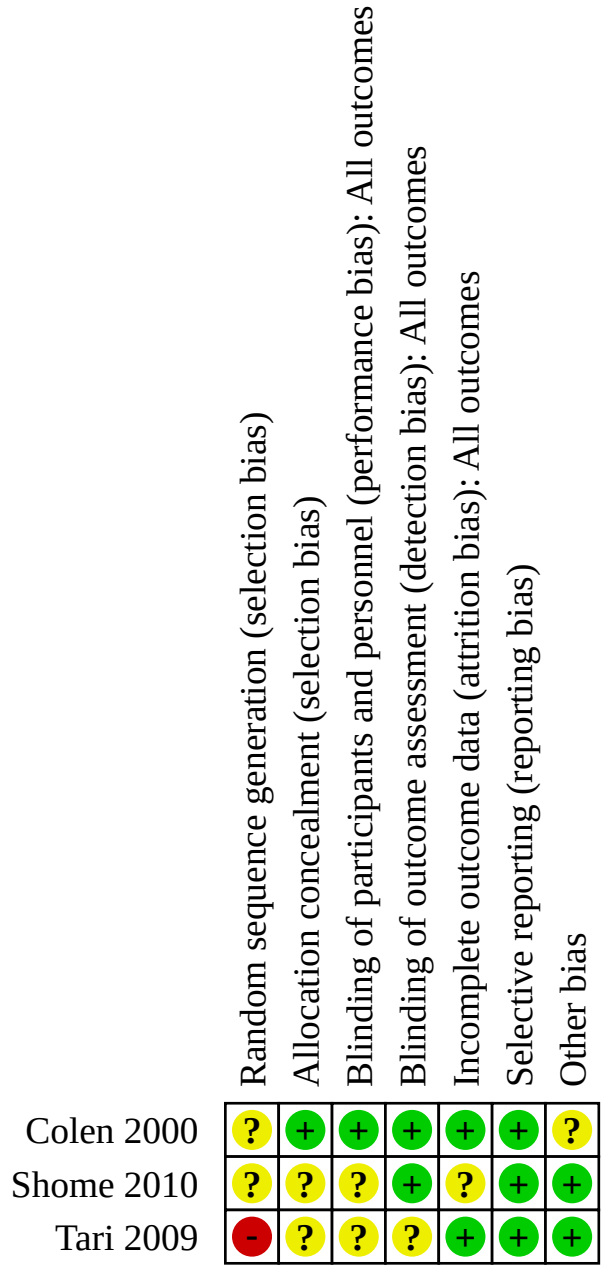
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We classified Colen 2000 and Shome 2010 as being at unclear risk of bias for random sequence allocation due to the lack of information reported in the papers. However, Tari 2009 used an alternative method to randomise participants, and we judged the risk of bias to be high. With regard to allocation concealment, only Colen 2000 reported the use of an envelope to mask the randomisation (low risk of bias) while Shome 2010 and Tari 2009 did not report this domain (unclear risk of bias).

Blinding

The masking of personnel does not apply for the clinical question under study, so we did not evaluate it in this review.

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Only Colen 2000 reported that participants were unaware of the type of implant (low risk of bias), while Shome 2010 and Tari 2009 did not report information related to this domain (unclear risk of bias).

In both Colen 2000 and Shome 2010, the investigators who recorded the outcomes were unaware of the type of implant, so we assessed these studies as being at low risk of detection bias.

Incomplete outcome data

With regard to incomplete outcome data, in Colen 2000 there was only 11.77% of dropouts and in Tari 2009 all participants completed the study (low risk of bias). Shome 2010 did not report on the number of participants completing the study (unclear risk of bias).

Selective reporting

There was no evidence of selective reporting in any of the included studies (low risk of bias) (Colen 2000; Shome 2010; Tari 2009).

Other potential sources of bias

There was no evidence of any conflict of interest in Shome 2010 and Tari 2009 (low risk of bias), and Colen 2000 did not report on it (unclear risk of bias).

Effects of interventions

See: **Summary of findings 1** Summary of findings

Please see Table 3 and Summary of findings 1.

We were unable to pool data from Shome 2010 and Tari 2009 in a meta-analysis because of the different surgical techniques used (evisceration versus enucleation) and due to the heterogeneity among the clinical outcomes ana lysed.

We did not include Colen 2000 in the meta-analysis as it did not report comparative effectiveness data. The authors compared vertical versus horizontal saccades gain, symmetry and curvilinearity between the operated and fellow eye instead of comparing it between both the intervention and comparator groups.

Proportion of successful procedures at one year and up to five years after surgery (no exposure/extrusion)

We found no statistically significant difference in the proportion of participants needing secondary reconstruction of the anophthalmic socket, implant extrusion or implant removal in the groups receiving integrated versus non-integrated implants at one year or more after surgery. We compared HA versus alloplastic evisceration in one trial (RR 1.02, 95% CI 0.95 to 1.09, P = 0.56, Tari 2009; N = 100), and in another single trial, we compared both PMMA traditional and myoconjunctival versus porous polyethylene (RR 0.92, 95% CI 0.84 to 1.01, P = 0.07, Shome 2010; N = 150).

Proportion of successful procedures after five years

None of the included studies reported on this outcome.

Socket and prosthesis motility

Two studies reported on socket and prosthesis motility (Shome 2010; Tari 2009). Follow-up for Shome 2010 was 16.4 months in the PMMA traditional group, 17.3 months in the PMMA myoconjunctival group, and 15.6 months in the porous polyethylene group; for Tari 2009, follow-up was 11.6 months for non-integrated and 13.2 months for integrated implants.

There was a statistically significant difference favouring the non-integrated (alloplastic) implant compared to the integrated (HA) with regard to horizontal implant motility in one trial (MD −3.35 mm, 95% CI −4.08 to −2.62, P < 0.001; Tari 2009; N = 100). In contrast, there was a statistically significant difference favouring the integrated (PP) implant compared to the non-integrated (PMMA traditional) implant in another (MD 1.96 mm, 95% CI 1.01 to 2.91, P < 0.001; Shome 2010; N = 100). There was no statistically significant difference with regard to horizontal implant motility between the integrated (PP) and non-integrated implants (PMMA myoconjunctival) in a single trial (MD −0.57 mm, 95% CI −1.63 to 0.49, P = 0.29; Shome 2010; N = 100).

With regard to vertical implant motility, there was a statistically significant difference favouring the non-integrated (alloplastic) implant compared to the integrated (HA) implant in one trial (MD −2.76 mm, 95% CI −3.45 to −2.07, P < 0.001, Tari 2009; N = 100). However, there was a statistically significant difference favouring the integrated (PP) implant compared to the non-integrated (PMMA traditional) implant in another (MD 3.12 mm, 95% CI 2.36 to 3.88, P < 0.001, Shome 2010; N = 100). The same single trial showed no statistically significant difference for vertical implant motility between the integrated (PP) and non-integrated (PMMA myoconjunctival) implants (MD −0.20 mm, 95% CI −1.28 to 0.88, P = 0.72, Shome 2010; N = 100).

Degree of vascularisation measured by magnetic resonance imaging

None of the included studies reported on this outcome.

Sphere size before and after surgery

None of the included studies reported on this outcome.

Cosmetic effect (self-reported)

None of the included studies reported on this outcome.

Quality of life measures

None of the included studies reported on this outcome.

Economic data

Two studies reported on economic data (Shome 2010; Tari 2009).

Shome 2010 reported that the costs of the porous polyethylene implant (integrated) is approximately USD 300.00 compared to the PMMA non-integrated implant that costs around USD 2.00.

Tari 2009 also quoted a lesser cost in the alloplastic compared to porous implant (integrated).

Adverse events

Shome 2010 was the only trial to report on this outcome.

There was no statistically significant difference between the non-integrated implant (PMMA traditional and myoconjunctival) versus the integrated (PP) implant (RR 17.82, 95% CI 0.98 to 324.67, P = 0.05, Shome 2010; N = 150).

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Furthermore, Shome 2010 reported that 6/50 participants from the traditional PMMA group presented significant superior sulcus deformity, and Tari 2009 reported that 10/50 and 7/50 participants in the alloplastic and HA groups, respectively, presented the same deformity.

DISCUSSION

Summary of main results

This review examined the effect of integrated versus non-integrated implants for treating anophthalmic sockets. We included three studies with a total of 280 participants. Overall, the quality of the included studies was low. Given the limited number of included studies, it was not possible to assess reporting bias, perform sensitivity analyses or explore all the planned subgroup analyses according to type of reconstruction and material, implant size and age. Because of our comprehensive search strategy and contact with experts in the field, we are confident that we have mapped all clinical trials of integrated versus non-integrated implants for treating anophthalmic sockets.

We saw very different results and effect estimates in these two trials; in the individual trials, a pooled average effect is not informative. There are several characteristics of these trials that could perhaps explain the differences: Shome 2010 used two different enucleation techniques (i.e. traditional versus myoconjunctival) while Tari 2009 used enucleation and scleral quadrisection evisceration. In addition, Tari 2009 presented a high risk of bias related to the random sequence generation, while Shome 2010 did not report the methods of the randomisation process.

Overall completeness and applicability of evidence

We think that there is not enough evidence to draw a robust conclusion, and this is not useful to guide clinical practice.

Quality of the evidence

The methodological quality of the included studies was generally low. Methodological aspects of all studies had an unclear risk of bias for masking of participants and personnel (performance bias) (Shome 2010; Tari 2009); only Colen 2000 masked personnel and participants. Only Colen 2000 and Shome 2010 masked outcome assessors to protect the reliability of results. For sequence generation, we assessed Tari 2009 as being at high risk of bias. Only Colen 2000 reported adequate methods of allocation concealment. Shome 2010 did not report whether the participants completed the study (unclear risk of bias); however, the remaining trials were at low risk of bias for this domain (Colen 2000; Tari 2009). We judged all the studies to be at low risk of bias for selective reporting and two studies to be at low risk of other bias (Shome 2010; Tari 2009).

Overall, this review contains very low-certainty evidence for the following reasons: the risk of bias was generally unclear for two of the three included trials; one trial was at high risk of bias for random sequence generation, as it used an alternative method (Tari 2009); the directness of the evidence was limited by the fact that there were only two studies that dealt with a population from low- and middle-income countries, there were different effects results between the included studies in the analysis due to the different surgical techniques used (enucleation and evisceration); we could not assess risk of publication bias due to the small number of studies; and the precision of effect estimates was very large.

Potential biases in the review process

We made every attempt to reduce the risk of bias in the review process, using broad inclusion criteria and a comprehensive search strategy to identify eligible trials. There were no language restrictions, and we obtained translations of non-English trials wherever possible. However, unclear reporting of trial methods and data limited the extent to which we could meaningfully compare all relevant data from the identified trials.

Agreements and disagreements with other studies or reviews

One published review aimed to evaluate biomaterials for orbital implants and ocular prostheses (Baino 2014). The authors described in a qualitative way the different types of implants and confirmed the need for well-designed, long-term clinical trials on orbital implants.

Although the first descriptions of integrated implants appeared in the 1940s, the introduction of natural hydroxyapatite in the 1980s marked a rise in their popularity. The main advantage seen in this material was the increased mobility it conferred due to the placement of a peg that fixed the prothesis to the eye socket (Perry 1990). However, complications with the coupled implants began to emerge almost immediately, and pegs have since fallen out of use. Thus, the main motivation for integrated implants has ceased to exist.

Since then, various new implants have become available, making it very important to determine if integrated implants are superior to and safer than non-integrated ones. Available literature supports the superiority of integrated implants, but most of these studies are from the 1990s and usually used retrospective, non-randomised or case study methodology (Ashworth 1996; Blázquez 1998). Many of them do not compare implants of different categories. However, a recent case series proportional meta-analysis showed lower chance of exposure with the use of PP implants compared to bioceramic implant for anophthalmic socket reconstruction (Schellini 2016).

Although there were few randomised studies in general, the greatest difficulty was in finding studies that dealt with non-integrated implants, especially those involving PMMA or silicone implants.

None of the three studies included in this review is categorical about the superiority of the tested implants. Thus, doubt about the superiority of integrated implants persists. And a tangible point that favours non-integrated implants is the dramatic price difference, as Shome 2010 highlighted that the porous polyethylene (integrated) implant costs approximately USD 300.00 compared USD 2.00 for the PMMA (non-integrated) implant.

The most important contribution of our review is our finding that non-integrated implants may be superior with regard to exposure or extrusion implants. Another study (not included in this review) also comments on higher exposures rates in the porous implants (Custer 2003).

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However, given the quality of the included studies, we believe it is very important to have more studies that employ appropriate randomisation and masking in order to definitively determine which kind(s) of implants are better.

AUTHORS' CONCLUSIONS

Implications for practice

Current very low-certainty evidence from three small published randomised controlled trials does not provide sufficient evidence to assess the effect of integrated and non-integrated material orbital implants for treating anophthalmic sockets. This review underlines the need to conduct further well-designed trials in this field.

Implications for research

This review highlights the need for continued research into the selection of the appropriate implants to treat anophthalmic sockets. The low statistical power of available data provides strong justification for designing new randomised trials that can fill the gap in existing knowledge. These trials in particular should compare integrated versus non-integrated orbital implants with the same technique (i.e. enucleation or evisceration) for the treatment of anophthalmic socket with a minimum follow-up of one year and larger sample size to evaluate proportion of successful procedures and adverse events.

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CHARACTERISTICS OF STUDIES

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

Colen 2000

Study characteristics	
Methods	Study design: randomised controlled trial Multicentre or single-centre: multicentre (two centres) Setting: the Rotterdam Eye Hospital, Rotterdam, and in the University Medical Center, Utrecht, Netherlands Period: February 1997 to May 1999 Sample size: a difference of 0.10 or more between the two types of implants would be clinically relevant Follow up: 3 months
Participants	34 patients eligible for the study; 30 ana lysed Mean age: 64.0 years for hydroxyapatite group and 57.8 years for acrylic group Sex: 7 men and 7 women for hydroxyapatite group; 9 men and 7 women in acrylic group Inclusion criteria: patients with intraocular melanoma, without extrascleral extension on ultrasound examination Exclusion criteria: patients with a visual acuity of less than 6/12 (20/40) in the remaining eye and patients with a history of abnormal eye motility, strabismus, any eye surgery, and chronic inflammatory ocular or orbital disorders
Interventions	Hydroxiapatite (integrated group) (n = 14) versus acrylic (non-integrated group) (n = 16) There was no peg device. All participants underwent the enucleation technique (scleral-covered spherical orbital implant).
Outcomes	Motility; saccadic gain (i.e. dividing the saccadic amplitude by the target amplitude) and saccadic symmetry (i.e. artificial eye amplitude divided by health eye amplitude)
Notes	21 healthy volunteers served as control participants. The reason for surgery was intraocular melanoma. This study was supported by Rotterdam Eye Hospital Research Fund, Rotterdam, Netherlands

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

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Colen 2000 *(Continued)*

Allocation concealment (selection bias)	Low risk	Selection by opening an envelope with a previously randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were unaware of the type of enucleation implant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators who recorded the eye movements were unaware of the type of enucleation implant.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11.77% dropouts
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Unclear risk	No evidence; no report of conflict of interest.

Shome 2010

Study characteristics	
Methods	Study design: randomised controlled trial Multicentre or single-centre: not reported Setting: Hyderabad, India Period: July 2004 to June 2007 Sample size: to ascertain a 30% difference with 80% power and 5% error in between the 3 groups, inclusion of a minimum of 39 patients in each group was necessary. Follow up: mean follow-up in months per group: PMMA traditional, 16.4; PMMA myoconjunctival, 17.3 and; porous polyethylene, 15.6.
Participants	150 participants Mean age: not reported Sex: not reported Inclusion criteria: not reported Exclusion criteria: participants who had undergone prior radiotherapy and periocular chemotherapy
Interventions	Integrated porous polyethylene (PP) (integrated group) (n = 50) versus PMMA traditional (non-integrated group) (n = 50) versus PMMA myoconjunctival (non-integrated group) (n = 50) There was no peg device. All patients underwent enucleation technique. In the PP group, the enucleation was performed using the scleral cap technique. In the PMMA traditional group, the enucleation was done with muscle imbrication.

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Shome 2010 *(Continued)*

	In the PMMA myoconjunctival group, the enucleation was done with myoconjunctival technique, which is an alternative to muscle imbrication.
Outcomes	The primary outcome measured was to compare and evaluate implant and prosthesis movement among these 3 groups of patients. The secondary outcomes were implant displacement and exposure.
Notes	There was no report of the reasons for surgery. This study was supported by Hyderabad Eye Institute, Hyderabad, India.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masked observer
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence. There was no proprietary or commercial interest in any materials discussed in this article.

Tari 2009

Study characteristics

Methods	Study design: quasi-randomised controlled trial Multicentre or single-centre: single-centre Setting: Tehran University Eye Research Center, Tehran, Iran Period: January 2006 to June 2007 Sample size: not reported Follow up: 11.56 months for non-integrated group and 13.16 months for integrated group
Participants	100 patients. Mean age: 42.32 years for evisceration group and 39.56 years for enucleation group

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Tari 2009 *(Continued)*

	Sex: 15 women and 35 men for evisceration group; and 9 women and 41 men for evaluation group Inclusion criteria: not reported Exclusion criteria: significant preoperative motility abnormalities, cases of severe phthisis, and cases that were not followed up for at least 4 months
Interventions	Enucleation with HA (integrated group) (n = 50) versus evisceration plus quadrisection of sclera with alloplastic implantation (non-integrated group) (n = 50) There was no peg device. Enucleation via the traditional technique and evisceration plus scleral quadrisection
Outcomes	The primary outcome was the presence or absence of exposure or extrusion and deep superior sulcus deformity, and the secondary outcome was implant motility measured by detecting the amount of overlying conjunctival movement.
Notes	Reasons for surgery were: painful blinded eye, cosmetic unacceptability, acute trauma, and endophthalmitis. The reason for the surgery was the same for both groups. However, all the trauma patients had enucleation and all the endophthalmitis patients had evisceration. There was no financial support.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly divided in 2 groups for alternate surgical plans including enucleation with HA implantation or evisceration plus quadrisection of sclera with alloplastic implantation.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence. The authors declare no financial support or relationships that may pose a conflict of interest.

HA: hydroxyapatite; **PMMA**: polymethylmethacrylate; **PP**: porous polyethylene.

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

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Study	Reason for exclusion
Agahan 2004	RCT, but evaluated two types of PMMA (non-integrated) implants
Alwitry 2007	Case series
Arat 2003	Retrospective study
Ashworth 1996	Case series
Ashworth 1998	Case series
Blázquez 1998	Non-randomised trial
Chen 1996	Case series
Chen 2000	Case series
Chen 2006	Retrospective study
Choi 2005	Retrospective study
Chuah 2004	Retrospective study
Clauser 2004	Case series
Custer 1999	Non-randomised clinical trial
Custer 2006	Case series
De Potter 1994	Case series
Downes 1992	Case series
Dutton 1991	Case series
Filatova 2008	Case series.
Genevois 2004	Retrospective study
Georgiadis 1998a	Case series
Georgiadis 1998b	Case series
Georgiadis 1999	Case series
González-Candial 2007	Retrospective study
Guillinta 2003	Case series
Gupta 2007	Another clinical question (wrapping material for hydroxyapatite implants)
Hashimoto 1994	Cross-sectional study
Hoyama 2000	Retrospective study
Iordanidou 2004	Case series

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Study	Reason for exclusion
Jordan 2004	Retrospective study
Jordan 2010	Retrospective study
Kamal 2012	Retrospective study
Karesh 1994	Case series
Kassaee 2006	Case series
Kim 2004	Case series
Klapper 2003	Retrospective study
Krastinova 2001	Retrospective study
Lee 2002	Retrospective study
Li 2001	Retrospective study
Li 2010	RCT, but evaluated only integrated orbital implants
Liang 2006	Retrospective study
Liu 2005	Non-randomised clinical trial
Liu 2012	Retrospective study
Long 2003	Another clinical question (wrapped and unwrapped hydroxyapatite orbital)
Lopes 2011	Retrospective study
Lucci 2007	Another clinical question (porous polyethylene either spherical or quad-motility orbital implant)
Lukáts 2002	Case series
Lyle 2007	Retrospective study
Manteiga 2006	Case series
Massry 1995	Retrospective study
Massry 2001	Retrospective study
Moura 2007	Case series.
Naik 2007	Another clinical question (Medpor and Medpor-Plus orbital implants)
Narikawa 2011	Retrospective study
Nikolaenko 2006a	Case series
Nikolaenko 2006b	Case series

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Study	Reason for exclusion
Ortiz 2012	Cross-sectional
Pan 2003	Retrospective study
Perry 2002	Case series
Perry 2004	Retrospective study
Saeed 2000	Case series
Schellini 2000	Retrospective study
Schellini 2007	Retrospective study
Sebastiá 2000	Non-randomised clinical trial
Shields 19993	Case series
Shkromida 1989	Case series
Sires 1998	Case series
Song 2002	Case series
Soto 2003	Cross-sectional study
Stephen 1999	Case series
Tabatabaee 2011	Retrospective study
Van Acker 2001	Case series
Villarroel 2001	Case series
Vittorino 2007	Retrospective study
Wang 2009	Retrospective study
Woog 2004	Case series
Yoon 2008	Retrospective study

PMMA: polymethylmethacrylate; **RCT**: randomised controlled trial.

ADDITIONAL TABLES

Table 1. Risk of bias criteria

Random sequence generation	Was the allocation sequence adequately generated, for example with random number tables or computer-generated random numbers? We assessed trials as being at low risk of bias (the method used is either adequate or unlikely to introduce confounding), uncertain risk of bias (there is insufficient information to assess whether the method used is likely to introduce confounding) or high

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Table 1. Risk of bias criteria *(Continued)*

	risk of bias (the method used (e.g. quasi-randomised trials) is improper and likely to introduce confounding).
Allocation concealment	Was allocation adequately concealed in a way that would not allow either the investigators or the participants to know or influence allocation to an intervention group before an eligible participant was entered into the study (for example using central randomisation or sequentially numbered, opaque, sealed envelopes held by a third party)? We judged trials to be at low risk of bias (the method used (e.g. central allocation) is unlikely to induce bias in the final observed effect), uncertain risk of bias (there is insufficient information to assess whether the method used is likely to induce bias in the estimate of effect) or high risk of bias (the method used (e.g. open random allocation schedule) is likely to induce bias in the final observed effect).
Masking (blinding)	We judged the possibility of masking being done on both participants and outcome assessors. We did not consider masking of personnel as this is not feasible in these trials. Were the participants and study outcome assessors masked from knowledge of which intervention a participant received? We judged trials to be at low risk of bias (the outcome measurement is not likely to be influenced by lack of masking), uncertain risk of bias (there is insufficient information to assess whether the type of masking used is likely to induce bias in the estimate of effect) or high risk of bias (the outcome or the outcome measurement is likely to be influenced by lack of masking).
Incomplete outcome data	Were incomplete outcome data adequately addressed? Incomplete outcome data essentially include: attrition, exclusions and missing data. If any withdrawals occurred, were they described and reported by treatment group with reasons given? We recorded whether or not there were clear explanations for withdrawals and dropouts in the treatment groups. An example of an adequate method to address incomplete outcome data is the use of an intention to-treat analysis (ITT). We judged trials to be at low risk of bias (the underlying reasons for missing data are unlikely to make treatment effects depart from plausible values, or proper methods have been employed to handle missing data), uncertain risk of bias (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias in the estimate of effect), or high risk of bias (the crude estimate of effects (e.g. complete case estimate) clearly was biased due to the underlying reasons for missing data, and the methods used to handle missing data are unsatisfactory).
Selective reporting	Are reports of the study free from any suggestion of selective outcome reporting? This was interpreted as no evidence that statistically non-significant results might have been selectively withheld from publication, for example selective under-reporting of data or selective reporting of a subset of data. We judged trials to be at low risk of bias (the trial protocol is available and all of the trials prespecified outcomes that are of interest in the review have been reported or similar), uncertain risk of bias (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting), or high risk of bias (not all of the trials prespecified primary outcomes have been reported or similar).
Other sources of bias	Was trial funded from parties that might not have conflicting interests (e.g. an antibacterial agent manufacturer), or any academic, professional, financial or other benefits to the person responsible for the trial were independent of the direction or statistical significance of trial results? We assessed trials as being at low risk of bias (if trial funding did not come), unclear risk of bias (if the source of funding was not clear, or if it was unclear whether the person responsible for the trial stands to benefit according to the direction or statistical significance of trial results) or high risk of bias (if the trial's source of funding had a conflict of interest, or if any academic, professional, financial or other benefits to the person responsible for the trial are dependent on the direction or statistical significance of trial results).

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Table 2. Clinical characteristics of the included studies

Study ID	No of participants randomised	Material		Technique used	Mean follow-up period (months)
Colen 2000	34	**Integrated**	Hydroxyapatite	Enucleation	3[a]
		Non-integrated	Acrylic	Enucleation	
Shome 2010	150	**Integrated**	Porous polyethylene	Enucleation	PP: 15.6
		Non-integrated	Polymethylmethacrylate	Enucleation (myoconjunctival or traditional)	Traditional: 16.4 Myoconjuntival: 17.3
Tari 2009	100	**Integrated**	Hydroxyapatite	Enucleation	13.16
		Non-integrated	Alloplastic	Evisceration	11.56

[a]Absolute number.

Table 3. Clinical outcome

Study ID	Type of material (surgical technique)		Proportion of successful procedures at 1-5 years after surgery (no exposure/extrusion)	Adverse outcomes (i.e.infection or migration)	Horizontal implant motility (mm)	Vertical implant motility (mm)
	Integrated	**Non-integrated**	**RR (95% CI)**	**RR (95% CI)**	**MD (95% CI)**	**MD (95% CI)**
Colen 2000	HA (enucleation)	Acrylic (enucleation)	—	—	—	—
Shome 2010	PP (enucleation)	PMMA traditional (enucleation)	0.92 (0.84 to 1.01) N = 150	17.82 (0.98 to 324.67) N = 150	1.96 (1.01 to 2.91) N = 100	(3.12 (2.36 to 3.88) N = 100
	PP (enucleation)	PMMA myoconjunctival (enucleation)			−0.57 (−1.63 to 0.49) N = 100	(−0.20 (−1.28 to 0.88) N = 100
Tari 2009	HA (enucleation)	Alloplastic (evisceration)	1.02 (0.95 to 1.09) N = 100	—	−3.35 (−4.08 to −2.62) N = 100	(−2.76 (−3.45 to −2.07) N = 100

HA: hydroxyapatite; MD: mean difference; PMMA: polymethylmethacrylate; PP: porous polyethylene; RR: risk ratio.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Anophthalmos
#2 anophthalm*
#3 MeSH descriptor Eye Enucleation
#4 MeSH descriptor Eye Evisceration
#5 MeSH descriptor Orbit Evisceration
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Orbital Implants
#8 MeSH descriptor Eye, Artificial
#9 MeSH descriptor Prostheses and Implants
#10 ((eye* or ocular or socket or orbit* or integrated or nonintegrated or non-integrated or non integrated) near/4 implant*)
#11 ((eye* or ocular or socket or orbit* or integrated or nonintegrated or non-integrated or non integrated) near/4 reconstruct*)
#12 MeSH descriptor Hydroxyapatites
#13 MeSH descriptor Durapatite
#14 durapatite* or hydroxylapatite*
#15 BioEye or Bio-Eye
#16 ((integrated or nonintegrated or non-integrated or non integrated) near/2 sphere*)
#17 Interpore-500 or Interpore 500 or Interpore500
#18 Interpore-200 or Interpore 200 or Interpore200
#19 Alveograf or Calcitite or Ossopan or Osteogen or Periograf or Osprovit
#20 MeSH descriptor Polymethyl Methacrylate
#21 MeSH descriptor Methacrylates
#22 Polyethylene or Polythene or Medpor or LDPE or HDPE or Polymethyl Methacrylate or Polymethylmetacrylate or PMMA or Acron or Implast
#23 Methyl Acrylic Plastic or Kallocryl or Lucite or Palacos or Plexiglas or Plexiglass or Superacryl or Palavit or Perspex or Silicone or silicones
#24 MeSH descriptor Bone Cements
#25 bone cement near/3 (CMW or Surgical Simplex or Acrylic Bone)
#26 material* near/3 (integrated or nonintegrated or non-integrated or non integrated or solid or porous or wrapped)
#27 (#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 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#28 #6 AND #27

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Anophthalmos/
14. anophthalm$.tw.
15. Eye Enucleation/
16. Eye Evisceration/
17. Orbit Evisceration/
18. or/13-17
19. Orbital Implants/
20. Eye, Artificial/
21. "Prostheses and Implants"/
22. ((eye$ or ocular or socket or orbit$ or integrated or nonintegrated or non-integrated or non integrated) adj4 implant$).tw.
23. ((eye$ or ocular or socket or orbit$ or integrated or nonintegrated or non-integrated or non integrated) adj4 reconstruct$).tw.
24. Hydroxyapatites/
25. Durapatite/
26. (durapatite$ or hydroxylapatite$).tw.

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27. (BioEye or Bio-Eye).tw.
28. ((integrated or nonintegrated or non-integrated or non integrated) adj2 sphere$).tw.
29. (Interpore-500 or Interpore 500 or Interpore500).tw.
30. (Interpore-200 or Interpore 200 or Interpore200).tw.
31. (Alveograf or Calcitite or Ossopan or Osteogen or Periograf or Osprovit).tw.
32. Polymethyl Methacrylate/
33. Methacrylates/
34. (Polyethylene or Polythene or Medpor or LDPE or HDPE or Polymethyl Methacrylate or Polymethylmetacrylate or PMMA or Acron or Implast).tw.
35. (Methyl Acrylic Plastic or Kallocryl or Lucite or Palacos or Plexiglas or Plexiglass or Superacryl or Palavit or Perspex or Silicone or silicones).tw.
36. Bone Cements/
37. (bone cement adj3 (CMW or Surgical Simplex or Acrylic Bone)).tw.
38. (material$ adj3 (integrated or nonintegrated or non-integrated or non integrated or solid or porous or wrapped)).tw.
39. or/19-38
40. 18 and 39
41. 12 and 40

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. anophthalmia/
34. anophthalm$.tw.
35. enucleation/
36. or/33-35
37. orbit implant/
38. visual prosthesis/
39. ((eye$ or ocular or socket or orbit$ or integrated or nonintegrated or non-integrated or non integrated) adj4 implant$).tw.
40. ((eye$ or ocular or socket or orbit$ or integrated or nonintegrated or non-integrated or non integrated) adj4 reconstruct$).tw.

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41. hydroxyapatite/
42. (durapatite$ or hydroxylapatite$).tw.
43. (BioEye or Bio-Eye).tw.
44. ((integrated or nonintegrated or non-integrated or non integrated) adj2 sphere$).tw.
45. (Interpore-500 or Interpore 500 or Interpore500).tw.
46. (Interpore-200 or Interpore 200 or Interpore200).tw.
47. (Alveograf or Calcitite or Ossopan or Osteogen or Periograf or Osprovit).tw.
48. "poly(methyl methacrylate)"/
49. (Polyethylene or Polythene or Medpor or LDPE or HDPE or Polymethyl Methacrylate or Polymethylmetacrylate or PMMA or Acron or Implast).tw.
50. (Methyl Acrylic Plastic or Kallocryl or Lucite or Palacos or Plexiglas or Plexiglass or Superacryl or Palavit or Perspex or Silicone or silicones).tw.
51. bone cement/
52.(bone cement adj3 (CMW or Surgical Simplex or Acrylic Bone)).tw.
53. (material$ adj3 (integrated or nonintegrated or non-integrated or non integrated or solid or porous or wrapped)).tw.
54. or/37-53
55. 36 and 54
56. 32 and 55

Appendix 4. LILACS search strategy

anophthalmi$ or enucleation or evisceration and eye$ or ocular or socket or orbit$ or integrated or nonintegrated or non-integrated or non integrated and implant$ or reconstruct$

Appendix 5. ISRCTN search strategy

Anophthalmia or Anophthalmic

Appendix 6. ClinicalTrials.gov search strategy

Anophthalmia or Anophthalmic

Appendix 7. ICTRP search strategy

Anophthalmia or Anophthalmic

WHAT'S NEW

Date	Event	Description
16 June 2021	Feedback has been incorporated	The Plain language summary has been amended in response to feedback about the use of the wording 'artificial eyes'.

HISTORY

Protocol first published: Issue 1, 2013
Review first published: Issue 11, 2016

CONTRIBUTIONS OF AUTHORS

Protocol
Conceiving the protocol: Silvana Schellini (SS) and Regina El Dib (RED)
Co-ordinating the protocol: RED
Writing drafts of the protocol: SS and RED
Responding to peer review comments: SS and RED
Responding to comments from the editorial base: SS and RED
Person responsible for reading and checking the protocol before submission: SS and RED

Review
Conceiving the review: Silvana Schellini (SS), Regina El Dib (RED) and Eliane C Jorge (ECJ)
Co-ordinating the review: RED

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Undertaking manual searches: ECJ and RED
Screening search results: Leandro Ramos e Silva (LRS), RED and ECJ
Organizing retrieval of papers: LRS and Joyce Farah (JF)
Screening retrieved papers against inclusion criteria: SS, RED and ECJ
Appraising quality of papers: SS, RED and ECJ
Abstracting data from papers: Yuqing Zhang (YZ) and JF
Writing to authors of papers for additional information: YZ and LRS
Obtaining additional data about papers: ECJ and LRS
Obtaining and screening data on unpublished studies: LRS and JF
Data management for the review: RED and ECJ
Data entry: RED and ECJ
Statistical data analysis: RED
Interpretation of data: SS, RED and ECJ
Statistical inferences: SS, RED and ECJ
Writing the review: SS, ECJ, LRS and RED
Guarantor for the review (one author): RED and ECJ
Person responsible for reading and checking review before submission: SS, RED and ECJ

DECLARATIONS OF INTEREST

Silvana Schellini: none known.
Regina El Dib: none known.
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Yuqing Zhang: none known.
Eliane C Jorge: none known.

SOURCES OF SUPPORT

Internal sources

- No source, Brazil

External sources

- No source, Brazil

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Anophthalmos [etiology] [*rehabilitation]; *Durapatite; Eye Enucleation [*rehabilitation]; Eye Evisceration [*rehabilitation]; *Orbital Implants [classification]; *Polyethylene; *Polymethyl Methacrylate; Prosthesis Design; Prosthesis Implantation [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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