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Infraorbital nerve block for postoperative pain following cleft lip repair in children (Review)

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[Intervention Review]

Infraorbital nerve block for postoperative pain following cleft lip repair in children

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ABSTRACT

Background

Postoperative pain is a barrier to the quality of paediatric care, the proper management of which is a challenge. Acute postoperative pain often leads to adverse functional and organic consequences that may compromise surgical outcome. Cleft lip is one of the most common craniofacial birth defects and requires surgical correction early in life. As expected after a surgical intervention in such a sensitive and delicate area, the immediate postoperative period of cleft lip repair may be associated with moderate to severe pain. Infraorbital nerve block associated with general anaesthesia has been used to reduce postoperative pain after cleft lip repair.

Objectives

To assess the effects of infraorbital nerve block for postoperative pain following cleft lip repair in children.

Search methods

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 6, 2015), MEDLINE, EMBASE, and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) from inception to 17 June 2015. There were no language restrictions. We searched for ongoing trials in the following platforms: the metaRegister of Controlled Trials; ClinicalTrials.gov (the US National Institutes of Health Ongoing Trials Register), and the World Health Organization International Clinical Trials Registry Platform (on 17 June 2015). We checked reference lists of the included studies to identify any additional studies. We contacted specialists in the field and authors of the included trials for unpublished data.

Selection criteria

We included randomised controlled clinical trials that tested perioperative infraorbital nerve block for cleft lip repair in children, compared with other types of analgesia procedure, no intervention, or placebo (sham nerve block). We considered the type of drug, dosage, and route of administration used in each study. For the purposes of this review, the term 'perioperative' refers to the three phases of surgery, that is preoperative, intraoperative, and postoperative, and commonly includes ward admission, anaesthesia, surgery, and recovery.

Data collection and analysis

Two review authors (GF and EH) independently identified, screened, and selected the studies, assessed trial quality, and performed data extraction using the Cochrane Pain, Palliative and Supportive Care Review Group criteria. In case of disagreements, a third review author (EMKS) was consulted. We assessed the evidence using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

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Main results

We included eight studies involving 353 children in the review. These studies reported different types of interventions (lignocaine or bupivacaine), observation times, and forms of measuring and describing the outcomes, making it difficult to conduct meta-analyses. In the comparison of infraorbital nerve block versus placebo, there was a large effect in mean postoperative pain scores (our first primary outcome) favouring the intervention group (standardised mean difference (SMD) -3.54, 95% confidence interval (CI) -6.13 to -0.95; very low-quality evidence; 3 studies; 120 children). Only one study reported the duration of analgesia (in hours) (second primary outcome) with a difference favouring the intervention group (mean difference (MD) 8.26 hours, 95% CI 5.41 to 11.11; very low-quality evidence) and less supplemental analgesic requirements in the intervention group (risk ratio (RR) 0.05, 95% CI 0.01 to 0.18; low-quality evidence). In the comparison of infraorbital nerve block versus intravenous analgesia, there was a difference favouring the intervention group in mean postoperative pain scores (SMD -1.50, 95% CI -2.40 to -0.60; very low-quality evidence; 2 studies; 107 children) and in the time to feeding (MD -9.45 minutes, 95% CI -17.37 to -1.53; moderate-quality evidence; 2 studies; 128 children). No significant adverse events (third primary outcome) were associated with the intervention, although three studies did not report this outcome. Five out of eight studies found no unwanted side effects after the nerve blocks. Overall, the included studies were at low or unclear risk of bias. The reasons for downgrading the quality of the evidence using GRADE related to the lack of information about randomisation methods and allocation concealment in the studies, very small sample sizes, and heterogeneity of outcome reporting.

Authors' conclusions

There is low- to very low-quality evidence that infraorbital nerve block with lignocaine or bupivacaine may reduce postoperative pain more than placebo and intravenous analgesia in children undergoing cleft lip repair. Further studies with larger samples are needed. Future studies should standardise the observation time and the instruments used to measure outcomes, and stratify children by age group.

PLAIN LANGUAGE SUMMARY

Infraorbital nerve block for pain after cleft lip surgery in children

Background

Cleft lip is one of the most common birth defects. The surgery to correct this defect can cause moderate to severe pain. Many of the drugs to reduce pain (analgesics) used in adults can have unwanted side effects in children. The treatment of the pain associated with the surgical correction of cleft lip can therefore be a challenge. One technique that can provide pain relief for these children is known as infraorbital nerve block which involves the injection of an anaesthetic around the nerve that is responsible for the sensation of touch and pain of the upper lip.

Review question

We reviewed the effectiveness of infraorbital nerve block compared with placebo ('sham' block) or other interventions for the control of pain in children having cleft lip surgery.

Study characteristics

We included eight studies with a total of 353 boys and girls, who ranged in age from 1 month to 13 years. These studies had been published up to June 2015. Three studies compared nerve block with sham block. Three studies compared nerve block with injected analgesics, and two studies compared nerve block with local anaesthesia.

Key results

The children who received the infraorbital nerve block (with lignocaine or bupivacaine) had less pain and more time between finishing surgery and needing more analgesics. These children also had less need for analgesics than those who received the sham block. The children who received the infraorbital nerve block also had less pain and were able to eat sooner than those who received injected (intravenous) analgesics. The nerve block did not appear to alter heart rate, breath rate, and blood pressure. Five out of eight studies found no unwanted side effects after the nerve blocks; the other three studies did not mention side effects.

Quality of the evidence

The overall quality of the evidence was low or very low due to the small number of children included in the studies and differences between the studies (heterogeneity) regarding the types of intervention, the observation time, and the forms of measuring and describing the outcomes. Further studies with larger numbers of children are needed.

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SUMMARY OF FINDINGS

Summary of findings 1. Infraorbital nerve block compared with placebo for cleft lip repair in children

Infraorbital nerve block compared with placebo for cleft lip repair in children

Patient or population: children with cleft lip

Settings: hospital

Intervention: infraorbital nerve block

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Infraorbital nerve block				
Pain score **control** Different scales (0 to 4 hours)	-	The mean pain in the intervention groups was -3.54 standard deviations lower (-6.13 to -0.95 lower)	-	120 (3)	⊕⊖⊖⊖ **very low** [1,2,3]	A standard deviation of 3.54 represents a large difference between groups
Duration of postoperative analgesia (in hours)	-	The mean duration of postoperative analgesia in the intervention group was 8.26 higher (5.41 to 11.11 higher)	-	60 (1)	⊕⊖⊖⊖ **very low** [1,2,4]	-
Adverse events	2 out of 3 studies reported this outcome. One study reported no differences between groups, and the other study reported more vomiting in the placebo group					
Supplemental analgesic requirements (at 4 hours)	**Low-risk population**		RR 0.05 (0.01 to 0.18)	120 (3)	⊕⊕⊖⊖ **low** [1,2]	-
	600 per 1000	**30 per 1000** (6 to132)				

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	High-risk population	
	567 per 1000	**28 per 1000** (6 to 125)
Time to feeding after surgery	This outcome was not reported	

*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; **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.

[1]Downgraded one level: few studies with small sample size.
[2]Downgraded one level due to risk of bias: randomisation and allocation concealment procedures were unclear.
[3]Downgraded one level due to inconsistency: heterogeneity in analysis.
[4]Downgraded one level due to uncertainty in outcome measurement.

Summary of findings 2. Infraorbital nerve block compared with intravenous analgesia for cleft lip repair in children

Infraorbital nerve block compared with intravenous analgesia for cleft lip repair in children

Patient or population: children with cleft lip

Settings: hospital

Intervention: infraorbital nerve block

Comparison: intravenous analgesia

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Intravenous analgesia	**Infraorbital nerve block**				

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Pain score **control** Different scales (0 to 4 hours)	-	The mean pain in the intervention groups was -1.5 standard deviations lower (-2.4 to -0.6 lower)	-	107 (2)	⊕⊖⊖⊖ **very low**[1,2,3]	A standard deviation of 1.5 represents a large difference between groups
Duration of postoperative analgesia	This outcome was not reported					
Adverse events	2 out of 3 studies reported this outcome. Both studies reported no difference between groups					
Supplemental analgesic requirements	**634 per 1000**	**171 per 1000** (82 to 349)	RR 0.27 (0.13 to 0.55)	82 (1)	⊕⊖⊖⊖ **very low** [1,2,4]	-
Time to feeding after surgery	-	The mean time to feeding in the intervention group was 9.45 lower (17.37 to 1.53 lower)	-	128 (2)	⊕⊕⊖⊖ **low** [1,2]	-

*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; **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.

[1]Downgraded one level: few studies with small sample size.
[2]Downgraded one level due to risk of bias: randomisation and allocation concealment procedures were unclear.
[3]Downgraded one level due to inconsistency: heterogeneity in analysis.
[4]Downgraded one level due to uncertainty in outcome measurement.

Summary of findings 3. Infraorbital nerve block compared with infiltration of the incision for cleft lip repair in children

Infraorbital nerve block compared with infiltration of the incision for cleft lip repair in children
Patient or population: children with cleft lip

Settings: hospital

Intervention: infraorbital nerve block

Comparison: infiltration of the incision

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Infiltration of the incision	Infraorbital nerve block			
Pain score **control**	No numeric data available; one study reported difference favouring control group only at 6 hourspostoperatively. One study reported that children in the intervention group had lower pain scores between 1 and 8 hours after the surgery				
Duration of postoperative analgesia	This outcome was not reported				
Adverse events	Of the 2 included studies, one study reported no difference between groups, and the other study did not report this outcome				
Supplemental analgesic requirements	**1000 per 1000**	**160 per 1000** (50 to 510)	RR 0.16 (0.05 to 0.51)	30 (1)	⊕⊖⊖⊖ **very low** [1,2,3]
Time to feeding after surgery	This outcome was not reported				

*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; **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.

[1]Downgraded one level: few studies with small sample size.
[2]Downgraded one level due to risk of bias: randomisation and allocation concealment procedures were unclear.
[3]Downgraded one level due to uncertainty in outcome measurement.

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BACKGROUND

Description of the condition

Postoperative pain is a barrier to quality of paediatric care, the proper management of which is a challenge. Acute pain often leads to adverse functional and organic consequences that may compromise surgical outcome. During the postoperative period, acute pain can also lead to psychological, cardiorespiratory, and metabolic repercussions (Helgadóttir 2000). Cleft lip is one of the most common craniofacial birth defects and requires surgical correction early in life (Arosarena 2007).

The connective tissue and skeleton of the face form during the third week of embryonic life by the migration of neural crest cells. Cleft lip is caused by failure in the fusion of the frontonasal and maxillary processes, which take place between the fourth and eighth weeks of embryonic development (Shkoukani 2013). The abnormal sequence of lip development can lead to abnormal positioning of the tongue and affect palatal development. Although often associated, cleft lip and palate are different malformations, both embryologically and aetiologically. Cleft lip may be part of a genetic syndrome or be associated with other birth defects (Sykes 2005). Orofacial clefting is estimated to affect 1 in 500 to 700 live births. It is more frequent in Asians and Native Americans and in boys (60% to 80%) (WHO 2004). Cleft lip is associated with cleft palate in 68% to 86% of cases (Arosarena 2007).

Cleft lip and palate are not associated with genetic syndromes in 70% of cases. Genetic predisposition, environmental factors, and teratogenic agents (for example maternal smoking, zinc and folate deficiency, alcohol, pesticides, chemical solvents, antiepileptic drugs, etc.) have been investigated as potential causes or risk factors for orofacial clefts (Mossey 2009). It is possible to identify cleft lip on prenatal ultrasounds, starting at approximately 18 weeks' gestation, although sensitivity is still low, especially on two-dimensional ultrasound. In cases of suspected cleft lip on ultrasound, the patient should be seen by maternal-foetal specialists, and genetic counselling is recommended (Gagnon 2009).

The varied morphology of facial clefts, which may involve four different structures (the upper lip, alveolar process, hard and soft palate) and the possibility of unilateral or bilateral, complete or incomplete involvement, are challenges to the creation of a single classification (Rodriguez 2001). Regardless of the extension of the clefts, early surgical repair must be planned to minimise physical, psychological, and social consequences. Affected individuals may have feeding and speech problems, in addition to increased risks of middle ear infections. The condition is associated with increased mortality from many causes, and the aesthetic defect may cause social rejection and decreased quality of life (Law 2002; Shkoukani 2013).

Surgical correction of cleft lip can be performed during the neonatal period or later. The ideal period for surgery depends on the severity of the deformity, the child's health, and other factors that may influence the efficacy and safety of the procedure (Shkoukani 2013). There is a consensus that the correction should be carried out as early as possible, and it is often performed between the third and sixth months of life (Delgado 2005; Sykes 2005). The management of cleft lip involves a multidisciplinary team to ensure comprehensive care including functional and aesthetic issues. There are several different treatment plans for the surgical correction of the deformity (Mathes 2006).

As expected after a surgical intervention in such a sensitive and delicate area, the immediate postoperative period of cleft lip repair may be associated with moderate to severe pain (Augsornwan 2008; Biazon 2008). This pain requires adequate analgesia to prevent the child from becoming agitated and touching the surgical site which could disrupt the wound-healing process and compromise the aesthetic results as well as extend the time of hospitalisation.

Description of the intervention

Treatment of acute postoperative pain usually involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and oral or intravenous opioids, which may be associated with adverse events such as nausea and vomiting, drowsiness, and respiratory depression. These treatments are frequently underutilised in children due to safety concerns and lack of experience in pain management (Jonnavithula 2007). Another option to control postoperative pain is the injection of local anaesthesia into the surgical incision, but the procedure may distort the margins of the cleft and interfere with the aesthetic repair (Prabhu 1999). In the last two decades there has been a growing interest in regional anaesthesia for paediatric surgical procedures. Several techniques have been evaluated and tested in several types of paediatric surgery, including cleft lip repair (Gaonkar 2004; Jonnavithula 2007; Simion 2008; Takmaz 2009).

Infraorbital nerve block associated with general anaesthesia has been used to reduce postoperative pain after cleft lip repair. The infraorbital nerve is the terminal branch of the second division of the trigeminal nerve, which differentiates into the infraorbital nerve after entering the ocular area through the inferior orbital fissure. It emerges through the infraorbital foramen, dividing into four branches (inferior palpebral, external nasal, internal nasal, and superior labial), innervating the skin of the upper cheek, the mucous membrane of the maxillary sinus, the incisor, canine and premolar teeth, upper gums, skin and conjunctiva of the lower eyelid, part of the nose, skin and mucosa of the upper lip (Simion 2008).

How the intervention might work

Infraorbital nerve block is performed by injecting an anaesthetic into the infraorbital foramen, either intra- or extraorally (percutaneous). In the percutaneous approach, the infraorbital foramen is identified as a point halfway between the midpoint of palpebral fissure and the angle of the mouth, approximately 7.5 mm from the alar base; a needle is then introduced perpendicular to the skin and advanced until bone resistance is felt. The needle is withdrawn slightly, and after a negative aspiration test for blood, the local anaesthetic is injected (Bosenberg 1995; Takmaz 2009). For intraoral infraorbital nerve block, a finger marks the approximate point of the infraorbital foramen externally, as described above, then the lip is everted and the needle is inserted into the mucobuccal fold above the second premolar toward the infraorbital foramen (Jonnavithula 2007). The injected anaesthetic blocks the generation and propagation of impulses in excitable tissues by blocking sodium channels in the cell receptors. The absence of this ion prevents the transmission of pain sensitivity which results in effective regional blockage of pain when these

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drugs are deposited near peripheral nerves, nerve roots, or the spinal cord. The effect of this process depends on the dose, concentration, and type of anaesthetic used (Strichartz 1976).

Why it is important to do this review

There are several procedures to control acute postoperative pain associated with cleft lip repair to ensure the comfort of the child and to preserve the integrity of the delicate surgical site. Infraorbital nerve block is frequently used because it can provide long-lasting pain relief and avoid the complications associated with pain relief drugs. There is a need to assess and synthesise the evidence available so far on the effectiveness and safety of this procedure.

OBJECTIVES

To assess the effects of infraorbital nerve block for postoperative pain following cleft lip repair in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised, published or unpublished, controlled clinical studies that tested perioperative infraorbital nerve block for cleft lip repair in children compared with other types of analgesia procedures, no intervention, or placebo.

Types of participants

We included children up to 13 years of age, undergoing cleft lip repair surgery.

Types of interventions

Perioperative infraorbital nerve block compared with another intervention (that is intravenous analgesia, peri-incisional infiltration), no intervention, or placebo. We considered the type of drug, dosage, and route of administration used in each study. For the purposes of this review, the term perioperative refers to the three phases of surgery: preoperative, intraoperative, and postoperative, and commonly includes ward admission, anaesthesia, surgery, and recovery.

Types of outcome measures

Primary outcomes

1. Pain measured by valid instruments (e.g. Neonatal Infant Pain Scale (NIPS) (Hudson-Barr 2002); the Face, Legs, Activity, Cry, Consolability (FLACC) Scale (Merkel 1997))
2. Duration of postoperative analgesia
3. Adverse events

Secondary outcomes

1. Need for analgesic prescription for pain
2. Time to first analgesic requirement
3. Heart rate, respiratory rate, and blood pressure
4. Time to feeding after surgery
5. Duration of hospitalisation

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 6, 2015);
- MEDLINE (OVID) 1946 to 17 June 2015;
- EMBASE (OVID) 1974 to 17 June 2015;
- Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) from inception to 17 June 2015.

The search strategies for MEDLINE, EMBASE, LILACS, and CENTRAL are presented in Appendix 1; Appendix 2; Appendix 3; Appendix 4.

Searching other resources

We searched for ongoing trials in the following sites: the metaRegister of Controlled Trials (www.controlled-trials.com); ClinicalTrials.gov (the US National Institutes of Health Ongoing Trials Register) (www.clinicaltrials.gov), and the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (last search performed in 17 June 2015).

We checked the reference lists of the included studies to identify any additional studies. We contacted specialists in the field and authors of the included trials for unpublished data. We did not impose any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (GF and EH) independently screened the trials identified by the literature search. After merging the search results and eliminating duplicate records, the review authors examined the titles and abstracts to identify relevant reports and then retrieved and examined the full text of these reports for compliance with eligibility criteria. The review authors documented the reasons for exclusion of individual trials and consulted a third review author (EMKS) in case of disagreement, not including data from trials under scrutiny until a consensus was reached. They used the PRISMA flow chart diagram to document the screening process (Liberati 2009).

Data extraction and management

Two review authors (GF and EH) independently extracted data using a standard form and entered data into Review Manager (RevMan 2014). They resolved disagreements by consensus or by discussion with a third review author (EMKS). Review authors extracted the following information from each study: characteristics of the study (design, setting); participants; type of surgery; interventions; outcomes (outcome measures, timing of outcomes, adverse events); and risk of bias. Where studies had multiple publications, we used the main trial report as the reference and supplemented it with additional details from secondary papers. We contacted the authors of all studies that did not provide complete information.

Assessment of risk of bias in included studies

We used the Oxford Quality Score to assess the methodological quality of included studies (Jadad 1996). We assessed the included studies using Cochrane's tool for assessing risk of bias

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(Higgins 2011). We analysed the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, sample size and other issues (for example extreme baseline imbalance). Two review authors independently assessed the risk of bias, resolving any disagreements by consensus or by discussion with a third review author. We categorised each domain as being at 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias (either lack of information or uncertainty over the potential for bias). We completed a 'Risk of bias' table for each eligible study and presented the assessment using a 'Risk of bias' summary figure, which displays all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give to the results of each study. We included all randomised controlled trials that met the inclusion criteria in the review, regardless of the risk of bias. In future updates, when appropriate, we will perform sensitivity analysis to evaluate the effect of including studies at high risk of bias.

Measures of treatment effect

For dichotomous variables, we calculated the risk ratio and 95% confidence intervals (CIs). For continuous data, we calculated mean differences and 95% CIs between treatment groups if studies reported exactly the same outcomes. If similar outcomes were reported on different scales, we calculated the standardised mean difference and 95% CI. If different scales measuring the same outcome increased with the symptom severity whilst others decreased with it, we subtracted the mean from the maximum possible value for the scale to ensure that all the scales pointed in the same direction. The most appropriate way of summarising time-to-event data is to use methods of survival analysis and to express the intervention effect as a hazard ratio, and we planned to obtain these data directly from the results of the studies (Higgins 2011).

Unit of analysis issues

The unit of analysis was the individual child (unit to be randomised for interventions to be compared), that is the number of observations in the analysis should match the number of children randomised.

Dealing with missing data

We contacted the study authors for additional information about any missing or unavailable data. In the case of no response, irrespective of the type of data, we reported drop-out rates in the 'Characteristics of included studies' tables of the review, and used intention-to-treat analyses (Higgins 2011). Only one author replied and sent us the information requested (Rajamani 2007).

Assessment of heterogeneity

We qualified inconsistency among the pooled estimates using the I^2 statistic: ((Q - df)/Q) x 100% test, where Q is the Chi^2 statistic and df represents the degree of freedom. This examines the percentage of total variation across studies due to heterogeneity rather than chance. We used a fixed-effect model in the absence of substantial heterogeneity (I^2 < 50%), otherwise we used a random-effects model (I^2 > 50%) (Higgins 2011).

Data synthesis

Methods of synthesising the studies depended on quality, design, and heterogeneity. We explored both clinical and statistical heterogeneity. In the absence of clinical and statistical heterogeneity (I^2 < 50%) we used a fixed-effect model to pool the data. In the presence of statistical heterogeneity (I^2 > 50%) we used a random-effects model for meta-analysis. Where synthesis was inappropriate, we presented a narrative overview. We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess overall quality of evidence for each outcome that included pooled results from meta-analysis (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

In case of substantial heterogeneity and if there were sufficient data, we planned to investigate the possible causes for the heterogeneity by further exploring the impact of the condition of the children and interventions (that is participant characteristics, type and duration of the surgery, type and doses of drugs, adjuvant drugs) using subgroup analyses. However, this was not possible for this review.

Sensitivity analysis

If the number of studies was sufficient, we planned to perform sensitivity analyses separating studies according to risk of bias. We planned do this by excluding the trials most susceptible to bias based on our 'Risk of bias' assessment: those with inadequate allocation concealment; high levels of postrandomisation losses or exclusions; and uncertain or unblinded outcome assessment (Deeks 2011). However, it was not possible to perform sensitivity analyses due to the small number of included studies.

Presentation of results

We presented the main results of the review in a Summary of findings 1 using the GRADE approach (GRADEpro GDT 2015), which provides key information concerning the quality of the evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes, as recommended by Cochrane (Schünemann 2011).

RESULTS

Description of studies

Results of the search

The search strategy (last run on 17 June 2015) retrieved 106 records: CENTRAL 12 references; MEDLINE (OVID) 25 references; EMBASE (OVID) 29 references; and LILACS 40 references. We did not identify any unpublished studies. After exclusion of duplicates, 83 records remained. We examined the titles and abstracts of these references and selected 12 potentially relevant studies for full-text reading. Eight fulfilled the selection criteria and were included in the review (Ahuja 1994; Delgado 2005; Gaonkar 2004; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Simion 2008; Takmaz 2009), and four did not and were excluded (Grewal 2015; Jindal 2011; Jonnavithula 2007; Mane 2011. The process of study identification and selection is depicted in Figure 1.

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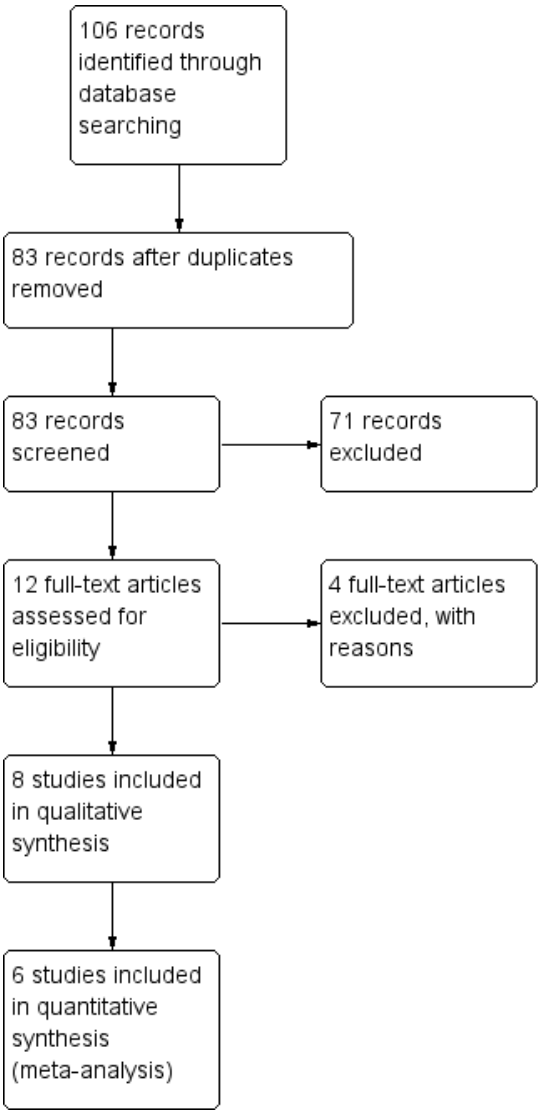
Figure 1. Study flow diagram.



Included studies

We included eight studies (Ahuja 1994; Delgado 2005; Gaonkar 2004; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Simion 2008; Takmaz 2009). Three compared infraorbital nerve block with placebo, that is sham block (Ahuja 1994; Nicodemus 1991; Takmaz 2009). Three studies compared infraorbital nerve block with intravenous analgesia (Delgado 2005; Rajamani 2007; Simion 2008), and two studies compared infraorbital nerve block with anaesthetic infiltration of the incision (Gaonkar 2004; Prabhu 1999).

Design

All included studies were prospective, randomised, controlled, and double-blind trials conducted in a single centre.

Sample sizes

The eight studies included a total of 353 children; sample sizes ranged from 20 to 82 children per study.

Setting

All eight studies were conducted in hospitals. Seven were conducted exclusively by anaesthesiologists, and one involved the department of anaesthesiology and plastic and reconstructive surgery (Takmaz 2009). Four studies were carried out in India (Ahuja 1994; Gaonkar 2004; Prabhu 1999; Rajamani 2007), two in the United States (Nicodemus 1991; Simion 2008), one in Turkey (Takmaz 2009), and one in Spain (Delgado 2005).

Participants

Participants were children of both genders. Three studies included only children under one year of age (Ahuja 1994; Delgado 2005; Simion 2008). Takmaz 2009 and Prabhu 1999 included children under two years of age. Rajamani 2007 included children under 10 years of age. Nicodemus 1991 included children up to 13 years of age. Although our review had established 10 years of age as a limit, we decided not to exclude this last study because it likely included few children over this age limit, as the authors reported that the mean age (standard deviation) of the intervention and placebo groups were 7.47 (3.68) years and 6.20 (3.59) years, respectively.

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Intervention

Three articles compared infraorbital nerve block with placebo; Ahuja 1994 applied 1 ml of 1% lignocaine with adrenaline (1:400,000); Nicodemus 1991 used 1 to 1.5 ml of 0.5% bupivacaine with epinephrine (1:200,000); and Takmaz 2009 applied 1.5 ml 0.25% bupivacaine.

Delgado 2005 compared infraorbital nerve block with 1 to 2 ml of 0.25% bupivacaine with adrenaline and intravenous 1.5 mg/kg of tramadol. Rajamani 2007 compared 1 ml of 0.25% bupivacaine with 2 µg/kg of intravenous fentanyl, and Simion 2008 compared 0.5 ml of 0.25% bupivacaine and 2 µg/kg of intravenous fentanyl.

Gaonkar 2004 compared 1 ml 0.25% bupivacaine with adrenaline (1:200,000), and Prabhu 1999compared 2 ml of 0.125% bupivacaine with the same doses of anaesthetic infiltration in the margin of the incision.

Outcomes

All included studies assessed pain as one of their outcomes but used different measurement scales. Only one study reported duration of postoperative analgesia (Nicodemus 1991). Five studies reported adverse events (Ahuja 1994; Gaonkar 2004; Rajamani 2007; Simion 2008; Takmaz 2009). Five studies reported the need for analgesic prescription for pain (Ahuja 1994; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Takmaz 2009). Five studies reported the time to first analgesic requirement (Delgado 2005; Gaonkar 2004; Rajamani 2007; Simion 2008; Takmaz 2009). Three studies reported heart rate, respiratory rate, and blood pressure (Ahuja 1994; Gaonkar 2004; Prabhu 1999). Two studies reported the time to feeding after surgery (Rajamani 2007; Simion 2008). No study reported the duration of hospitalisation.

Excluded studies

We excluded three studies because they compared different anaesthetics and because all children received infraorbital nerve block (Jindal 2011; Jonnavithula 2007; Mane 2011). We excluded one study because it was not randomised (Grewal 2015). See Characteristics of excluded studies.

Risk of bias in included studies

The included studies were of low to moderate methodological quality (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.

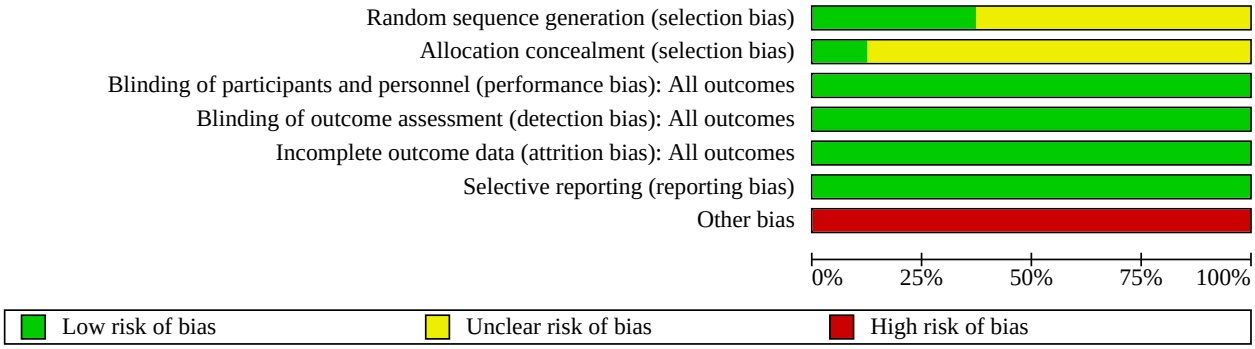

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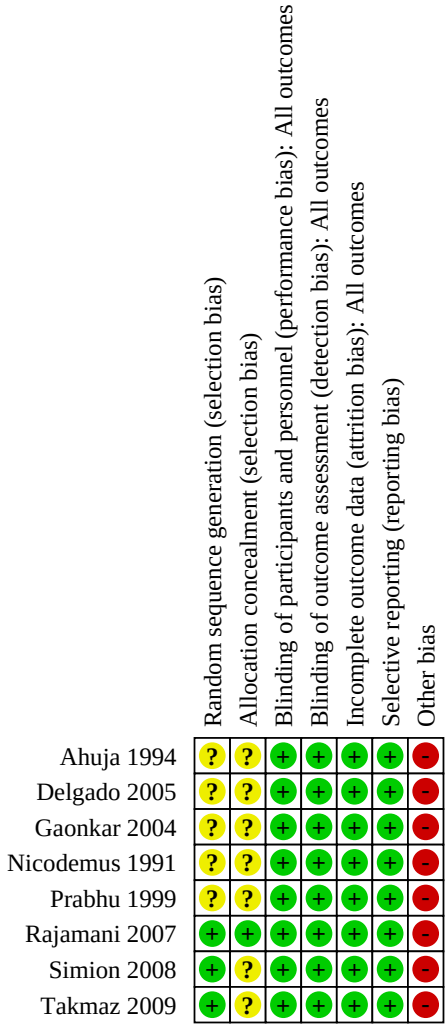
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We assessed the included studies on the method used to generate the allocation sequence, and categorised the method as low risk of bias (any truly random process, for example random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated); or high risk of bias (any non-random process, for example odd or even date of birth; hospital or clinic record number). Only three studies reported the method of randomisation (Rajamani 2007; Simion 2008; Takmaz 2009), and these were classified as having a low risk of bias for this domain. We classified the other five studies as having an unclear risk of bias for random sequence generation.

We assessed the included studies on the method used to conceal allocation to interventions prior to assignment and whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We categorised the method as: low risk of bias (for example telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated); or high risk of bias (open random allocation; unsealed or non-opaque envelopes). We classified seven studies as having an unclear risk of bias for allocation concealment because they provided no information on this. Only one study reported the randomisation and allocation concealment method and was assessed as low risk of bias (Rajamani 2007).

Blinding

For each included study we assessed the methods used, if any, to blind study participants and personnel from knowledge of which intervention a child received. We considered studies to be at low risk of bias if they were blinded, unclear risk of bias when the method was not clearly stated, and high risk of bias when they were not blinded. All eight studies were double blinded, with low risk of performance and detection bias.

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Incomplete outcome data

We assessed the included studies for the completeness of data including attrition and exclusions from the analysis. We categorised the domain as: low risk of bias (for example no missing outcome data; missing outcome data balanced across groups); high risk of bias (for example numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation); and unclear risk of bias (not clearly stated). None of the included studies reported losses and were all therefore classified as having a low risk of attrition bias.

Selective reporting

We assessed the possibility of selective outcome reporting bias and classified the studies as low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported); high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes was not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); and unclear risk of bias (not clearly stated). We judged all included studies to be at low risk for selective reporting bias.

Other potential sources of bias

We assessed possible bias by small size of the included studies, as small studies have been shown to overestimate treatment effects, allowing critical criteria to be compromised. We considered studies to be at low risk of bias if they had 200 children or more per arm, at unclear risk if they had 50 to 200 children, and at high risk if they had fewer than 50 children (Dechartres 2013; Nüesch 2010). We therefore judged all studies to be at high risk of bias.

Effects of interventions

See: **Summary of findings 1** Infraorbital nerve block compared with placebo for cleft lip repair in children; **Summary of findings 2** Infraorbital nerve block compared with intravenous analgesia for cleft lip repair in children; **Summary of findings 3** Infraorbital nerve block compared with infiltration of the incision for cleft lip repair in children

The eight included studies reported different types of interventions, observation times, and forms of measuring and describing the outcomes, making it difficult to pool their data. We therefore performed a few meta-analyses, but have presented mostly narrative descriptions of the outcomes for each comparison. See: Summary of findings 1, Summary of findings 2 and Summary of findings 3.

1. Infraorbital nerve block versus placebo

Three of the studies compared infraorbital nerve block to placebo (Ahuja 1994; Nicodemus 1991; Takmaz 2009).

Primary outcomes

1. Pain measured by valid instruments

The meta-analysis of the three studies that reported this outcome showed a significant difference in favour of the intervention group in the peak of pain, measured during the postoperative period (standardised mean difference (SMD) -3.54, 95% confidence interval (CI) -6.13 to -0.95; 3 studies; 120 children; P =0.007; I^2= 94%). There was significant heterogeneity in this analysis, and the random-effects model was used (Analysis 1.1). After we excluded one study (Takmaz 2009), heterogeneity disappeared (SMD -1.80, 95% CI -2.33 to -1.27; 2 studies; 80 children; P < 0.00001; I^2 = 0%). This outcome was downgraded three levels of evidence (to very low quality) due to few studies with a limited number of children, unclear methodology of the studies, and the heterogeneity of analysis.

2. Duration of postoperative analgesia

In Nicodemus 1991, the intervention group had a significantly longer duration of analgesia than the placebo group: 19.43 ± 5.06 hours versus 11.17 ± 6.16 hours (mean difference (MD) 8.26, 95% CI 5.41 to 11.11; P < 0.00001).

3. Adverse events

Ahuja 1994 reported no adverse events in the children. Takmaz 2009 reported more episodes of vomiting in the placebo than in the intervention group (40% versus 10%; P = 0.001). Nicodemus 1991 did not report this outcome.

Secondary outcomes

4. Need for analgesic prescription for pain

Three studies reported this outcome (Ahuja 1994; Nicodemus 1991; Takmaz 2009). There was a significant difference, with more supplemental analgesic required by the children in the placebo group compared with the intervention group (risk ratio (RR) 0.05, 95% CI 0.01 to 0.18; 3 studies; 120 children; P < 0.0001; I^2 = 19%) (Analysis 1.2). We classified this outcome as low-quality evidence, with one level of downgrading due to the small number of children and unclear methodology of the studies.

5. Time to first analgesic requirement

Takmaz 2009 reported that the time to first analgesic requirement (defined as the time from arrival in the recovery room until the administration of any rescue analgesic) was significantly longer in the intervention compared with the placebo group (8.3 ± 0.9 hours versus 1.6 ± 0.8 hours; P = 0.001).

6. Heart rate, respiratory rate, and blood pressure

Ahuja 1994 reported no significant difference in heart rate, respiratory rate, and blood pressure between the groups. Takmaz 2009 reported no differences in the respiratory rate and blood pressure between groups, but the children in the placebo group had significantly higher heart rates than those in the intervention group.

7. Time to feeding after surgery

None of the included reported this outcome.

8. Duration of hospitalisation

None of the included studies reported this outcome.

2. Infraorbital nerve block versus intravenous analgesia

Three studies compared infraorbital nerve block and intravenous analgesia (Delgado 2005; Rajamani 2007; Simion 2008).

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Primary outcomes

1. Pain measured by valid instruments

The meta-analysis of two studies, Delgado 2005 and Rajamani 2007, showed a significant difference between the groups favouring the intervention group in mean peak pain measured in the first four hours after surgery (SMD -1.50, 95% CI -2.40 to -0.60; 2 studies; 107 children; P = 0.001; I^2 = 64%) (Analysis 2.1). Simion 2008 stated that there were no differences between the groups (only graphic available), but the observation was made only one hour after surgery. This outcome was downgraded three levels to very low-quality evidence due to few studies with a limited number of children, unclear methodology of the studies, and heterogeneity.

2. Duration of postoperative analgesia

None of the included studies reported this outcome.

3. Adverse events

No adverse events attributable to either analgesic technique were reported by Rajamani 2007 or Simion 2008. Delgado 2005 did not report this outcome.

Secondary outcomes

4. Need for analgesic prescription for pain

In Rajamani 2007 more children required rescue analgesics in the control group than in the intervention group (RR 0.27, 95% CI 0.13 to 0.55; P < 0.001).

5. Time to first analgesic requirement

It was not possible perform meta-analysis of this outcome as planned due to the lack of necessary data in the included studies. Delgado 2005 reported that the time to first analgesic requirement (defined as the time from arrival in the recovery room until the administration of any rescue analgesic) was longer in the infraorbital block group (7.3 ± 5.1 hours) compared with the intravenous analgesia (2.8 ± 2.2 hours) (P < 0.01). Moreover, Simion 2008 reported no statically significant difference between groups (195.32 ± 71.21 minutes versus 146.94 ± 70 minutes) (P = 0.07), as well as Rajamani 2007 (31.43 ± 34.12 versus 39.31 ± 21.05) (P = 0.45).

6. Heart rate, respiratory rate, and blood pressure

The included studies did not report these outcomes.

7. Time to feeding after surgery

The meta-analysis of the two studies that reported this outcome, Rajamani 2007 and Simion 2008, showed a significant difference favouring the intervention group compared with control group (MD -9.45, 95% CI -17.37 to -1.53; 2 studies; 128 children; P = 0.02; I^2 = 0%) (Analysis 2.2). This outcome was downgraded one level to moderate-quality evidence due to few studies with a limited number of children.

8. Duration of hospitalisation

None of the included studies reported this outcome.

3. Infraorbital nerve block versus infiltration of the incision

Two studies compared infraorbital nerve block with anaesthetic infiltration of the incision (Gaonkar 2004; Prabhu 1999).

Primary outcomes

1. Pain measured by valid instruments

The authors of Gaonkar 2004 stated that postoperative pain was comparable in the first 24 hours in both groups except at 6 hours, where children in the control group had lower pain scores (P < 0.05) compared to those in the intervention group (no data provided by the authors). Prabhu 1999 reported that children in the intervention group had significantly lower pain scores (P < 0.05) between one to eight hours after the surgery than those in the control group (only graphics data).

2. Duration of postoperative analgesia

The included studies did not report this outcome.

3. Adverse events

Gaonkar 2004 reported no adverse events attributable to either analgesic technique. Prabhu 1999 did not report this outcome.

Secondary outcomes

4. Need for analgesic prescription for pain

Prabhu 1999 reported that significantly more children required rescue analgesics in the control group than in the intervention group (RR 0.16, 95% CI 0.05 to 0.51; P = 0.002).

5. Time to first analgesic requirement

Gaonkar 2004 reported that the time to first analgesic requirement was significantly longer in the intervention compared with the control group (MD 4.92, 95% CI 3.84 to 6.00; 1 study; 50 children; P < 0.001).

6. Heart rate, respiratory rate, and blood pressure

Gaonkar 2004 reported no differences between groups in postoperative heart rate and blood pressure. Prabhu 1999 reported significantly lower heart rates in the intervention group than in the control group throughout the postoperative period, and no differences in respiratory rate and blood pressure.

7. Time to feeding after surgery

The included studies did not report this outcome.

8. Duration of hospitalisation

The included studies did not report this outcome.

DISCUSSION

Summary of main results

Cleft lip is one of the most common craniofacial birth defects and requires surgical correction, which can be performed during the neonatal period or later. A surgical procedure in children requires excellent postoperative analgesia. We identified 11 randomised controlled trials (Ahuja 1994; Delgado 2005; Gaonkar 2004; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Simion 2008; Takmaz 2009; Jindal 2011; Jonnavithula 2007, and eight fulfilled the inclusion criteria for this systematic review (Ahuja 1994; Delgado 2005; Gaonkar 2004; Nicodemus 1991; Prabhu 1999; Rajamani 2007; Simion 2008; Takmaz 2009).

Three studies compared infraorbital nerve block with placebo and measured postoperative pain (Ahuja 1994; Nicodemus 1991;

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Takmaz 2009). These studies showed a significant difference between the groups favouring the intervention group and no adverse events. More supplemental analgesics were required by the children in the placebo group, and the time to first analgesic requirement was significantly longer in the intervention group. These studies did not report duration of analgesia.

Three studies compared infraorbital nerve block and intravenous analgesia (Delgado 2005; Rajamani 2007; Simion 2008). Two of these studies reported that pain in the first hour after surgery was significantly lower in the intervention group (Delgado 2005; Rajamani 2007). The third study reported no differences between groups one hour after surgery (Simion 2008). Duration of postoperative analgesia and adverse events were not reported. Rajamani 2007 reported that more children in the control group required rescue analgesic. The time to first analgesic requirement showed conflicting results in the three studies: in two studies it was not different between the groups (Rajamani 2007; Simion 2008), and in one study it was longer in the intervention group (Delgado 2005). Rajamani 2007 and Simion 2008 showed a significant difference in time to feeding after surgery favouring the intervention group compared with the control group.

Two studies compared infraorbital nerve block with anaesthetic infiltration of the incision (Gaonkar 2004; Prabhu 1999). Gaonkar 2004 reported no differences in pain scores measured during the first 24 hours after surgery between the groups. Prabhu 1999 reported lower pain scores one to eight hours after surgery in the intervention group. Duration of postoperative analgesia and adverse events were not reported. In Prabhu 1999 more children required rescue analgesics in the control group, and in Gaonkar 2004 the intervention group had a significantly longer time to the first analgesic requirement. Gaonkar 2004 reported no differences between groups in postoperative heart rate and blood pressure, while Prabhu 1999 reported significantly lower heart rates in the intervention group.

None of the studies reported duration of hospitalisation.

Overall completeness and applicability of evidence

There was heterogeneity in the interventions, participant age, duration of follow-up, and outcome measurement tools in the studies included in this review, which made it difficult to analyse them and draw reliable conclusions.

One of the primary outcomes of this review, the duration of analgesia, was only reported by one study, and another important primary outcome, adverse events, was poorly reported. Of the eight included studies, five reported no significant adverse events, and three did not report this outcome. There is low-quality evidence from a small number of studies and children that infraorbital nerve block with lignocaine and bupivacaine may provide effective pain relief compared to placebo and intravenous analgesia. In fact, the two most recent controlled studies identified in our search started from the hypothesis of superiority of the infraorbital nerve block to compare different types of anaesthetic in cleft lip repair surgery (Jindal 2011; Mane 2011).

Quality of the evidence

Overall, the included studies were of moderate methodological quality at low or unclear risk of bias. The reasons for downgrading the quality of the evidence related to lack of information about randomisation methods and allocation concealment in the studies, very small sample sizes, and heterogeneity of outcome reporting. The quality of all outcomes included in the 'Summary of findings' tables was downgraded two or three levels. The pooled results for the primary outcome pain showed significant statistical heterogeneity, probably because of the different scales used for measurement and other differences mentioned above. This led to further downgrading of the quality of the evidence for this outcome to very low (GRADEpro GDT 2015).

Potential biases in the review process

We strived to prevent bias in the review process by involving two independent review authors in each step of the review and by performing a comprehensive search with no language restrictions.

Agreements and disagreements with other studies or reviews

We could not identify other systematic reviews on infraorbital nerve block for postoperative analgesia after cleft lip repair in children. However, the descriptive studies and expert reports on the efficacy of this treatment are consistent with the findings of our review.

AUTHORS' CONCLUSIONS

Implications for practice

For children with postoperative pain following cleft lip repair surgery

Infraorbital nerve block with lignocaine or bupivacaine may reduce postoperative pain compared with placebo (sham block) and intravenous analgesia. This finding is uncertain due to the very small samples sizes and differences in the interventions and outcomes in the included trials (very low-quality evidence). There is a lack of information about adverse events in many studies and the absence of evidence for some outcomes of interest.

For clinicians and policymakers

There is low- to very low-quality evidence that infraorbital nerve block may be an effective intervention to be routinely adopted in surgery for cleft lip repair in children.

Implications for research

General

Further studies, probably multicentre to obtain a larger sample, are needed to consolidate this evidence, and the most appropriate anaesthetic agent as well as the optimal dosage should also be evaluated.

Design

Double-blind randomised clinical trials with high methodology quality (that is adequate report of randomisation, allocation concealment, blinding, etc.) are needed. Future studies should standardise the observation time and the instruments used to measure outcomes, and stratify children by age group.

Measurement

The main outcome should be pain measured by validated instruments proper for each age group. The measurements must be made long enough to measure analgesia time and predefined as

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an hourly basis. The parameters to provide rescue analgesia should be described and standardised across studies. Studies should also report the time to feeding, parental satisfaction, and duration of hospitalisation.

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CHARACTERISTICS OF STUDIES

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

Ahuja 1994

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat:not stated Sample size calculation: not stated Setting: single centre. India Follow up: 3 hours
Participants	N = 20 (45% male) Age: 2 to 11 months
Interventions	Group 1: (n = 10) extra oral infraorbital nerve block with 1 ml of 1% lignocaine with adrenaline Group 2: (n = 10) "sham" block
Outcomes	• Postoperative pain assessment score (PAS) • Heart rate • Blood pressure • Respiratory rate • Supplemental analgesic requirements
Notes	Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients in control group were given sham blocks at the same site to avoid observer bias"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Observations were made by a single independent observer who was unaware of the analgesic technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting

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Ahuja 1994 *(Continued)*

Other bias	High risk	Size: sample size less than 50 per treatment arm

Delgado 2005

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: not stated Sample size calculation: not stated Setting: single centre. Spain Follow up: 6 hours
Participants	N = 25 Age: 3 to 10 months
Interventions	Group 1: (n = 12) intraoral infraorbital nerve block with 1 to 2 ml of bupivacaine 0.25% plus adrenaline was administered and intravenous saline solution instead of intravenous analgesia with tramadol Group 2: (n = 13) saline solution was administered for nerve blockade, instead of bupivacaine, and intravenous tramadol (1.5 mg/kg) was provided
Outcomes	• Length of analgesia • Pain intensity - subjective measure by observer with 0 to 5 scale • Discomfort grade - measured by objective scale
Notes	Jadad score: 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Saline solution used as control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medical staff and nurses were fully unaware of the analgesic technique used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses

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Delgado 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Gaonkar 2004

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: not stated Sample size calculation: not stated Setting: single centre. India Follow up: 36 hours
Participants	N = 50 Age: 4 to 72 months
Interventions	Group 1: (n = 25) extraoral infraorbital nerve block with 1 ml bupivacaine 0.25% plus adrenaline was administered and saline solution infiltration of the incision Group 2: (n = 25) saline solution was administered for nerve blockade, and 1 ml bupivacaine 0.25% plus adrenaline was infiltrated in the incision
Outcomes	• Postoperative pain relief scoring was measured according to Hanallah's 10-point score • Time to first analgesic given as a rescue
Notes	Jadad score: 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Saline solution used as control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded. Saline solution used as control
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses

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Gaonkar 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Nicodemus 1991

Study characteristics

Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: not stated Sample size calculation: not stated Setting: single centre. USA Follow up: 24 hours
Participants	N = 60 (60% male) Age: 2 to 13 years
Interventions	Group 1: (n = 30) intraoral infraorbital nerve block with 1 to 1.5 ml bupivacaine 0.5% plus adrenaline Group 2: (n = 30) saline placebo in the infraorbital area
Outcomes	• Pain reported by the children through visual analogue scale (0 to 5) • Pain evaluated by nurses and parents through score (0 to 4) • Length of analgesia • Supplemental analgesic requirements
Notes	Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The anaesthetist who performed the block and the subsequent evaluation, the nurses and the parents who evaluated the patient's comfort were all kept unaware of the identity of the solution used for block"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses

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Nicodemus 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Prabhu 1999

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: Not stated Sample size calculation: Not stated Setting: single centre. India Follow up: 24 hours
Participants	N = 30 (63.3% male) Age: 4 to 20 months
Interventions	Group 1: (n = 15) extraoral infraorbital nerve block with 2 ml bupivacaine 0.125% plus adrenaline and peri-incisional infiltration with saline solution Group 2: (n = 15) saline placebo in the infraorbital area and peri-incisional infiltration with 2 ml bupivacaine 0.125% plus adrenaline
Outcomes	• Pain assessed using a 2-point pain relief score consisting of 10 behavioural variables • Heart rate, blood pressure, and respiratory rate • Supplemental analgesic requirements
Notes	Jadad score: 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both the surgeon and the anaesthetist were handed prefilled syringes and were unaware of the nature of the solution that they were injecting"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias)	Low risk	No losses

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Prabhu 1999 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Rajamani 2007

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: Not stated Sample size calculation: Not stated Setting: single centre. India Follow up: 2 hours
Participants	N = 82 (60.9% male) Age: 3 months to 10 years
Interventions	Group 1: (n = 41) extraoral infraorbital nerve block with 2 ml of bupivacaine 0.25% was administered and intravenous saline solution instead of intravenous analgesia Group 2: (n = 41) saline solution was administered for nerve blockade, instead of bupivacaine, and intravenous fentanyl (2 µg/kg) was provided
Outcomes	• Pain: measured by Children and Infants Postoperative Pain Scale score • Supplemental analgesic requirements • Length of analgesia • Time to feed
Notes	Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The author informed us by email that randomisation was by drawing lots from a box including folded papers with the 2 anaesthetic options being pre-written
Allocation concealment (selection bias)	Low risk	The author informed us by email that randomisation was by drawing lots from a box including folded papers with the 2 anaesthetic options being pre-written
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"anaesthesiologist (blinded to the analgesic used) assessed the child's airway reflexes, recovery from anaesthesia, respiratory and cardiovascular status and operative site bleeding"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"child was handed over to the mother, and was monitored by the recovery room nurse. The nurse was blinded to the analgesia used"

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Rajamani 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Simion 2008

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: Not stated Sample size calculation: "A power analysis estimated a sample size of 46 patients would have an 80% power at the 0.05 level of significance to detect a 50% reduction in number of the patients requiring rescue analgesia" Setting: single centre. USA Follow up: 24 hours
Participants	N = 46 Age: 1 to 12 months
Interventions	Group 1: (n = 23) intraoral infraorbital nerve block with 0.5 ml of bupivacaine 0.25% with adrenaline was administered and intravenous saline solution instead of intravenous analgesia Group 2: (n = 23) saline solution was administered for nerve blockade, instead of bupivacaine, and intravenous fentanyl (2 µg/kg) was provided
Outcomes	• Pain measured by neonatal infant pain score • Need for rescue medication • Time to first feeding • Length of analgesia
Notes	Jada score: 5

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were randomised to one of two groups using a computer generated randomizations table"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients were transported to the postanaesthesia care unit (PACU) where a blinded observer evaluated pain and discomfort"

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Simion 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients were observed by a blinded observer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

Takmaz 2009

Study characteristics	
Methods	Study design: prospective, randomised, double-blind, controlled trial Intention-to-treat: Not stated Sample size calculation: "The calculated sample size for a clinical difference of 4.5 hours between the groups, at an alpha error of 5% and a beta error of 90%, was 20 per group" Setting: single centre. Turkey Follow up: 24 hours
Participants	N = 40 (65% male)
Interventions	Group 1: (n = 20) extraoral infraorbital nerve block with 1.5 ml of bupivacaine 0.25% with adrenaline Group 2: (n = 20) "sham" block with saline solution
Outcomes	• Pain measured by the Face, Legs, Activity, Cry, Consolability (FLACC) Scale • Heart rate, blood pressure, and respiratory rate • Time to first analgesic requirement • Rescue analgesia requirement • Parent satisfaction • Adverse effect
Notes	Jadad score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	Low risk	"In all patients, the nerve block was performed by the anaesthetist who was unaware of the content of the solution"

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Takmaz 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Postoperative assessment was performed by an investigator blinded to the patient's group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	The report of the study was free of suggestion of selective outcome reporting
Other bias	High risk	Size: sample size less than 50 per treatment arm

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

Study	Reason for exclusion
Grewal 2015	Not randomised
Jindal 2011	Both groups received infraorbital block. The study compared addition of clonidine to bupivacaine
Jonnavithula 2007	Both groups received infraorbital block. The study compared addition of pethidine to bupivacaine
Mane 2011	Both groups received infraorbital block. The study compared addition of pethidine or fentanyl to bupivacaine

DATA AND ANALYSES

Comparison 1. Infraorbital nerve block vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain	3	120	Std. Mean Difference (IV, Random, 95% CI)	-3.54 [-6.13, -0.95]
1.2 Supplemental analgesic requirements	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.18]

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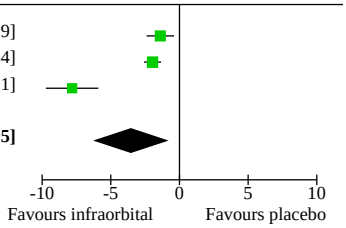
Analysis 1.1. Comparison 1: Infraorbital nerve block vs placebo, Outcome 1: Pain

Study or Subgroup	Infraorbital nerve block Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ahuja 1994	4.4	3.17	10	10.7	5.23	10	34.3%	-1.40 [-2.40 , -0.39]
Nicodemus 1991	1.7	0.4	30	2.6	0.5	30	35.4%	-1.96 [-2.58 , -1.34]
Takmaz 2009	2	0.6	20	8.1	0.9	20	30.2%	-7.82 [-9.72 , -5.91]
Total (95% CI)			**60**			**60**	**100.0%**	**-3.54 [-6.13 , -0.95]**

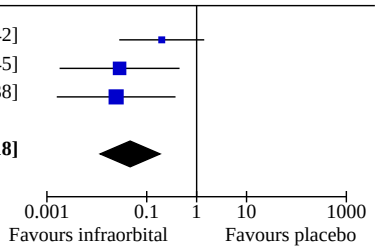
Heterogeneity: Tau² = 4.84; Chi² = 36.34, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.67 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Infraorbital nerve block vs placebo, Outcome 2: Supplemental analgesic requirements

Study or Subgroup	Infraorbital nerve block Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahuja 1994	1	10	5	10	11.6%	0.20 [0.03 , 1.42]
Nicodemus 1991	0	30	17	30	40.7%	0.03 [0.00 , 0.45]
Takmaz 2009	0	20	20	20	47.7%	0.02 [0.00 , 0.38]
Total (95% CI)		**60**		**60**	**100.0%**	**0.05 [0.01 , 0.18]**
Total events:	1		42			

Heterogeneity: Chi² = 2.46, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 4.37 (P < 0.0001)
Test for subgroup differences: Not applicable



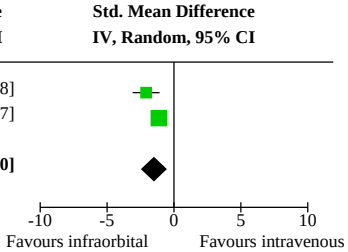
Comparison 2. Infraorbital nerve block vs intravenous analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Pain	2	107	Std. Mean Difference (IV, Random, 95% CI)	-1.50 [-2.40, -0.60]
2.2 Time to feeding	2	128	Mean Difference (IV, Fixed, 95% CI)	-9.45 [-17.37, -1.53]

Analysis 2.1. Comparison 2: Infraorbital nerve block vs intravenous analgesia, Outcome 1: Pain

Study or Subgroup	Infraorbital nerve block Mean	SD	Total	Intravenous analgesia Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Delgado 2005	0.66	0.6	12	2.23	0.83	13	38.5%	-2.08 [-3.09 , -1.08]
Rajamani 2007	2.81	1.38	41	4.71	1.89	41	61.5%	-1.14 [-1.61 , -0.67]
Total (95% CI)			**53**			**54**	**100.0%**	**-1.50 [-2.40 , -0.60]**

Heterogeneity: Tau² = 0.29; Chi² = 2.79, df = 1 (P = 0.09); I² = 64%
Test for overall effect: Z = 3.26 (P = 0.001)
Test for subgroup differences: Not applicable



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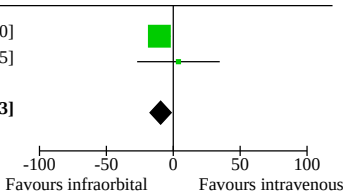
Analysis 2.2. Comparison 2: Infraorbital nerve block vs intravenous analgesia, Outcome 2: Time to feeding

Study or Subgroup	Infraorbital nerve block Mean	SD	Total	Intravenous analgesia Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rajamani 2007	62.05	20.06	41	72.44	17.72	41	93.4%	-10.39 [-18.58 , -2.20]
Simion 2008	50.05	52.6	23	46.17	54.2	23	6.6%	3.88 [-26.99 , 34.75]
Total (95% CI)			**64**			**64**	**100.0%**	**-9.45 [-17.37 , -1.53]**

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.34 (P = 0.02)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE search strategy

1. Cleft Lip/
2. cheiloschisis.tw.
3. (cleft lip* or harelip*).tw.
4. or/1-3
5. Pain, Postoperative/
6. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.
7. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.
9. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.
10. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.
11. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.
12. exp Surgical Procedures, Operative/
13. or/5-12
14. Nerve Block/
15. Infra-orbital nerve block*.tw.
16. Infraorbital nerve block*.tw.
17. Anesthetics, Local/
18. nerve block*.tw.
19. or/14-18
20. 4 and 13 and 19

Appendix 2. EMBASE search strategy

1 Cleft Lip/ (12152)

2 cheiloschisis.tw. (32)

3 (cleft lip* or harelip*).tw. (10813)

4 or/1-3 (15302)

5 Pain, Postoperative/ (41904)

6 ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (84681)

7 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (709)

8 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (803)

9 (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (2682)

10 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (3725)

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11 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (756)

12 exp Surgical Procedures, Operative/ (3376669)

13 or/5-12 (3400440)

14 Nerve Block/ (20534)

15 Infra-orbital nerve block*.tw. (10)

16 Infraorbital nerve block*.tw. (71)

17 Anesthetics, Local/ (23801)

18 nerve block*.tw. (10053)

19 or/14-18 (43663)

20 4 and 13 and 19 (27)

Appendix 3. LILACS search strategy

#1 AO #3

#4 MH:"Fenda Labial" OR (Fissura Labial) OR (Labio Leporino) OR (FENDA LABIAL) OR (cleft lip) OR MH:C07.465.409.225$ OR MH:C07.465.525.164$ OR MH:C07.650.525.164$ OR MH:C16.131.850.525.164$ OR HARELIP$ OR CHEILOSCHISIS

#5 AO #12

#13 (MH:"Dor Pós-Operatória" OR (DOR POS OPERATORIA) OR (Dolor Postoperatorio) OR (Pain$ Postoperative) OR MH:C23.550.767.700$ OR MH:C23.888.646.530$ OR (post-operative analgesi$) OR (postoperative analgesi$) OR (post surgical pain$) OR (post surgery pain$) OR (pain relief after surg$) OR (pain following surg$) OR (pain control after) OR ((post surg$) and (pain$ or discomfort))) OR MH:"Procedimentos Cirúrgicos Operatórios" OR (Procedimentos Cirúrgicos Operatórios) OR (Procedimientos Quirúrgicos Operativos) OR (Surgical Procedures Operative) OR (Intervenção Cirúrgica) OR (Operação Cirúrgica) OR (Operações Cirúrgicas) OR (Procedimento Cirúrgico) OR (Procedimentos Cirúrgicos) OR MH:E04$ OR MH:VS3.003.001.006.002$

#14 AO #18

#19 MH:"Bloqueio Nervoso" OR (Bloqueo Nervioso) OR (Nerve Block) OR (BLOQUEIO NERVOSO) OR MH:E03.155.086.711$ OR MH:E04.525.210.550$ OR (Infraorbital nerve block$) OR MH:"Anestésicos Locais" OR (Anestésico$ Loca$) OR (Anestésicos Bloqueadores de Condução) OR (Anestésicos Locales) OR (Anesthetics Local) OR MH:D27.505.696.277.100.200$ OR MH:D27.505.696.663.850.025$ OR MH:D27.505.954.427.210.100.200$

#20 #4 AND #13 AND #19

Appendix 4. CENTRAL search strategy

#1 MESH DESCRIPTOR Cleft Lip EXPLODE ALL TREES 119

#2 cheiloschisis:TI,AB,KY 0

#3 ((cleft lip* or harelip*)):TI,AB,KY 203

#4 #1 OR #2 OR #3 203

#5 MESH DESCRIPTOR Nerve Block 2351

#6 (Infra-orbital nerve block*):TI,AB,KY 4

#7 (Infraorbital nerve block*):TI,AB,KY 16

#8 MESH DESCRIPTOR Anesthetics, Local 5785

#9 (nerve block*):TI,AB,KY 3436

#10 #5 OR #6 OR #7 OR #8 OR #9 7867

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#11 (((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*))):TI,AB,KY 83

#12 (((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*")):TI,AB,KY 13980

#13 (("pain-relief after surg*" or "pain following surg*" or "pain control after")):TI,AB,KY 275

#14 ((("post surg*" or post-surg*) and (pain* or discomfort))):TI,AB,KY 283

#15 (((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*"))):TI,AB,KY 659

#16 (((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*"))):TI,AB,KY 276

#17 MESH DESCRIPTOR Pain, Postoperative EXPLODE ALL TREES 9121

#18 MESH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL TREES 83773

#19 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 91808

#20 #4 AND #10 AND #19 11

WHAT'S NEW

Date	Event	Description
22 June 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 5, 2014
Review first published: Issue 4, 2016

Date	Event	Description
10 October 2019	Amended	Amended terminology in the Plain Language Summary.
20 February 2018	Review declared as stable	See Published notes

CONTRIBUTIONS OF AUTHORS

Protocol stage: draft the protocol	EMKS, GF, MRT
Review stage: select which trials to include	GF, EH, EMKS
Review stage: extract data from trials	GF, EH
Review stage: enter data into RevMan	GF, EH
Review stage: carry out the analysis	GF, EMKS
Review stage: interpret the analysis	GF, EMKS, MRT
Review stage: draft the final review	GF, EMKS, MRT

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Update stage: update the review	GF, EMKS

DECLARATIONS OF INTEREST

Gustavo Feriani: none known.

Eric Hatanaka: none known.

Maria R Torloni: none known.

Edina MK da Silva: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

It was not possible to analyse time-to-event data with method of survival analysis due to lack of adequate data in the included studies.

One study included children up to 13 years of age. Although our review had established 10 years of age as a limit, we decided not to exclude this last study because it likely included few children over this age.

NOTES

Assessed for updating in 2018

A restricted search in February 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in early 2020. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2020

A restricted search in February 2020 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review earlier if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Local; Bupivacaine; Cleft Lip [*surgery]; Lidocaine; Nerve Block [*methods]; Orbit; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Infant; Male

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