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Maxillary distraction osteogenesis versus orthognathic surgery for cleft lip and palate patients (Review)

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[Intervention Review]

Maxillary distraction osteogenesis versus orthognathic surgery for cleft lip and palate patients

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ABSTRACT

Background

Cleft lip and palate is one of the most common birth defects and can cause difficulties with feeding, speech and hearing, as well as psychosocial problems. Treatment of orofacial clefts is prolonged; it typically commences after birth and lasts until the child reaches adulthood or even into adulthood. Residual deformities, functional disturbances, or both, are frequently seen in adults with a repaired cleft. Conventional orthognathic surgery, such as Le Fort I osteotomy, is often performed for the correction of maxillary hypoplasia. An alternative intervention is distraction osteogenesis, which achieves bone lengthening by gradual mechanical distraction. This review is an update of the original version that was published in 2016.

Objectives

To provide evidence regarding the effects and long-term results of maxillary distraction osteogenesis compared to orthognathic surgery for the treatment of hypoplastic maxilla in people with cleft lip and palate.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 15 May 2018), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2018, Issue 4), MEDLINE Ovid (1946 to 15 May 2018), Embase Ovid (1980 to 15 May 2018), and LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; from 1982 to 15 May 2018). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria

We included randomised controlled trials (RCTs) comparing maxillary distraction osteogenesis to conventional Le Fort I osteotomy for the correction of cleft lip and palate maxillary hypoplasia in non-syndromic cleft patients aged 15 years or older.

Data collection and analysis

Two review authors assessed studies for eligibility. Two review authors independently extracted data and assessed the risk of bias in the included studies. We contacted trial authors for clarification or missing information whenever possible. All standard methodological procedures expected by Cochrane were used.

Main results

We found six publications involving a total of 47 participants requiring maxillary advancement of 4 mm to 10 mm. All of them related to a single trial performed between 2002 and 2008 at the University of Hong Kong, but not all of the publications reported outcomes from all 47 participants. The study compared maxillary distraction osteogenesis with orthognathic surgery, and included participants from 13 to 45 years of age.

Results and conclusions should be interpreted with caution given the fact that this was a single trial at high risk of bias, with a small sample size.

The main outcomes assessed were hard and soft tissue changes, skeletal relapse, effects on speech and velopharyngeal function, psychological status, and clinical morbidities.

Both interventions produced notable hard and soft tissue improvements. Nevertheless, the distraction group demonstrated a greater maxillary advancement, evaluated as the advancement of Subspinale A-point: a mean difference of 4.40 mm (95% CI 0.24 to 8.56) was recorded two years postoperatively.

Horizontal relapse of the maxilla was significantly less in the distraction osteogenesis group five years after surgery. A total forward movement of A-point of 2.27 mm was noted for the distraction group, whereas a backward movement of 2.53 mm was recorded for the osteotomy group (mean difference 4.8 mm, 95% CI 0.41 to 9.19).

No statistically significant differences could be detected between the groups in speech outcomes, when evaluated through resonance (hypernasality) at 17 months postoperatively (RR 0.11, 95% CI 0.01 to 1.85) and nasal emissions at 17 months postoperatively (RR 3.00, 95% CI 0.14 to 66.53), or in velopharyngeal function at the same time point (RR 1.28, 95% CI 0.65 to 2.52).

Maxillary distraction initially lowered social self-esteem at least until the distractors were removed, at three months postoperatively, compared to the osteotomy group, but this improved over time and the distraction group had higher satisfaction with life in the long term (two years after surgery) (MD 2.95, 95% CI 014 to 5.76).

Adverse effects, in terms of clinical morbidities, included mainly occlusal relapse and mucosal infection, with the frequency being similar between groups (3/15 participants in the distraction osteogenesis group and 3/14 participants in the osteotomy group). There was no severe harm to any participant.

Authors' conclusions

This review found only one small randomised controlled trial concerning the effectiveness of distraction osteogenesis compared to conventional orthognathic surgery. The available evidence is of very low quality, which indicates that further research is likely to change the estimate of the effect. Based on measured outcomes, distraction osteogenesis may produce more satisfactory results; however, further prospective research comprising assessment of a larger sample size with participants with different facial characteristics is required to confirm possible true differences between interventions.

PLAIN LANGUAGE SUMMARY

Maxillary distraction osteogenesis versus orthognathic surgery for cleft patients

Background

Cleft lip and palate is one of the most common birth defects and can cause difficulties with feeding, speech and hearing, as well as psychosocial problems. Treatment of clefts is lengthy, typically taking from birth to adulthood to complete. Upper jaw growth in cleft patients is highly variable, and in a relatively high percentage, it does not develop completely. A type of surgery called orthognathic surgery, which involves surgical cutting of bone to realign the upper jaw (osteotomy), is usually performed in this situation. An alternative intervention is known as distraction osteogenesis, which achieves bone lengthening by gradual mechanical distraction (cutting of bone and moving the ends apart incrementally to allow new bone to form in the gap). This review is an update of the original version that was published in 2016.

Review question

This review, produced through Cochrane Oral Health, examines the benefits and risks of distraction osteogenesis for advancing the upper jaw compared to conventional orthognathic surgery in adolescents and adults.

Study characteristics

The evidence on which this review is based is up to date as of 15 May 2018. We found six relevant articles to include in this review. All are related to one single study conducted in Hong Kong between 2002 and 2008. The study involved 47 participants aged 13 to 45 years of age. It investigated the effects of the two surgical procedures on alteration of face morphology, stability of upper jaw after surgery, speech and

velopharyngeal function (ability to close the gap between the soft palate and nasal cavity to produce sound), psychological status of the participants and clinical side effects.

Key results

Both procedures were effective in producing better facial structure in cleft patients. Upper jaw was more stable in the distraction osteogenesis group than the conventional osteotomy group five years after surgery. There was no difference in speech and velopharyngeal function between the procedures. Social self esteem in the maxillary distraction group initially seemed to be lower than in the conventional surgery group, but this improved over time and the distraction group had higher satisfaction with life two years after surgery. Side effects included deterioration of the fit between the teeth when the mouth is closed and infection of muscous membranes of the nose and mouth, but the frequency of these problems was similar between groups. There was no severe harm to any participant.

Quality of the evidence

We judged the quality of the evidence to be very low. The one study was small and there were concerns about aspects of its design and reporting; therefore we have found no reliable evidence as to which procedure should be regarded superior. High quality clinical trials, which involve lots of people, and different face types, are required to guide decision making.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table for patient-important outcomes

Maxillary distraction osteogenesis versus orthognathic surgery for cleft patients

Patient or population: Cleft patients
Setting: University hospital in Hong Kong
Intervention: Maxillary distraction osteogenesis
Comparison: Orthognathic surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with orthognathic surgery	Risk with maxillary distraction osteogenesis				
Maxillary advancement (in mm) assessed with lateral cephalograms Follow-up 2 years	Mean maxillary advancement was 4.90 mm	Mean maxillary advancement in the intervention group was 4.4 mm more (0.24 more to 8.56 more)	-	39 (1 RCT)	⊕⊖⊖⊖ **very low** [1, 2, 3]	Statistically significant difference between groups, in favour of distraction osteogenesis
Long-term skeletal relapse (in mm) assessed with lateral cephalograms Follow-up 5 years	Mean relapse was −2.53 mm (horizontal movement of A-point)	Mean net gain in forward movement in the intervention group was 4.8 mm more (horizontal movement of A-point) (0.41 more to 9.19 more)	-	16 (1 RCT)	⊕⊖⊖⊖ **very low** [1, 2]	Only 16 participants (out of the 47) assessed 5 years postoperatively Short-term relapse was assessed in 24 participants 1 year postoperatively: mean relapse in CO group was −3.5 mm (horizontal movement of A-point), whereas the net gain of the DO group was 7.2 mm (0.4 more to 14 more)
Speech (deterioration/improvement) assessed with resonance	Deteriorated participants		RR 0.11 (0.01 to 1.85)	22 (1 RCT)	⊕⊖⊖⊖	

Follow-up mean 17 months	364 out of 1000	40 out of 1000 (4 to 673)			**very low** [2, 3, 4]	
Velopharyngeal function (deterioration/improvement) assessed with nasoendoscopy Follow-up mean 17 months	Participants with complete velopharyngeal closure		RR 1.28 (0.65 to 2.52)	21 (1 RCT)	⊕⊖⊖⊖ **very low** [2, 3, 4]	
	545 out of 1000	425 out of 1000 (218 to 834)				
Psychological status assessed with Satisfaction with Life Scale (SWLS), a 7-point Likert-type scale from strongly disagree to strongly agree, where higher scores indicate greater satisfaction with life Follow-up 2 years	Mean score was 24	Mean score was 2.95 higher (0.14 higher to 5.76 higher)	-	30 (1 RCT)	⊕⊖⊖⊖ **very low** [1, 2, 3]	Statistically significant difference between groups, in favour of distraction osteogenesis Social self esteem measured by Cultural-Free Self-Esteem Inventory showed a difference between the groups at 2 to 8 weeks and at 3 months postoperatively, with lower scores for the distraction group
Clinical morbidities assessed with questionnaires Follow-up 12 months	3/14	3/15	-	29 (1 RCT)	⊕⊖⊖⊖ **very low** [1, 2, 3]	Morbidities similar in type and frequency between groups

*__The risk in the intervention group__ (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels for limitation in design and implementation due to selection, performance, detection, attrition and reporting bias

2 Downgraded one level for indirectness of evidence: very narrow range of participants with specific ethnic and disease characteristics
3 Downgraded one level for imprecision: wide confidence Interval and no power calculation reported for this outcome
4 Downgraded two levels for limitation in design and implementation due to selection, performance, attrition and reporting bias

BACKGROUND

Orofacial cleft (OC) can be defined as the non-fusion of the facial structures that occurs between the 5th and 10th week of gestation. The global prevalence of OCs is about 1 per 500 to 700 of live births. This rate varies considerably across different ethnic groups and geographical regions (WHO 2012). OCs are, therefore, one of the most common congenital anomalies, with a higher birth prevalence than neural tube defects or Down's syndrome.

Although unique causal factors remain unknown, it is currently widely accepted that OCs are of multifactorial aetiology, with genetic predisposition and environmental influence playing a role (Hayes 2002). While no strong risk factors have been identified, maternal cigarette smoking (Chung 2000), alcohol consumption (Romitti 1999; Romitti 2007; Shaw 1999), anti-epileptic drugs (Hecht 1989; Hecht 1990) or corticosteroids administered topically or systematically (Czeizel 1997) have been associated with increased incidence of various subtypes of clefts. Inadequate maternal nutrition during pregnancy, and lower socioeconomic status, have also been suspected as conducive to occurrence of oral clefts (Shaw 1995; Wong 1999). Influence of a genetic defect is obvious in some syndromic forms of orofacial clefts. For example, a deletion in chromosome 1q32-q41 or in a second chromosomal locus at 1p34 has been linked to the Van der Woude syndrome that manifests with cleft lip and/or palate and lower lip pits, but the exact mechanism of influence of this mutation on craniofacial development is uncertain (Oberoi 2005). In non-syndromic clefts, however, understanding of multi-gene and gene-environmental interactions in the development of the cleft is incomplete (Mossey 2007).

Description of the condition

Treatment of OCs is prolonged and is usually delivered by multidisciplinary teams. The cleft patient is typically treated from birth until he or she reaches adulthood or even into adulthood. Despite the fact that a great volume of research concerning treatment strategies of OCs has been undertaken, there is still much debate concerning the best treatment protocol. This was highlighted in the 1996 to 2000 Eurocleft project, where substantial differences between the registered centres were found. Two hundred and one participating teams practised 194 different protocols for one cleft subtype (Shaw 2001).

Furthermore, residual deformities or functional disturbances, or both, are frequently seen in adults with a repaired cleft. The extent of residual deformities varies, and depends on the cleft subtype. In a relatively homogeneous category (cleft lip and palate), the resulting growth disturbances range from increased interocular width to a general retrusion of the midface relative to the cranial base. In fact, maxillary retrusion/hypoplasia can be a common clinical problem because a relatively high percentage of patients with cleft lip and palate develop a severe maxillary hypoplasia, which cannot be treated with orthodontics alone but requires complex orthognathic surgical procedures (Mølsted 2005; Nollet 2008; Scolozzi 2008).

The aim of the orthognathic operation is to achieve an aesthetic and functional result by a displacement of the maxilla that will correct the pathological condition in all three planes of space (vertical, horizontal, and transversal), which, in turn, is associated with the patient's psychological adjustment. This displacement of the maxilla, however, could influence other parameters, such as velopharyngeal function and speech ability. There are two widely used types of orthognathic procedures: conventional orthognathic surgery and distraction osteogenesis.

Description of the intervention

The conventional orthognathic surgery for correction of maxillary retrusion/hypoplasia is a Le Fort I osteotomy. The word 'osteotomy' designates the division, or excision of bone. The bony segment is cut, adapted, and repositioned to correct a dentofacial deformity. It is held in the correct position (fixed) with the aid of wires or rigid fixation plates. Over the past decades, a Le Fort I osteotomy with rigid fixation has become a standard approach.

Distraction osteogenesis is the surgical process of correction of skeletal deformity using bone lengthening by gradual mechanical distraction. It was first introduced in orthopaedics by Codivilla in 1905 but it was further developed and popularised by Ilizarov in the 1950s (Ilizarov 1989). Following the favourable outcomes of distraction osteogenesis in orthopaedics, it was first used in orthognathic surgery in 1992 (McCarthy 1992). Since then, distraction osteogenesis has been accepted as an effective method for the treatment of various craniofacial anomalies ranging from cleft lip and palate to craniosynostosis, to hemifacial microsomia and transverse discrepancies (Iannetti 2004).

How the intervention might work

In people with OCs, Le Fort I surgery can be performed as a single-piece or multi-piece osteotomy. The former is carried out if there is adequate alveolar continuity achieved after a successful bone graft, whereas the latter is performed in circumstances where a notable residual alveolar defect with a substantial dental gap and oronasal fistulae are present. Also, in cases where additional expansion of the maxillary arch is needed, segmentalization of the maxilla may be required during Le Fort I surgery (Phillips 2012). Irrespective of the type of Le Fort I surgery (single- or multi-piece), the goal is to displace the maxilla forward to obtain adequate occlusion, and good support for the nose and upper lip; and close fistulae, if present.

Distraction osteogenesis consists of several phases. After attachment of the distracting device and the bone cuts, latency phase ensues. In this three- to seven-day period after the initial bone cuts, the callus forms. In the next phase (activation), bony in-growth is induced by distraction of the callus. This phase lasts from a few to more than 15 days, depending on the required change. Once the desired bone length has been attained, the distraction device remains in situ. It acts as a rigid skeletal fixation device until maturation of the new bone is accomplished. This phase is termed as a consolidation period. Distraction osteogenesis has been suggested to be an equivalent, or even superior, alternative to conventional orthognathic surgery for people who have a midface deficiency associated with cleft lip and palate (Shaw 2002).

Various designs for both internal and external distraction devices have been used and described in the literature. Current intraoral systems provide reasonable patient acceptance, multidirectional force exertion and improved vector control, often on an ongoing basis during the distraction phase. On the other hand, external distractors do not require a second operation for removal of the device following bone consolidation (Phillips 2012). The clinical

indications for, and use of, external or internal distractors, or a combination of them, remain subjective (Nada 2010).

Facial structure is influenced by racial and ethnic background as well as cleft lip and palate, and whether the treatment effect varies across different ethnic groups is unclear. For example, concave profiles, either from retruding maxilla or protruding mandible, often indicating an Angle Class III occlusion that is more prevalent in Asian populations, may have different results than straight or convex profiles.

Why it is important to do this review

McCarthy 2001 reported the first 11 years of experimental and clinical experience with mandibular distraction osteogenesis indicating that distraction osteogenesis of the craniofacial skeleton produced favourable results. However, Shaw 2002's critical appraisal of 88 studies on distraction osteogenesis published from 1995 to 2000 found that almost all publications were based on retrospective studies, with short-term evaluation of small numbers of patients deriving from heterogeneous patient populations without controls. Some have argued that the outcome of orthognathic surgery might not be as stable as the one produced by distraction osteogenesis. In a systematic review on maxillary advancement with conventional orthognathic surgery in patients with cleft lip and palate, Saltaji 2012a found that the maxilla suffers a moderate relapse in the horizontal plane and a higher relapse in the vertical plane. Another systematic review by the same author came to the conclusion that maxillary advancement with distraction osteogenesis has good stability in cleft patients with moderate and severe maxillary hypoplasia (Saltaji 2012b). Distraction osteogenesis and orthognathic surgery have, thus, been both widely used in cleft surgery, but there is still great uncertainty as to which is the optimal corrective method, especially when patient-related outcomes, such as speech or velopharyngeal function, psychological aspects and quality of life are considered, as well as potential variation in the treatment effect across different ethnic groups.

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain on the Cochrane Library (Worthington 2015). This review was identified as a priority title by the oral and maxillofacial surgery expert panel (Cochrane OHG priority review portfolio).

Hence, taking into account that most evidence regarding the relative value of distraction osteogenesis and orthognathic surgery is of low quality, and that systematic reviews already published focused either solely on maxillary advancement or did not directly compare distraction osteogenesis and orthognathic surgery, there is an urgent need to identify the best available evidence and to conclude which of the two — distraction osteogenesis or orthognathic surgery — is a better treatment for people with OC in need of surgical correction.

OBJECTIVES

To provide evidence regarding the effects and long-term results of maxillary distraction osteogenesis compared to orthognathic surgery for the treatment of hypoplastic maxilla in people with cleft lip and palate.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Non-randomised or quasi-randomised controlled trials were not eligible for inclusion.

Types of participants

Adults or adolescents, 15 years of age or older, with an established diagnosis of complete cleft lip and alveolar process, complete unilateral cleft lip and palate, and complete bilateral cleft lip and palate (involving the alveolar process).

We excluded studies with participants presenting syndromic conditions, atypical clefts (for example, midline) or unclear diagnosis regarding the type of cleft.

Types of interventions

Surgical procedures, namely maxillary distraction osteogenesis or orthognathic surgery (conventional Le Fort I maxillary osteotomy), to correct cleft lip and palate maxillary hypoplasia.

Types of outcome measures

In order to be included, studies had to report at least one of the outcomes of interest in the review.

Primary outcomes

1. Midfacial soft and hard tissue changes, assessed with lateral cephalometric radiography and/or photographic archives and their superimposition, when applicable. Transversal maxillary changes assessed with anteroposterior cephalometric radiography or digital cast models of the occlusion.
2. Surgical relapse/stability, assessed with lateral cephalographs taken at different postoperative times.
3. Perceptual speech assessment, i.e. articulation, resonance (hypernasality and hyponasality) and nasal emission using video or any other form of voice recording device, conducted by a professional speech-language therapist.

Secondary outcomes

1. Instrumental assessment of velopharyngeal function. Nasoendoscopy or videonasopharyngoscopy or videofluoroscopy to assess the velopharyngeal gap size at rest and closure.
2. Patient-reported outcomes: assessment of self-esteem and psychological adjustment by validated and internationally accepted questionnaires.
3. Adverse effects or clinical morbidities of the surgical procedures, such as mucosal infection, sinusitis, transection of vessels.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 15 May 2018) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4) in the Cochrane Library (searched 15 May 2018) (Appendix 2);
- MEDLINE Ovid (1946 to 15 May 2018) (Appendix 3);
- Embase Ovid (1980 to 15 May 2018) (Appendix 4);
- LILACS BIREME (Latin American and Caribbean Health Science Information database; 1982 to 15 May 2018) (see Appendix 5).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

Ongoing trials

The following trial registries were searched for ongoing studies (see Appendix 6 for details of the search strategy):

- US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov; searched 15 May 2018);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 15 May 2018).

Handsearching

We examined the reference lists of relevant articles and contacted the investigators of included studies by electronic mail to ask for details of additional published and unpublished trials.

We identified the following journals as being important to search for this review. Where these had not already been searched as part of the Cochrane Journal Handsearching Programme, we handsearched these journals:

- *Cleft Palate and Craniofacial Journal* (2003 to 04 June 2018);
- *International Journal of Oral and Maxillofacial Surgery* (2003 to 04 June 2018);
- *Plastic and Reconstructive Surgery* (2005 to 04 June 2018);
- *Journal of Oral and Maxillofacial Surgery* (2009 to 04 June 2018);
- *British Journal of Oral and Maxillofacial Surgery* (2005 to 04 June 2018);
- *Journal of Cranio-Maxillofacial Surgery* (2005 to 04 June 2018).

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of studies identified through the searches. We managed the citations using a reference management software program (Endnote X7 2015). The search was designed to be sensitive and include controlled clinical trials, these were filtered out early in the selection process if they were not randomised. We obtained full copies of all studies appearing to meet the inclusion criteria and those for which there were insufficient data in the title and abstract to make a clear decision. Two review authors assessed the full-text papers independently and resolved any disagreement about the eligibility of included studies through discussion with a third review author. From this group of studies, we recorded the studies that did not meet the inclusion criteria and reported the reasons for exclusion in the Characteristics of excluded studies section of the review.

Data extraction and management

We designed and piloted data extraction forms to record authorship, year of publication, country of origin and details of the participants including demographic characteristics and criteria for inclusion. We entered study details into the Characteristics of included studies tables in Review Manager 5 (RevMan; RevMan 2014). Two review authors extracted data independently; any disagreements were resolved by consulting with a third review author. We extracted the following details, where reported.

1. Trial methods: method of randomisation; method of allocation and whether concealed or not; conduct of sample size calculation; blinding of participants, trialists and outcome assessors; exclusion of participants after randomisation; proportion of, and reasons for, losses at follow-up; and number of centres.
2. Participants: country of origin, year and study setting; sample size; age; gender; inclusion and exclusion criteria.
3. Intervention: type; surgical technique used; duration of treatment; details of surgical devices (for example, type of distractor); time of follow-up.
4. Control: type; surgical technique used; time of follow-up.
5. Outcomes: primary and secondary outcomes mentioned in the Types of outcome measures section of this review.

If stated, we recorded sources of funding, trial registration and publishing of the trial's protocol. We used this information to aid assessment of heterogeneity and the external validity of the included trials.

Assessment of risk of bias in included studies

Two review authors (DK, PF) independently assessed risk of bias in the included trials using Cochrane's tool for assessing risk of bias as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the assessments and resolved any disagreements through discussion. We assessed the following domains as at low, high or unclear risk of bias:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias), and outcome assessors (detection bias);
4. incomplete outcome data addressed (attrition bias);
5. selective outcome reporting (reporting bias);
6. other bias.

We categorised and reported the overall risk of bias of each included study according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were assessed as at low risk of bias;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were assessed as at unclear risk of bias; or

- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were assessed as at high risk of bias.

Measures of treatment effect

We planned to assess outcomes at more than one time point in the follow-up period. All such assessments were recorded and decisions on which time-of-outcome assessment to use from each study were based on the most commonly reported timing of assessment among all included studies.

We presented outcomes using continuous data (for example, cephalometric landmarks for maxillary relapse/stability and hard/soft tissue changes) as mean differences with 95% confidence intervals (CI) between the intervention and control groups. We presented dichotomous data (for the assessment of speech) as risk ratios (RR) and 95% CI.

Unit of analysis issues

We anticipated that some of the included studies would present data from repeated observations on participants, which could lead to unit-of-analysis errors. In this case, we would have followed the advice provided in section 9.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

In studies where data were unclear or missing, we contacted the principal investigators or the corresponding author, or both. If missing data were unavailable, we followed the advice given in section 16.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions,* i.e. explicitly describe the assumptions to cope with missing data, perform sensitivity analyses and explore the potential impact of missing data on findings (Higgins 2011).

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in Criteria for considering studies for this review.

Assessment of reporting biases

Reporting biases arise when the reporting of research findings is affected by the nature or direction of the findings themselves. We attempted to minimise potential reporting biases including publication bias, multiple (duplicate reports) publication bias and language bias in this review, by conducting an accurate and at the same time a sensitive search of multiple sources with no restriction on language. We also searched for ongoing trials. If there had been more than 10 studies in one outcome, we would have constructed a funnel plot (Egger 1997) and investigated any asymmetry detected.

Data synthesis

We planned to conduct meta-analyses if there were studies of similar comparisons reporting the same outcomes. Risk ratios would have been combined for dichotomous data using fixed-effect models, unless there were more than three studies in the meta-analysis, when random-effects models would have been used.

Subgroup analysis and investigation of heterogeneity

In future updates, should there be sufficient data, we will conduct subgroup analyses to explore the influence of study characteristics such as various cleft subtypes, gender and treatment centres.

Sensitivity analysis

We planned to explore whether analysing studies stratified by risk of bias (overall low risk versus high risk) produced similar or different results.

Presentation of main results

We present Summary of findings for the main comparison, constructed using GradePro software (GradePro 2015), for the following patient-important outcomes.

- Maxillary advancement two years postoperatively.
- Long-term (and short-term) skeletal relapse.
- Speech, evaluated through resonance.
- Velopharyngeal function.
- Psychological status, evaluated with Satisfaction With Life Scale (SWLS).
- Clinical morbidities.

We assessed the quality of the body of evidence with reference to the overall risk of bias of the included studies, the directness of the evidence, the consistency of the results, the precision of the estimates, the risk of publication bias and the magnitude of the effect. The quality of the body of evidence for each of the primary outcomes was categorised as high, moderate, low or very low.

RESULTS

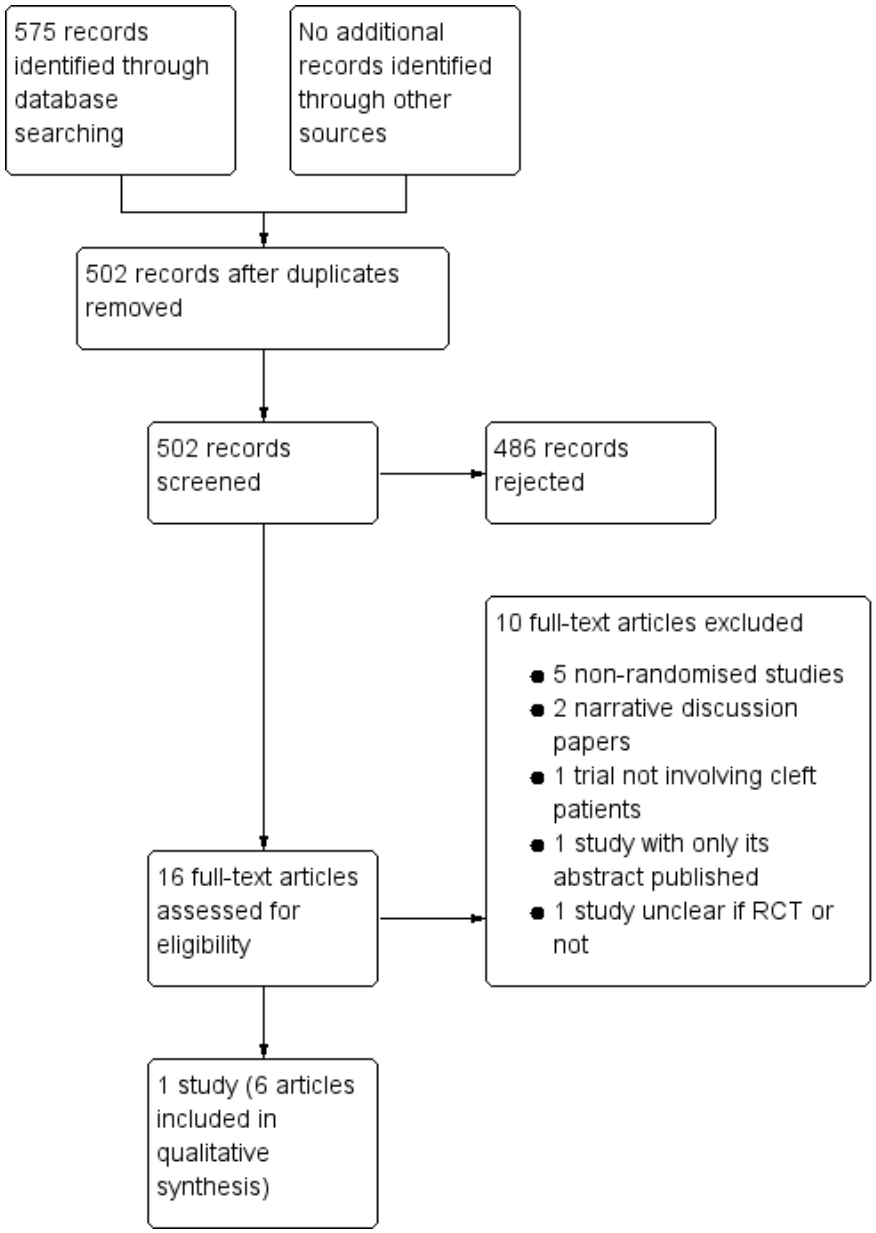
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The electronic searches resulted in 575 references, 502 remained after duplicates were removed. No further references were identified through other sources. We examined the titles and abstracts of these for eligibility and eliminated those not matching the inclusion criteria. Sixteen potentially relevant studies were identified. We obtained full-text articles of these studies. We subjected them to further evaluation and eliminated eight studies (see Characteristics of excluded studies). We excluded two studies previously categorised as 'awaiting classification': only a conference abstract was retrieved for Khader 2014, even after mail correspondence, and it remained unclear whether Yu 2012 was a RCT or not, although the corresponding author was e-mailed twice (Table 1). Careful examination of six papers eligible for inclusion indicated that all publications related to one single trial performed in University of Hong Kong (Chanchareonsook 2007; Cheung 2006a; Chua 2010a; Chua 2010b; Chua 2012a; Chua 2012b; Hong Kong Study 2002 to 2008). The principal investigators were e-mailed to clarify this and confirmed that all papers related to one randomised trial (see Table 1 for correspondence). We therefore had one study with six published papers to include in the review (see study selection process in Figure 1).

Figure 1. Study flow diagram



Included studies

We included one study in this review (Hong Kong Study 2002 to 2008). See Characteristics of included studies.

Characteristics of the trial settings and investigators

The study was carried out by specialists based in a university hospital setting in Hong Kong between June 2002 and 2008.

Characteristics of the participants

A total of 47 participants were included in the study. People aged 13 years old or more with mature skeletal growth (assessed as complete bone fusion of the radial epiphysis by radiography) requiring maxillary advancement ranging from 4 mm to 10 mm were eligible. Syndromic patients and patients with systemic diseases were excluded; as were patients requiring maxillary advancement of more than 10 mm or of less than 4 mm. There is some discrepancy in reporting of age: Cheung 2006a, Chua 2010a, Chua 2010b, Chua 2012a, and Chua 2012b reported recruitment of patients 15 years old or older; but one paper reported involving participants younger than 15 years old (one 13-year-old and one 14-year-old, out of the 22 participants included) (Chanchareonsook 2007).

Characteristics of the interventions

A standardised technique of maxillary distraction with the use of internal distractors was developed for the distraction osteogenesis (DO) group. Vestibular incisions and bone cuts were performed. The maxilla was fully mobilised but not moved to the final occlusal position. Internal bone-borne maxillary distractors were subsequently inserted and activated for a few millimetres to check the accuracy of maxillary transport. The mucosal wound was then

sutured to leave the activator rod external to the mucosal wound for later activation. Mandibular osteotomies were undertaken during the same operation, where planned. After a latency of three days, activation was commenced at 1 mm per day in two rhythms until a class I incisal relationship was achieved.

As control, there was a standard Le Fort I osteotomy group (CO). A standard Le Fort I osteotomy and down fracturing of the maxilla was performed. Maxillary segmentalization was carried out if planned. In this group, the maxilla was fully mobilised to the pre-planned final position. The mobilised maxilla was fixed with two titanium mini-plates on each side at the zygomatic buttress and the pyriform region (Chanchareonsook 2007; Cheung 2006a; Chua 2010a; Chua 2010b; Chua 2012a; Chua 2012b).

Characteristics of the outcomes

Study outcomes included:

- soft and hard tissue changes (Chua 2012b), assessed with lateral cephalograms;
- surgical relapse, either short- or long-term (Cheung 2006a; Chua 2010a), assessed with a sequence of lateral cephalograms. Short-term changes were considered to be these taking place in the first year postoperatively. Those occurring thereafter were considered as long term;
- effects of surgery on speech and velopharyngeal function (Chanchareonsook 2007; Chua 2010b): speech was evaluated by experts, examining resonance (hypernasality and hyponasality), nasal emission and articulation. Velopharyngeal function was also assessed by specialists, performing nasoendoscopy;
- psychological status of participants preoperatively and postoperatively (Chua 2012a): a set of standardised questionnaires was employed to quantify the psychological profile of each participant;
- clinical morbidities (Cheung 2006a), evaluated with questionnaires.

Excluded studies

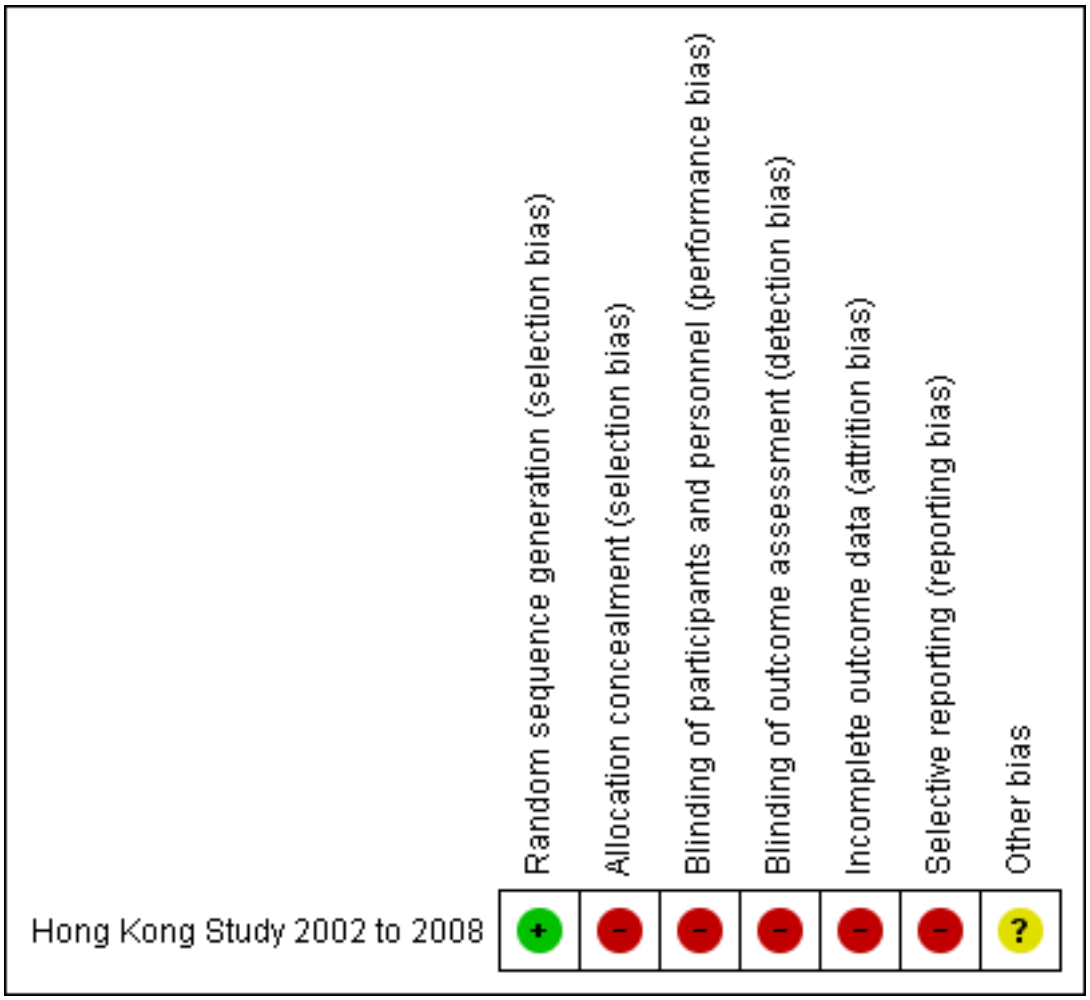
We excluded eight studies from this review: two were not trials, five were not randomised and one RCT did not include cleft participants. See Characteristics of excluded studies.

Risk of bias in included studies

Hong Kong Study 2002 to 2008, the only included study, was assessed as being at high risk of bias overall.

Further details of the assessments below are given in the 'Risk of bias' table corresponding to the study in the Characteristics of included studies section. Overall ratings are also presented in the 'Risk of bias' summary table (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item



Allocation

The methods used to generate the allocation sequence and the procedure of concealing this sequence, so that participants and investigators cannot predict the upcoming intervention assignment, are the most important and sensitive indicators for minimising bias in a clinical trial (Schulz 1995). Although the method of sequence generation was described, allocation concealment was not reported. The e-mail communication with the corresponding author confirmed that intervention allocation was not concealed (Table 1). The study was therefore at high risk of selection bias.

Blinding

Blinding participants and personnel to the interventions considered in this review is probably not feasible. Two of the six publications relating to the study stated that the outcome assessments were independent of the investigators (Chanchareonsook 2007; Chua 2010b). In the other four publications, it was unclear whether the outcome assessors were blinded to the allocated interventions (detection bias) (Cheung 2006a; Chua 2010a; Chua 2012a; Chua 2012b); therefore, we judged the study to be at high risk of bias overall for this domain.

Incomplete outcome data

Only one publication reported no losses to follow-up (Chua 2010a). Two other publications can be considered as preliminary studies, although they examined almost half of the participants (Chanchareonsook 2007; Cheung 2006a). The remaining three reported many losses to follow-up, mainly because participants refused to be assessed (Chua 2010b; Chua 2012a; Chua 2012b); hence, the study overall was evaluated as at high risk of bias.

Selective reporting

Although the study protocol was unavailable, in general the outcomes listed in the Methods section were comparable to the reported results. Nevertheless, in two publications (Chua 2010a; Chua 2012b), the method of cephalometric analysis was not well established; Cheung 2006a provided no description of the standardised questionnaires and Chua 2010b gave no information about five participants in the control group. The study, overall, was judged to be at high risk of bias.

Other potential sources of bias

Since the study protocol was unavailable and the reporting of the methodology often conflicted among the six publications, the

study overall was judged as being at unclear risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table for patient-important outcomes

The results of the single included study, Hong Kong Study 2002 to 2008, are discussed for each outcome below and the data are presented in Data and analyses (Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.3; Analysis 1.4; Analysis 1.1; Analysis 1.5; Analysis 1.2). Some outcomes could only be presented narratively in text.

Soft and hard tissue changes

Soft and hard tissue alterations were presented in one article including 39 participants through the change in position of various cephalometric landmarks horizontally and vertically in relation to X and Y reference lines respectively (Chua 2012b). Assessments were performed from baseline to six months, one year and two years postoperatively. In both distraction osteogenesis (DO) and conventional osteotomy (CO) groups, notable positive soft tissue changes of the upper lip and nose were induced after maxillary advancement. The DO group demonstrated a greater maxillary advancement, evaluated as the advancement of Subspinale A-point: mean differences (MDs) of 5.63 mm (P = 0.003) six months postoperatively, 5.27 mm (P = 0.005) one year postoperatively and 4.40 mm (95% CI 0.24 to 8.56) two years postoperatively were recorded, compared to the CO group (Analysis 1.1).

Nevertheless, other between-group soft tissue differences were not statistically significant after two years of follow-up: changes in pronasale (MD 0.94 mm, P = 0.74), subnasale (MD −1.53 mm, P = 0.33) and stomion superius (MD −4.20 mm, P = 0.12). Changes in labrale superius reached statistical significance (MD −3.42 mm, P = 0.023) in the two-year follow-up period but, overall, did not provide firm evidence of aesthetic differences between groups, despite the fact that changes tended to be greater in the DO group (Chua 2012b).

Skeletal relapse

Two of the papers assessed short-term (Cheung 2006a) and long-term (Chua 2010a) relapse of the maxilla by comparing a series of lateral cephalograms, in 29 and 47 participants, respectively. A decision was made after we published our protocol regarding the definition of short- and long-term outcomes: we considered the outcomes evaluated in the first year postoperatively as short term; those occurring thereafter we considered as long term. Since data overlapped, only those from the later study, Chua 2010a, were used for the analysis (Analysis 1.2).

Short-term relapse of the maxilla was found to be greater in the CO group than in the DO group. This was indicated by a backward and upward movement of the maxilla at each postoperative time period assessed (up to one year postoperatively) compared to the distraction group (Cheung 2006a). The DO group demonstrated a mean forward horizontal change of the maxilla at A-point (Subspinale A-point) of 3.7 mm (mean difference 7.2 mm for distraction group, 95% CI 0.40 to 14.00). P-point (micro-screw above the mesial root of the upper first molar) also moved forward 2.4 mm. In comparison, the CO group experienced 3.5 mm of backward movement at A-point and 1.8 mm of backward movement at P-point.

Assessment of the long-term relapse of the maxilla at the five-year follow-up was found to produce similar results as the short-term assessment between groups (Analysis 1.2). Although more participants were evaluated (N = 47) during the five years, only 16 were assessed at the time point of five years postoperatively: following maxillary distraction, the mean horizontal change of the maxilla at A-point was an overall forward movement of 2.27 mm (mean difference 4.8 mm, 95% CI 0.41 to 9.19). P-point also moved forward 2.51 mm. In comparison, the CO group experienced 2.53 mm of backward movement at A-point and 2.45 mm of backward movement at P-point (Chua 2010a).

As far as dental occlusion and not superimposition of cephalometric landmarks is concerned, three of the 25 CO participants relapsed into a Class III malocclusion at five years postoperatively, despite orthodontic intervention and surgical repositioning. This compared to one of the 22 participants in the DO group (Chua 2010a).

Speech and velopharyngeal function

Two papers demonstrating results from 22 out of the 47 participants assessed these outcomes associated with speech and velopharyngeal function, both pre- and postoperatively (Chanchareonsook 2007; Chua 2010b). Since there was a definite overlap of participants presented in the two papers, only those presented in the later paper were used for the analysis (Analysis 1.3; Analysis 1.4; Analysis 1.5). No statistically significant differences could be detected between the groups in speech outcomes, when evaluated through resonance (hypernasality) at 17 months postoperatively (RR 0.11, 95% CI 0.01 to 1.85) or nasal emission at 17 months postoperatively (RR 3.00, 95% CI 0.14 to 66.53). There was no evidence of a difference in velopharyngeal function at the same time point (RR 1.28, 95% CI 0.65 to 2.52).

Psychological status

The psychological status of 30 participants (15 in each group) was assessed up to two years postoperatively (Analysis 1.6; Analysis 1.7; Analysis 1.8). Three self-reported questionnaires were employed: a) Social Avoidance and Distress Scale (SADS) to assess social anxiety and distress behaviour; b) Cultural-Free Self-Esteem Inventory (CFSEI) to assess the level of self-esteem of participants; and c) Satisfaction With Life Scale (SWLS) to measure the subjective well-being of the participants (Chua 2012a).

There was no evidence of a difference between the DO and CO groups in terms of SADS score at any timepoint (Analysis 1.6). Nor was there any evidence of a difference between the groups in terms of general self esteem measured by CFSEI (Analysis 1.7), though in terms of social self-esteem (subset of the CFSEI), DO participants had lower social self-esteem in the first three months postoperatively, with a statistically significant difference between groups at that time point (P = 0.023). At six months postoperatively, there was no evidence of a difference in social self-esteem between groups (P = 0.896).

CO participants considered themselves to be 'slightly satisfied' with life at every follow-up period (preoperatively and two to eight weeks, three months, six months, one year and two years postoperatively). DO participants were 'slightly satisfied'

preoperatively and there was a gradual rise in SWLS scores from three months postoperatively onwards. At two years postoperatively, life satisfaction was statistically significantly greater in the DO group than in the CO group (P = 0.001) (Analysis 1.8).

Clinical morbidities

One paper reported clinical postoperative complications (up to one year postoperatively) and intraoperative difficulties (Cheung 2006a). No difference was found in the frequency of the short-term complications among the 29 participants of the two groups: 3/15 participants in the DO group and 3/14 participants in the CO group presented with clinical complications. Moreover, intra- and post-operative complications were similar across groups and no severe harm to any participant was observed. The recorded side effects in both groups were infection around the distractors, intraoperative haemorrhage, sinusitis and occlusal relapse. The trial authors acknowledged, however, that the complications experienced in both groups may be of limited generalisability due to the small sample size.

DISCUSSION

Summary of main results

In this review, we identified and included only one trial (reported in six publications). The trial assessed the effectiveness of distraction osteogenesis compared to conventional orthognathic surgery for the correction of moderate maxillary hypoplasia in individuals with cleft lip and palate by evaluating different outcomes. Our risk-of-bias analysis exposed serious limitations in the trial's methodological quality and reporting, and we judged it to be at very high risk of bias overall. It was a small study with a total of 47 participants.

The findings of the review suggest that both distraction osteogenesis and conventional osteotomy can produce significant soft tissue improvement of the lip and nose, although there are some small aesthetic differences between the two groups. There appears to be a possible differentiation between the two surgical modalities in relation to skeletal stability of the maxilla. Distraction osteogenesis may produce more stable results, especially in the long term. On the other hand, no difference could be detected as far as effects on speech and velopharyngeal status are concerned. Finally, with respect to psychological status of participants, distraction osteogenesis in the early postoperative period (until the distractors are removed at three months postoperatively) seems to reduce social self-esteem. Nevertheless, in the long term, it may result in better life satisfaction when compared to the osteotomy group.

The overall quality of the evidence is very low and therefore findings should be interpreted with caution (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

With any surgical procedure, there are associated benefits and risks; on the basis of the present review there is limited evidence demonstrating a significant advantage of one procedure over the other. The optimal approach to comparing the effectiveness of two different surgical interventions is the randomised controlled trial (RCT) as the potential for bias and confounding variables can be kept to a minimum. The limited amount of evidence identified in this review may reflect the relative difficulties in conducting RCTs in such patients or context. This perspective is reinforced by the fact that no registered clinical trial was identified on this topic during initial development and when updating this review. Several clinical studies exist in the literature, but most of them are retrospective studies, case series or case reports.

Although six publications were identified for inclusion in this review, all proved to be part of the same trial, recruiting a small number of participants from Hong Kong. This trial appeared to have serious deficiencies in the way it was designed, conducted and reported. Sample size calculation prior to study commencement was not reported, but provided by the corresponding author after e-mail contact (Table 1). The power calculation was reportedly carried out for 'skeletal relapse' only, therefore the study may not have been adequately powered to detect a true difference between interventions for the other outcomes reported. This is even more pronounced when it was evident that not all participants were evaluated for each outcome studied, across the six publications. Conflicting reporting in the six published papers was also an important issue. The trial was classified as at 'high risk' of bias and, unfortunately, cannot provide reliable evidence to guide clinical decision making.

Quality of the evidence

Limitations in study design and implementation

Although Hong Kong Study 2002 to 2008 was a randomised trial, our assessment of risk of bias exposed serious limitations in its quality. Assessment of study quality was, moreover, complicated by incomplete and often contradictory reporting between the six published papers. Applying GRADE criteria, the quality of evidence was downgraded two levels for susceptibility to very serious risk of bias, since the study proved to be prone to selection, performance, detection, attrition and reporting bias (Summary of findings for the main comparison). Most importantly, while blinding of the investigators and participants to the interventions was not possible in this context, blinding the outcome assessors was feasible, but reporting was unclear. Independent and masked postoperative evaluation could have helped to limit the effects of subjectivity in the assessment of the outcomes.

Indirectness of the evidence

This review is based on a single trial that treated a narrow range of participants with specific ethnic and disease characteristics. Applying GRADE criteria, we downgraded the quality of evidence one level for this reason (Summary of findings for the main comparison). The study focused, moreover, on internal distraction, ignoring alternative distraction treatment protocols, such as external distraction. The outcome measures reported are likely to be indicative of the effect of distraction osteogenesis in general; however, given that they constitute just one treatment modality, it is possible that use of these measures may overstate or understate the impact of other distraction procedures.

Imprecision of results

The fact that only one study was included in this review, of small sample size and with various outcome variables being examined, did not permit any substantive assessment of the degree of precision of effect. Applying GRADE criteria, we downgraded

the quality of the evidence twice: once because of vulnerability to attrition and reporting bias, leading to results mostly not statistically significant with wide confidence intervals; and another one level for all outcomes except skeletal relapse, since power calculation was reported only for this outcome (Summary of findings for the main comparison).

Inconsistency of results

There was only one study in the review; therefore it was not possible to assess inconsistency.

Publication bias

Every effort was made to identify additional published and unpublished studies. As there was only one study, funnel plot assessment of publication bias was not possible (Higgins 2011).

Potential biases in the review process

Cleft lip, cleft palate and cleft lip and palate are three different cleft subphenotypes that might have a significant effect in terms of outcomes. However, the included study through its six published papers did not provide enough information about the proportions of each subphenotype to allow us to draw firmer conclusions.

Efforts were made to limit bias in the review process by ensuring a comprehensive and broad search for potentially eligible studies. The independent, duplicate assessments of eligibility of studies for inclusion in this review and the extraction of data limited the likelihood of additional bias.

Agreements and disagreements with other studies or reviews

The findings of this review almost concur with those of a systematic review that analysed the same study, treating and presenting its published articles as separate trials, although inferring that they were part of a single trial (Austin 2015). Review methodology and risk of bias assessment differed between the two reviews, but Austin 2015 also concluded that the existing evidence base is insufficient for clinical decision making.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support or refute the effectiveness of distraction osteogenesis over orthognathic surgery for cleft patients. While significant inter-individual variation exists, distraction osteogenesis may exhibit less skeletal relapse in the long term. However, there is currently no robust evidence to suggest which treatment modality produces best results. Further prospective research is required to confirm the possible benefits of distraction osteogenesis over orthognathic surgery.

Implications for research

The difficulty encountered with all new and emerging techniques is that whenever an intervention is not supported by high quality evidence, it cannot be inferred that the intervention is ineffective; it can only be concluded that there is inadequate evidence. Only new studies can then contribute to acquiring the evidence needed. On the other hand, the control of multiple variables necessary for such randomised controlled trials makes the designing of new studies difficult. Finally, the strict inclusion criteria and the scarcity of patients with specific characteristics willing to participate in a study make it difficult to achieve a proper sample size.

Nevertheless, there is always room for improvement in research. Only if further trials are robust, properly designed and reported in accordance with the CONSORT statement (www.consort-statement.org) or the extensions of the CONSORT statement, can firm conclusions be drawn. Trialists should also carefully consider the IDEAL recommendations for clinical trials evaluating surgical interventions (Ergina 2009; McCulloch 2009). Clear conduct and reporting will help with appraisal of study results, and accurate judgements about risk of bias and the overall quality of the evidence. Moreover, studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995).

Consideration should also be given to the necessity of developing a core outcome set for future cleft trials. A core outcome set is a standardised set of outcomes that should be assessed and reported, as a minimum, in all trials for a specific health area. This would allow results of studies to be compared, contrasted and combined as appropriate, as well as ensuring that all trials contribute usable information, reducing inconsistency in outcome measurement (Gargon 2014). This core outcome set could include long-term outcomes and outcomes that demonstrate patient values, so that the needs and perspectives of cleft patients are reflected (Bruce 2015; Harman 2015; Tsichlaki 2014).

No registered clinical trial was identified on this topic during initial development or when updating this review. Several clinical studies exist, but most of them are retrospective studies, case series or case reports. Since present data do not allow to draw firm conclusions on the topic, there is an urgent need for high-quality RCTs.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [author-defined order]

Hong Kong Study 2002 to 2008

Methods	Design: single-centre RCT, University of Hong Kong, 2002 to 2008 Length of follow-up: Cheung 2006a: 2 and 8 weeks and 3, 6 and 12 months postoperatively Chanchareonsook 2007: 3 months postoperatively Chua 2010a: 2 and 8 weeks, 3 and 6 months and 1, 2, 3, 4 and 5 years postoperatively Chua 2010b: 3 months, 1 and 2 years postoperatively Chua 2012a: preoperatively and postoperatively at the 2nd to 8th week, 3 and 6 months, 1 and 2 years Chua 2012b: preoperatively and postoperatively at the 2nd week, 2, 3 and 6 months, 1 and 2 years
Participants	Inclusion criteria: patients aged 13 years old or more (age range 13 to 45) with mature skeletal growth (assessed as complete bone fusion of the radial epiphysis by radiography); patients who required maxillary advancement ranging from 4 mm to 10 mm Exclusion criteria: syndromic patients and patients who presented with systemic diseases; patients who required maxillary advancement of more than 10 mm or of less than 4 mm Number, sex, age of participants: Cheung 2006a: 29 randomised, 15 males and 14 females, age range not reported Chanchareonsook 2007: 22 randomised, 11 males and 11 females, age range: 13 to 45 years old Chua 2010a: 47 randomised, sex not reported, age range not reported Chua 2010b: 47 randomised, but only 22 analysed, 11 males and 11 females, age range: 16 to 22 years old Chua 2012a: 30 randomised, 17 males and 13 females, age range not reported Chua 2012b: 47 randomised, 39 analysed (8 had soft tissue surgery within 6 months postoperatively), 20 males and 19 females, age range: 16 to 22 years old
Interventions	Intervention group receiving maxillary distraction osteogenesis: a conventional Le Fort I was performed and maxilla was mobilised. Bilateral intraoral distractors were inserted and fixed on the zygomatic buttress and molar alveolar region Control group of Le Fort I surgery: the maxilla was fully mobilised to the planned position. The mobilised maxilla was fixed by titanium miniplates at the zygomatic buttress and the pyriform region

Hong Kong Study 2002 to 2008 *(Continued)*

	Treatment duration Distraction osteogenesis group: activation phase of distraction started on postoperative day 3 at a distraction rate of 1 mm/day in two rhythms until a class I incisal relationship was achieved Cheung 2006a: intervention (n = 15), control (n = 14) Chanchareonsook 2007: intervention (n = 12), control (n = 10) Chua 2010a: intervention (n = 22), control (n = 25) Chua 2010b: intervention (n = 22), control (n = 25) Chua 2012a: intervention (n = 15), control (n = 15) Chua 2012b: intervention (n = 22), control (n = 25)
Outcomes	Primary outcomes (secondary outcomes n/a) Cheung 2006a: comparison of the postoperative clinical morbidities in the two groups with standardised questionnaires; comparison of surgical relapse through lateral cephalometric assessment Chanchareonsook 2007: velopharyngeal function (nasoendoscopy); hypernasality, hyponasality and nasal emissions (perceptual speech assessment); nasalance assessment (nasometer) Chua 2010a: comparison of relapse of the maxilla by evaluating its horizontal and vertical movement through lateral cephalometric assessment; changes in maxillary incisor angulation Chua 2010b: velopharyngeal function (nasoendoscopy); hypernasality, hyponasality and nasal emissions (perceptual speech assessment); nasalance assessment (nasometer) Chua 2012a: Social Avoidance and Distress Scale; Cultural-Free Self-Esteem Inventory; Satisfaction with Life Scale questionnaires Chua 2012b: hard and soft tissue changes and ratios; changes in lip thickness; nasolabial angle and nasal projection through lateral cephalometric assessment
Notes	Funding source not described Sample size calculation not reported, but provided by the authors (Table 1) No registration, no protocol available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a random numbers table, generated by computer
Allocation concealment (selection bias)	High risk	Intervention allocation not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible for participants and surgeons
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only two articles reported blinded outcome assessors, who were blinded to the patient group and whether the samples were preoperative or postoperative (Chanchareonsook 2007; Chua 2010b). In all other publications (Cheung 2006a; Chua 2010a; Chua 2012a; Chua 2012b), outcome assessors were not blinded. (Information provided by corresponding author, Table 1)

Hong Kong Study 2002 to 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Although 47 participants were enrolled in the study, different numbers of participants were analysed across different outcomes
Selective reporting (reporting bias)	High risk	No description of the standardised questionnaires provided (Cheung 2006a). Method of analysis not well established (Chua 2010a; Chua 2012b) No information about 5 participants in the control group: probably lost to follow-up, but no explanation provided (Chua 2010b)
Other bias	Unclear risk	No protocol available, conflicting reporting between published papers

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

Study	Reason for exclusion
Baek 2007	Non-randomised study
Bradley 2006	Only participants with craniosynostotic syndromes and midface hypoplasia were operated on – no cleft patients
Cheung 2006b	Cleft versus non-cleft patients in a non-randomised design
Cheung 2008	A narrative review of other published studies
Daimaruya 2010	Controlled clinical trial, but non-randomised
Harada 2002	Controlled clinical trial, but non-randomised
Harada 2004	Cleft versus non-cleft patients in a non-randomised design
Khader 2014	Only abstract published; no information available on future publication and no response from trial author
Rachmiel 2007	A discussion paper and not a clinical trial
Yu 2012	No information available on whether or not this study is a RCT. We contacted the author but there was no response

ADDITIONAL TABLES

Table 1. Email contact with trial authors

Author	Date	Request	Reply
Dr. Cheung (Cheung 2006a; Chua 2010a; Chua 2012a; Chua 2012b)	10.05.2015 and 22.12.2015	We would be grateful if you could possibly provide further information on the following: 1. We have identified five papers you have authored that have relevant data for the review. Please could you confirm by return whether these relate to one trial?	Dr Cheung replied on 23 December 2015 that his five papers related to one clinical trial where participants were randomly assigned using a random numbers table, and neither participants nor the surgeon were blinded.

Table 1. Email contact with trial authors *(Continued)*

		2. Was the randomisation done using a random numbers table? Study (Chua 2012b) states 'simple randomisation procedures' and it is not clear if this was a random numbers table? 3. What method, if any, was used to conceal allocation from participants or personnel before the experiment started? 4. Was a pre-study sample size calculation performed? If yes, what was the power calculation? 5. Was the assessment of the outcomes blind? Only paper (Chua 2010b) provides details about assessors' blinding. 6. What was the number of patients randomised? Study (2006a) reports 29 patients randomised, study (Chua 2010a) reports 47 patients randomised, study (Chua 2010b) 47 randomised and only 22 analysed, study (Chua 2012a) 30 patients randomised and study (Chua 2012b) 39 patients analysed. Should some be regarded as nested trials?	The authors had calculated a sample size of 30 for each group (total = 60) sufficient to determine a difference of 1.22 mm on skeletal replase between the two surgical techniques at a power of 80%. Assessment of stability and soft tissue changes was based on on lateral cephalographs. Distractors were no longer present at 6 months, 1-year and 2-year assessment. Dr Cheung reported that the total number of participants was 47, but that Cheung 2006a was a preliminary study, and Chua 2010b, Chua 2012a and Chua 2012b analysed a smaller number because some participants refused further nasoendoscopy.
Dr. Chua (Chua 2010b)	10.05.2015	Same as above, except question 5	No reply received
Dr. Shen (Yu 2012)	28.12.2015 and 02.07.2018	Your study may be eligible for inclusion in our review. In order to definitely decide on this, we would be grateful if you could possibly provide us further information on the following issues: 1. Is your study a Randomized Controlled Trial? If yes, which was the exact method of randomization ? 2. Did you use any methods for allocation concealment? 3. Was a pre-study sample size calculation performed? If yes, could you please provide us with the power calculation? 4. Was the assessment of the outcomes blind?	No reply received
Dr. Cheung and Dr. Samman (Chanchareonsook 2007)	21.04.2016	I wanted to check with you how the paper attached (Chanchareonsook 2007) relates to the study described below (Hong Kong Study 2002 to 2008). The review authors have assumed it is part of the same trial but there are 7 participants who are younger than 16 while in the main study it seemed that 16 was the lower age limit.	Dr Samman replied on 18 May 2016 to say that he was unsure about the cohort but he considered it the same study, and that the Chanchareonsook 2007 paper was an early evaluation of speech outcome results at 3 months, with the other papers assessing outcomes at longer-term follow-up.
Dr. Khader (Khader 2014)	02.07.2018	There is a study of you that may be eligible for inclusion in our review. In order to definitely decide on this, we must know if this study is on progress or if it has find its way for publication.	No reply received

WHAT'S NEW

Date	Event	Description
2 July 2018	New citation required but conclusions have not changed	No new randomised controlled trials identified

Date	Event	Description
15 May 2018	New search has been performed	Search updated Studies that had been awaiting classification have now been excluded

CONTRIBUTIONS OF AUTHORS

- Dimitrios Kloukos was responsible for designing, co-ordinating and updating this review and will be responsible for further updating of this review.
- Dimitrios Kloukos and Piotr Fudalej were responsible for screening search results, screening retrieved papers against inclusion criteria, extracting data from papers, and data collection for the review.
- Dimitrios Kloukos, Piotr Fudalej and Patrick Sequeira-Byron were responsible for appraising the quality of papers and for data analysis.
- All review authors contributed to analysis and interpretation of the data, and to writing the review.

DECLARATIONS OF INTEREST

Dimitrios Kloukos: none known
Piotr Fudalej: none known
Patrick Sequeira-Byron: none known
Christos Katsaros: none known

The participating review authors declare that there is no financial conflict of interest and that they do not have any associations with industry regarding the subject of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We planned in the protocol that studies involving participants 15 years old or older would be eligible for inclusion in this review. The study we have included reported in one article that two participants were younger than 15 years old (one was 13 years old and one was 14) (Chanchareonsook 2007) (despite reporting in other papers that the lower end of the age range was 16 years). We did not exclude the study on this basis as the vast majority of participants were within the age range specified and the review team considered that this would not affect the direction of the results or the effect estimates overall.

2. Minor edits were made to the Background section of the review.

3. A 'post hoc' decision was made regarding the definition of short- and long-term outcomes. 'Short term' were considered the outcomes evaluated in the first year postoperatively. Those occurring thereafter were considered as long term.

INDEX TERMS

Medical Subject Headings (MeSH)

*Orthognathic Surgery; *Osteogenesis, Distraction [psychology]; Cleft Lip [*surgery]; Cleft Palate [*surgery]; Maxilla [*abnormalities] [*surgery]; Randomized Controlled Trials as Topic; Speech; Treatment Outcome

MeSH check words

Adolescent; Adult; Humans; Middle Aged