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

Kloukos D, Fudalej P, Sequeira-Byron P, Katsaros C

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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.

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

We searched the following electronic databases: Cochrane Oral Health's Trials Register (to 16 February 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 1), MEDLINE Ovid (1946 to 16 February 2016), Embase Ovid (1980 to 16 February 2016), LILACS BIREME (1982 to 16 February 2016), the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) (to 16 February 2016), and the World Health Organization (WHO) International Clinical Trials Registry Platform (to 16 February 2016). There were no restrictions regarding language or date of publication in the electronic searches. We performed handsearching of six specialty journals and we checked the reference lists of all trials identified for further studies.

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 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).
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 16 February 2016. We found six relevant articles to include in this review. All are related to one single study conducted in Hong Kong. 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 mucous 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

The quality of the evidence was judged 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.
Maxillary advancement (in mm) assessed with lateral cephalograms  
Follow-up 2 years

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects** (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<tr>
<td>Risk with orthognathic surgery</td>
<td>Mean maxillary advancement was 4.90 mm</td>
<td>Mean maxillary advancement in the intervention group was 4.4 mm more (0.24 more to 8.56 more)</td>
<td>39 (1 RCT)</td>
<td>◆◆◆◆ very low 1,2,3</td>
<td>Statistically significant difference between groups, in favour of distraction osteogenesis</td>
</tr>
<tr>
<td>Risk with maxillary distraction osteogenesis</td>
<td>-</td>
<td>-</td>
<td>16 (1 RCT)</td>
<td>◆◆◆◆ very low 1,2</td>
<td>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)</td>
</tr>
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Maxillary advancement (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)
<table>
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<tr>
<th>Speech (deterioration/improvement) assessed with resonance</th>
<th>Deteriorated participants</th>
<th>RR 0.11 (0.01 to 1.85)</th>
<th>22 (1 RCT)</th>
<th>⊕⊕⊕ very low 2,3,4</th>
</tr>
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<tr>
<td>Follow-up mean 17 months</td>
<td>364 out of 1000 (4 to 673)</td>
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<tr>
<td>Velopharyngeal function (deterioration/improvement) assessed with nasendoscopy</td>
<td>Participants with complete velopharyngeal closure</td>
<td>RR 1.28 (0.65 to 2.52)</td>
<td>21 (1 RCT)</td>
<td>⊕⊕⊕ very low 2,3,4</td>
</tr>
<tr>
<td>Follow-up mean 17 months</td>
<td>545 out of 1000 (218 to 834)</td>
<td></td>
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<tr>
<td>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</td>
<td>Mean score was 24 higher (0.14 higher to 5.76 higher)</td>
<td>-</td>
<td>30 (1 RCT)</td>
<td>⊕⊕⊕ very low 1,2,3</td>
</tr>
<tr>
<td>Follow-up 2 years</td>
<td>Mean score was 2.95 higher</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clinical morbidities assessed with questionnaires</td>
<td>3/14</td>
<td>-</td>
<td>29 (1 RCT)</td>
<td>⊕⊕⊕ very low 1,2,3</td>
</tr>
<tr>
<td>Follow-up 12 months</td>
<td>3/15</td>
<td></td>
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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. 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

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<th>GRADE Working Group grades of evidence</th>
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<td>High quality: We are very confident that the true effect lies close to that of the estimate of the effect</td>
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<tr>
<td>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</td>
</tr>
<tr>
<td>Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td>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 the effect</td>
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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 multi-disciplinary 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 video nasopharyngoscopy 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

To identify studies for this review, detailed search strategies were developed for each database. These were based on the search strategy developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The subject search used a combination of controlled vocabulary and free text terms based on the search strategy for searching MEDLINE.

Electronic searches

The following electronic databases were searched:
- Cochrane Oral Health’s Trials Register (searched 16 February 2016) (see Appendix 1);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1) in the Cochrane Library (searched 16 February 2016) (see Appendix 2);
- MEDLINE Ovid (1946 to 16 February 2016) (see Appendix 3);
- Embase Ovid (1980 to 16 February 2016) (see Appendix 4);
- LILACS BIREME (Latin American and Caribbean Health Science Information database; 1982 to 16 February 2016) (see Appendix 5).

Searching other resources

Ongoing trials

We conducted searches in the following databases to identify ongoing trials (see Appendix 6 for details of the search strategy):
- US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov; searched 16 February 2016);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 16 February 2016).

Language

There were no language restrictions applied in the databases we searched.

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 hand-searched these journals:
- Cleft Palate and Craniofacial Journal (2003 to 29 February 2016);
- International Journal of Oral and Maxillofacial Surgery (2003 to 29 February 2016);
- Plastic and Reconstructive Surgery (2005 to 29 February 2016);
- Journal of Oral and Maxillofacial Surgery (2009 to 29 February 2016);
- British Journal of Oral and Maxillofacial Surgery (2005 to 29 February 2016);

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). 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 416 references. 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). Two studies were categorised as Characteristics of studies awaiting classification: only the conference abstract was retrieved for Khader 2014, and it remained unclear whether Yu 2012 was an RCT or not, although the corresponding author was e-mailed (Table 1; Table 2). 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 and Table 2 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

474 records identified through database searching

No additional records identified through other sources

416 records after duplicates removed

416 records screened

400 records rejected

2 studies await classification
8 full-text articles excluded:
- 5 non-randomised studies
- 2 narrative discussion papers
- 1 trial not involving cleft patients

16 full-text articles assessed for eligibility

1 study (6 articles included in qualitative synthesis)
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 preplanned 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).
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; Table 2). 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 postoperative period 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 DO group than in the CO 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 (microscrew 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 (
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 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, intra-operative 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 overall quality of the evidence is very low and therefore findings should be interpreted with caution (Summary of findings for the main comparison).

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 (Chua 2012b). 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 (Cheung 2006a; Chua 2010a).

On the other hand, no difference could be detected as far as effects on speech and velopharyngeal status are concerned (Chua 2010b). 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 (Chua 2012a).

**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.
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 underestimate 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 recent 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

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; Table 2). 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.

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.

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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 if further trials are robust, properly designed and reported 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).

Finally, and probably most importantly, consideration should 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 (Garg 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).

Acknowledgements

The review team would like to especially thank Laura C.I. MacDonald, Cochrane Oral Health, for her assistance with developing the review. Anne Littlewood, Trials Search Co-ordinator for Cochrane Oral Health, performed all electronic searches for this review. We would also like to thank those who previously provided comments on the protocol; Anne-Marie Glenny, Zipporah Theoboror Ejiofor, Scott Deacon and Hend ElSayed for their extremely helpful comments on this version of the review; and Jason Elliott-Smith for copy editing.

References to studies included in this review

Hong Kong Study 2002 to 2008 {published and unpublished data}


References to studies excluded from this review

Baek 2007 {published data only}

Baek SH, Lee JK, Lee JH, Kim MJ, Kim JR. Comparison of treatment outcome and stability between distraction osteogenesis and LeFort I osteotomy in cleft patients with...

**Bradley 2006** *(published data only)*

**Cheung 2006b** *(published data only)*

**Cheung 2008** *(published data only)*
Cheung LK, Chua HD. Distraction or orthognathic surgery for cleft lip and palate patients: which is better?. *Annals of the Royal Australasian College of Dental Surgeons* 2008;19:133–5.

**Daimaruya 2010** *(published data only)*

**Harada 2002** *(published data only)*

**Harada 2004** *(published data only)*

**Rachmiel 2007** *(published data only)*

**References to studies awaiting assessment**

**Khader 2014** *(published data only)*

**Yu 2012** *(published data only)*

**Austin 2015**

**Bruce 2015**

**Chanchareonsook 2007**

**Cheung 2006a**


**Chung 2000**

**Czeizel 1997**
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Maxillary distraction osteogenesis versus orthognathic surgery for cleft lip and palate patients (Review) 20


Endnote X7 2015 [Computer program]


RevMan 2014 [Computer program]

Romitti 2007

Saltaji 2012a

Saltaji 2012b

Schulz 1995

Scolozzi 2008

Shaw 1995

Shaw 2001

Shaw 2002

Tischlaki 2014

WHO 2012

Wong 1999

Worthington 2015

* Indicates the major publication for the study
**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, 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 mobilized maxilla was fixed by titanium miniplates at the zygomatic buttress and the pyriform region  
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

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<th>Outcome</th>
<th>Reference</th>
<th>Description</th>
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<tr>
<td>Primary outcomes (secondary outcomes n/a)</td>
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<td>Cheung 2006a: comparison of the postoperative clinical morbidities in the two groups with standardised questionnaires; comparison of surgical relapse through lateral cephalometric assessment</td>
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<td></td>
<td>Chanchareonsook 2007: velopharyngeal function (nasoendoscopy); hypernasality, hyponasality and nasal emissions (perceptual speech assessment); nasalance assessment (nasometer)</td>
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<td></td>
<td>Chua 2010a: comparison of relapse of the maxilla by evaluating its horizontal and vertical movement through lateral cephalometric assessment; changes in maxillary incisor angulation</td>
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<td></td>
<td>Chua 2010b: velopharyngeal function (nasoendoscopy); hypernasality, hyponasality and nasal emissions (perceptual speech assessment); nasalance assessment (nasometer)</td>
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<td></td>
<td>Chua 2012a: Social Avoidance and Distress Scale; Cultural-Free Self-Esteem Inventory; Satisfaction with Life Scale questionnaires</td>
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<tr>
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<td>Chua 2012b: hard and soft tissue changes and ratios; changes in lip thickness; nasolabial angle and nasal projection through lateral cephalometric assessment</td>
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Notes

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<td>Funding source not described</td>
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<td></td>
<td>Sample size calculation not reported, but provided by the authors (Table 1; Table 2)</td>
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<tr>
<td></td>
<td>No registration, no protocol available</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomisation using a random numbers table, generated by computer</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Intervention allocation not concealed</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Blinding not feasible for participants and surgeons</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>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 2)</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Although 47 participants were enrolled in the study, different numbers of participants were analysed across different outcomes</td>
</tr>
</tbody>
</table>
### Hong Kong Study 2002 to 2008  *(Continued)*

|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]*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baek 2007</td>
<td>Non-randomised study</td>
</tr>
<tr>
<td>Bradley 2006</td>
<td>Only participants with craniosynostotic syndromes and midface hypoplasia were operated on - no cleft patients</td>
</tr>
<tr>
<td>Cheung 2006b</td>
<td>Cleft versus non-cleft patients in a non-randomised design</td>
</tr>
<tr>
<td>Cheung 2008</td>
<td>A narrative review of other published studies</td>
</tr>
<tr>
<td>Daimaruya 2010</td>
<td>Controlled clinical trial, but non-randomised</td>
</tr>
<tr>
<td>Harada 2002</td>
<td>Controlled clinical trial, but non-randomised</td>
</tr>
<tr>
<td>Harada 2004</td>
<td>Cleft versus non-cleft patients in a non-randomised design</td>
</tr>
<tr>
<td>Rachmiel 2007</td>
<td>A discussion paper and not a clinical trial</td>
</tr>
</tbody>
</table>

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

**Khader 2014**

|Methods | Design: single-centre RCT, Yenepoya University, Mangalore, Karnataka, India  
Follow-up: 4, 6, 9, 12 months |
|Participants | Number: 40 participants randomised  
Sex: not reported  
Age range: 18 to 25 years old  
Inclusion criteria: patients with hypoplastic maxilla in need of maxillary advancement. All 40 participants underwent alveolar bone grafting and presurgical orthodontics. |
<table>
<thead>
<tr>
<th><strong>Khader 2014</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusion criteria:</strong> not reported</td>
<td></td>
</tr>
</tbody>
</table>
| **Interventions** | **Intervention** (n = 20): group receiving maxillary distraction osteogenesis  
**Control** (n = 20): group of Le Fort I surgery  
**Treatment duration in distraction group:** rhythm: morning 3 turns; evening 2 turns, **Pitch:** 0.25 mm/turn, 1 mm/day and then 3-month consolidation period |  |
| **Outcomes** | **Primary:** changes in the soft tissue profile; relapse rate between groups; speech variables: nasality, articulation, intelligibility and acceptability  
**Secondary:** N/A |  |
| **Notes** | Abstract from the proceedings of the 71st Annual Meeting of the American Cleft Palate-Craniofacial Association; 2014, Mar 24-29; Indianapolis, Indiana, United States |  |

<table>
<thead>
<tr>
<th><strong>Yu 2012</strong></th>
<th></th>
</tr>
</thead>
</table>
| **Methods** | **Design:** single-centre RCT, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 2007 to 2010  
**Follow-up:** before/after operation or distraction |  |
| **Participants** | **Number:** 10 participants randomised  
**Sex:** 7 males, 3 females  
**Age range:** 12 to 26 years old  
**Inclusion criteria:** severe maxillary hypoplasia secondary to CLP. All patients had previously undergone alveolar grafts with ilial bone. Only maxillary procedures needed  
**Exclusion criteria:** not reported |  |
| **Interventions** | **Intervention** (n = 5): group receiving maxillary distraction osteogenesis  
**Control** (n = 5): group of Le Fort I surgery. Osteotomy in the posterior maxillae was performed at the distal region of second molar and maxillary tuberosity, not at the pterygomaxillary suture, as is routine  
**Treatment duration in distraction group:** after a 5-day latency period, the maxilla was advanced at a rate of 0.4 mm every 12 hours. Duration of the distraction was determined separately for each case |  |
| **Outcomes** | **Primary:** maxillary sagittal and vertical changes; velopharyngeal closure function; hypernasal speech  
**Secondary:** N/A |  |
| **Notes** | A number of methodological and reporting aspects required clarification. We tried to contact trial authors but no reply was received (Table 1; Table 2) |  |
## Comparison 1. Maxillary distraction osteogenesis versus orthognathic surgery

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<td>1 Maxillary advancement  (hard tissue - dA)</td>
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<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
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<tr>
<td>1.1 12 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>1.2 24 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>2 Skeletal stability  (dA)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>2.1 5 years post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>3 Resonance - hypernasality</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>3.1 4 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>3.2 17 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>4 Resonance - nasal emission</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>4.1 4 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>4.2 17 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>5 Velopharyngeal function  - (no velopharyngeal incompetence or complete closure)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>5.1 4 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>5.2 17 months post-operatively (mean follow-up)</td>
<td>1</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>6 Social Avoidance and Distress Scale (SADS)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>6.1 3 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>6.2 12 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>6.3 24 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
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</tr>
<tr>
<td>7 Cultural-Free Self-Esteem Inventory (CFSEI) - general</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>7.1 3 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>7.2 12 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>7.3 24 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>8 Satisfaction with Life Scale (SWLS)</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>8.1 12 months post-operatively</td>
<td>1</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
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</table>
8.2 12 months post-operatively 1 Mean Difference (IV, Fixed, 95% CI) 0.0 [0.0, 0.0]
8.3 24 months post-operatively 1 Mean Difference (IV, Fixed, 95% CI) 0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 1 Maxillary advancement (hard tissue - dA).

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

Comparison: 1 Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 1 Maxillary advancement (hard tissue - dA)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
<th>CO</th>
<th>Mean Difference IV (Fixed, 95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
</tr>
<tr>
<td>1 12 months post-operatively</td>
<td>16</td>
<td>9.48 (3.24)</td>
<td>23</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>16</td>
<td>9.3 (3.24)</td>
<td>23</td>
</tr>
</tbody>
</table>

-10 -5 0 5 10
Favours CO Favours DO
### Analysis 1.2. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 2 Skeletal stability (dA).

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

Comparison: 1 Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 2 Skeletal stability (dA)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Mean Difference</th>
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<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>1 5 years post-operatively</td>
<td>7</td>
<td>2.27 (4.44)</td>
<td>9</td>
<td>-2.53 (4.44)</td>
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### Analysis 1.3. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 3 Resonance - hypernasality.

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

Comparison: 1 Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 3 Resonance - hypernasality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
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<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
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<tr>
<td>1 4 months post-operatively (mean follow-up)</td>
<td>3/11</td>
<td>4/11</td>
<td></td>
<td>0.75 [0.22, 2.60]</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 17 months post-operatively (mean follow-up)</td>
<td>0/11</td>
<td>4/11</td>
<td></td>
<td>0.11 [0.01, 1.85]</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td></td>
<td></td>
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</tbody>
</table>
### Analysis 1.4. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 4
**Resonance - nasal emission.**

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

Comparison: Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 4 Resonance - nasal emission

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
<th>CO</th>
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<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
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<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
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</tr>
<tr>
<td>1. 4 months post-operatively (mean follow-up)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>0/11</td>
<td>2/11</td>
<td>0.20 [0.01, 3.74]</td>
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</tr>
<tr>
<td>2. 17 months post-operatively (mean follow-up)</td>
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<td>Hong Kong Study 2002 to 2008</td>
<td>0/11</td>
<td>1/11</td>
<td>3.00 [0.14, 66.53]</td>
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</tbody>
</table>

### Analysis 1.5. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 5
**Velopharyngeal function - (no velopharyngeal incompetence or complete closure).**

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

Comparison: Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 5 Velopharyngeal function - (no velopharyngeal incompetence or complete closure)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
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<th>Risk Ratio M-H,Fixed 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. 4 months post-operatively (mean follow-up)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>6/10</td>
<td>8/11</td>
<td>0.83 [0.44, 1.54]</td>
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</tr>
<tr>
<td>2. 17 months post-operatively (mean follow-up)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>7/10</td>
<td>6/11</td>
<td>1.28 [0.65, 2.52]</td>
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</table>
### Analysis 1.6. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 6 Social Avoidance and Distress Scale (SADS).

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

Comparison: 1 Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 6 Social Avoidance and Distress Scale (SADS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
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<th>IV, Fixed, 95% CI</th>
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<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>1 3 months post-operatively</td>
<td>15</td>
<td>10.3 (6.24)</td>
<td>15</td>
<td>10.46 (8.7)</td>
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<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 12 months post-operatively</td>
<td>15</td>
<td>9 (5.06)</td>
<td>15</td>
<td>9.58 (7)</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 24 months post-operatively</td>
<td>15</td>
<td>8.24 (5.66)</td>
<td>15</td>
<td>8.84 (7.09)</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
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<td></td>
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### Analysis 1.7. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 7 Cultural-Free Self-Esteem Inventory (CFSEI) - general.

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

Comparison: Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: Cultural-Free Self-Esteem Inventory (CFSEI) - general

<table>
<thead>
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<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>1 3 months post-operatively</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
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<td>12.8 (4.16)</td>
<td>15</td>
<td>15.08 (2.9)</td>
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<tr>
<td>2 12 months post-operatively</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>15</td>
<td>14.6 (2.7)</td>
<td>15</td>
<td>14.93 (3.22)</td>
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<tr>
<td>3 24 months post-operatively</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>15</td>
<td>15.09 (3.5)</td>
<td>15</td>
<td>14.92 (2.84)</td>
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</tbody>
</table>

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Analysis 1.8. Comparison 1 Maxillary distraction osteogenesis versus orthognathic surgery, Outcome 8 Satisfaction with Life Scale (SWLS).

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

Comparison: 1 Maxillary distraction osteogenesis versus orthognathic surgery

Outcome: 8 Satisfaction with Life Scale (SWLS)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DO</th>
<th>CO</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>1 3 months post-operatively</td>
<td>15</td>
<td>23.52 (5.13)</td>
<td>15</td>
<td>24.01 (5.39)</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
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<td>25.53 (4.36)</td>
<td>15</td>
<td>22.12 (5.5)</td>
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<tr>
<td>2 12 months post-operatively</td>
<td>15</td>
<td>26.95 (3.1)</td>
<td>15</td>
<td>24 (4.6)</td>
</tr>
<tr>
<td>Hong Kong Study 2002 to 2008</td>
<td>15</td>
<td>24.01 (5.39)</td>
<td>15</td>
<td>22.12 (5.5)</td>
</tr>
</tbody>
</table>

ADDITIONAL TABLES

Table 1. Email contact with trial authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Email address</th>
<th>Date</th>
<th>Request</th>
</tr>
</thead>
</table>
| Dr. Cheung (Cheung 2006a; Chua 2010a; Chua 2012a; Chua 2012b) | lkcheung@hku.hk | 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? 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 ex-
Table 1. Email contact with trial authors  (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Email Address</th>
<th>Date</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Chua (Chua 2010b)</td>
<td><a href="mailto:hdchua@gmail.com">hdchua@gmail.com</a></td>
<td>10.05.2015</td>
<td>Same as above, except question 5</td>
</tr>
<tr>
<td>Dr. Shen (Yu 2012)</td>
<td>maxillofac <a href="mailto:Surg@163.com">Surg@163.com</a></td>
<td>28.12.2015</td>
<td>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?</td>
</tr>
<tr>
<td>Dr. Cheung and Dr. Samman (Chanchareonsook 2007)</td>
<td><a href="mailto:lkcheung@hku.hk">lkcheung@hku.hk</a> and <a href="mailto:nsamman@hkucc.hku.hk">nsamman@hkucc.hku.hk</a></td>
<td>21.04.2016</td>
<td>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</td>
</tr>
</tbody>
</table>
Table 1. Email contact with trial authors  

Continued but there are 7 participants who are younger than 16 while in the main study it seemed that 16 was the lower age limit

Table 2. Email reply from trial authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Email address</th>
<th>Date</th>
<th>Reply</th>
</tr>
</thead>
</table>
| Dr. Cheung| lkcheung@hku.hk        | 23.12.2015| Please find my reply to your queries below:  
1. Yes. I would like to confirm that the papers are related to one clinical trial looking at different parameters
2. Yes, the randomization was done using a random numbers table.
3. The participants were informed on which group they were allocated after they agreed to be involved in the study. As to the surgeon, they were informed on which group the patient were allocated because distractors and titanium miniplates and screws had to be prepared prior to the surgery.
4. A sample size of 30 for each group (n = 60) was found to be sufficient to determine the difference of 1.22mm on the skeletal replase between the two surgical technique at a power of 80%.
5. The assessment of the stability and soft tissue changes was based on lateral cephalographs. It was not possible to blind the assessors as there were titanium plates and screws present on those who received orthognathic surgery and presence of distractors for patients who had distraction surgery. Distractors were no longer present during the 6 months, 1 year and 2 years assessment.
6. Study (Cheung 2006a) was a preliminary study. The total number of patients recruited in this study was 47 as reported in study (Chua 2010a). In study (Chua 2010b), which looked at the parameters on speech and velopharyngeal function, some of the patients refused to have further nasoendoscopy and therefore, only 22 were analyzed. Same explanation for paper (Chua 2012a) and (Chua 2012b). |
| Dr. Chua  | hychua@gmail.com        | N/A       | No reply received, but all issues were clarified by Dr. Cheung (Email above)                                                                                   |
| Dr. Shen  | maxillofacsurg@163.com | N/A       | No reply received                                                                                                                                              |
| Dr. Samman| nsamman@hkucc.hku.hk   | 18.05.2016| The attached article was based on a study whose main purpose was to establish and publish the speech evaluation protocol utilising the (slightly too) early results (3 months). The same cohort is supposed to have been followed up for a longer period and is represented by article (c) listed in the body of your e-mail. I am not sure if the cohorts in the 2 studies are exactly the same or not...I would say yes, same study |
APPENDICES

Appendix 1. Cochrane Oral Health’s Trials Register search strategy
#1 (cleft* and (palat* or lip* or maxilla* or oral or orofacial or alveolar)):ti,ab
#2 (harelip* or "hare lip" or hare-lip*):ti,ab
#3 (hypoplas* and maxilla*):ti,ab
#4 (maxilla* and (defect* or abnorm* or malform*)):ti,ab
#5 (alveolar* and (defect* or abnorm* or malform*)):ti,ab
#6 (palate* and (defect* or abnorm* or malform*)):ti,ab
#7 (lip* and (defect* or abnorm* or malform*)):ti,ab
#8 UCLP or CLP:ti,ab
#9 (palatopharyngeal and (dysfunction* or insufficien* or incomplet*)):ti,ab
#10 (velopharyngeal and (dysfunction* or insufficien* or incomplet*)):ti,ab
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12 (callotasis):ti,ab
#13 (distract* and osteogene*):ti,ab
#14 (maxilla* and distract*):ti,ab
#15 #12 OR #13 OR #14
#16 (orthognathic* and surg*):ti,ab
#17 (convention* and osteotom*):ti,ab
#18 (“le fort”):ti,ab
#19 (LF1):ti,ab
#20 (maxilla* and (surg* or osteotom* or reposition* or re-position* or section* or advanc*)):ti,ab
#21 (cleft* and (surg* or osteotom*)):ti,ab
#22 (mandib* and (setback* or set-back* or "set back*" or surger* or surgical*)):ti,ab
#23 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24 #15 AND #23
#25 #11 AND #24

Appendix 2. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy
#1 [mh “cleft lip”]
#2 [mh “cleft palate”]
#3 [mh “mouth abnormalities”]
#4 [mh “velopharyngeal insufficiency”]
#5 (cleft* near/5 (palat* or lip* or maxilla* or oral or orofacial or alveolar))
#6 (harelip* or hare-lip* or “hare lip*”) 
#7 (hypoplas* and maxilla*)
#8 (maxilla* near/5 (defect* or abnorm* or malform*))
#9 (alveolar near/5 (defect* or abnorm* or malform*))
#10 (palate* near/5 (defect* or abnorm* or malform*))
#11 (lip* near/5 (defect* or abnorm* or malform*))
#12 (UCLP or CLP):ti,ab
#13 (velopharyngeal near/5 (dysfunction* or insufficien* or incompet*))
#14 (palatopharyngeal near/5 (dysfunction* or insufficien* or incompet*))
#15 [or #1-#14]
#16 [mh “Distraction osteogenesis”]
#17 (distract* near/5 osteogene*)
#18 callotasis
#19 (maxilla* near/5 distract*)
#20 [or #16-#19]
#21 [mh “Orthognathic surgical procedures”]
Appendix 3. MEDLINE Ovid search strategy

1. Cleft lip/
2. Cleft palate/
3. Mouth abnormalities/
4. exp Velopharyngeal insufficiency/
5. (cleft$ adj5 (palat$ or lip$ or maxilla$ or oral or orofacial or alveolar)).mp.
6. (harelip$ or "hare lip$" or hare-lip$).mp.
7. (hypoplas$ and maxilla$).mp.
8. (maxilla$ adj5 (defect$ or abnorm$ or malform$)).mp.
9. (alveolar$ adj5 (defect$ or abnorm$ or malform$)).mp.
10. (palate$ adj5 (defect$ or abnorm$ or malform$)).mp.
11. (lip$ adj5 (defect$ or abnorm$ or malform$)).mp.
12. (UCLP or CLP).ti,ab.
13. (velopharyngeal adj5 (dysfunction$ or insufficien$ or inco mpet$)).mp.
14. (palatopharyngeal adj5 (dysfunction$ or insufficien$ or incom pet$)).mp.
15. or/1-14
16. Distraction osteogenesis/
17. (distract$ adj5 osteogene$).mp.
18. callotasis.mp.
19. (maxilla adj5 distract$).mp.
20. or/16-19
21. Orthognathic surgical procedures/
22. Orthognathic surgery/
23. Le Fort Osteotomy/
24. (orthognathic adj5 surg$).mp.
25. (convention$ adj5 osteotom$).mp.
27. LF1.ti,ab.
28. (maxilla$ adj5 (surg$ or osteotom$ or reposition$ or re-position$ or section$ or advance$)).mp.
29. (cleft and (surg$ or osteotom$)).mp.
30. (mandib$ and (setback$ or set-back$ or "set back$" or surger$ or surgical$)).mp.
31. or/21-30
32. 20 and 31
33. 15 and 32
Appendix 4. Embase Ovid search strategy

1. Cleft lip/
2. Cleft palate/
3. Palatopharyngeal incompetence/
4. (cleft$ adj5 (palat$ or lip$ or maxilla$ or oral or orofacial or alveolar$)).mp.
5. (harelip$ or "hare lip"$ or hare-lip$).mp.
6. (hypoplas$ and maxilla$).mp.
7. (maxilla$ adj5 (defect$ or abnorm$ or malform$)).mp.
8. (alveolar$ adj5 (defect$ or abnorm$ or malform$)).mp.
9. (palat$ adj5 (defect$ or abnorm$ or malform$)).mp.
10. (lip$ adj5 (defect$ or abnorm$ or malform$)).mp.
11. (UCLP or CLP).ti,ab.
12. (velopharyngeal adj5 (dysfunction$ or insufficien$ or incompet$)).mp.
13. (palatopharyngeal adj5 (dysfunction$ or insufficien$ or incompet$)).mp.
14. or/1-13
15. Distraction osteogenesis/
17. callotasis.mp.
18. (maxilla adj5 distract$).mp.
19. or/15-18
20. Orthognathic surgery/
21. Maxilla osteotomy/
22. (orthognathic adj5 surg$).mp.
23. (convention$ adj5 osteotom$).mp.
24. "le fort".mp.
25. LF1.ti,ab.
26. (maxilla$ adj5 (surg$ or osteotom$ or reposition$ or re-position$ or section$ or advance$)).mp.
27. (cleft and (surg$ or osteotom$)).mp.
28. (mandib$ and (setback$ or set-back$ or "set back" or surger$ or surgical$)).mp.
29. or/20-28
30. 19 and 29
31. 14 and 30

The above subject search was linked to Cochrane Oral Health’s filter for identifying RCTs in Embase Ovid:
1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doub$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw . or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15
Appendix 5. LILACS BIREME search strategy
(Mh "cleft lip" or "cleft lip$" or "labio$ leporino" or "fenda labial$" or Mh "cleft palate" or "cleft palate$" or "fisura del paladar$" or "fissura palatina$") [words] and (Mh "osteogenesis, distraction" or "distraction osteogenesis" or "maxillary distraction" or "osteogénesis por distracción" or "osteogênese por distração") [words] and (Mh "orthognathic surgery" or surgery or surgical or cirugía or cirurgia) [words]

Appendix 6. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform search strategy

cleft AND osteogenesis AND surgery
cleft AND distraction AND surgery
cleft AND osteogenesis AND osteotomy
cleft AND distraction AND osteotomy

CONTRIBUTIONS OF AUTHORS

- Dimitrios Kloukos was responsible for designing and co-ordinating and will be responsible for updating the 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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Internal sources

- School of Dentistry, The University of Manchester, UK.

External sources

- Cochrane Oral Health Global Alliance, Other.
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- National Institute for Health Research (NIHR), UK.
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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.