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[Intervention Review]

Secondary bone grafting for alveolar cleft in children with cleft lip or cleft lip and palate

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ABSTRACT

Background

Secondary alveolar bone grafting has been widely used to reconstruct alveolar cleft. However, there is still some controversy.

Objectives

To compare the effectiveness and safety of different secondary bone grafting methods.

Search methods

The final electronic and handsearches were carried out on 11 February 2011, and included the Cochrane Oral Health Group's Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Chinese Biomedical Literature Database and WHO International Clinical Trials Registry Platform. All the Chinese professional journals in the oral and dental field were handsearched and conference proceedings consulted. There was no language or time restriction.

Selection criteria

Only randomized clinical trials were selected. Patients with the diagnosis of cleft lip and alveolar process only, unilateral cleft lip and palate and bilateral cleft lip and palate involving the alveolar process and greater than 5 years of age were included.

Data collection and analysis

Two review authors extracted data and assessed the quality of included studies independently. Disagreement between the two review authors was resolved by discussion in the review team. The first authors of the included studies were contacted for additional information, if necessary.

Main results

Two of 582 potential studies met the inclusion criteria and were included. One trial compared alveolar bone grafting using artificial materials (InFuse bone graft substitute impregnated with BMP-2) with a traditional iliac graft. The other trial investigated the application of fibrin glue to the bone graft. Both trials were small with 21 and 27 patients and were assessed as being at high risk of bias. Any apparent differences between the interventions for outcomes in either study must therefore be treated with great caution and are not highlighted here.

Authors' conclusions

Due to the high level of risk of bias in the two included trials there is insufficient evidence to conclude that one intervention is superior to another.

PLAIN LANGUAGE SUMMARY

Secondary bone grafting for alveolar cleft in children with cleft lip or cleft lip and palate

Alveolar cleft is a bony defect in the gum of the mouth, which affects approximately 75% of cleft lip or cleft lip and palate patients. Failure to repair this defect may give rise to many problems. Although alveolar bone grafting has been widely accepted by professionals within cleft care, there is still controversy around the technique, timing, site from which bone is taken and whether artificial bone substitutes offer any benefits. One question is whether the type of graft material using artificial bone materials alone might have similar success to the traditional bone harvested from the hip when assessed clinically, by radiographic images and in reducing problems in the operated area.

This review found two small studies, one comparing a graft using a new material with a traditional graft, the other looking at the benefit of applying a special type of glue to the graft. Both studies were considered to be of poor quality and so no conclusions can be reached about whether either of these new techniques is better than the traditional type of graft.

BACKGROUND

Description of the condition

Alveolar cleft (osseous defect in the alveolus) is a common congenital anomaly which affects approximately 75% of cleft lip or cleft lip and palate patients. The aetiology of this cleft is still poorly understood, but it is most likely considered to be multifactorial involving genetic and environmental factors (Malcolm 1990). The alveolar cleft may affect the developing dentition and contribute to the collapse of the alveolar segments. Failure to reconstruct the alveolar cleft may give rise to problems including oronasal fistula, fluid reflux, speech pathology, anteroposterior and transverse deficiency of the maxilla, lack of bone support for the anterior teeth, dental crowding, and facial asymmetry (Waite 1996). Patients with a bony defect in the alveolar process with a symptomatic oronasal fistula and/or a lack of bone impairing tooth eruption or orthodontic treatment or prosthodontic rehabilitation in this area, should be considered for alveolar bone grafting (Enemark 1985).

Description of the intervention

Bone grafting of the alveolus is now generally acknowledged to be as integral to the management of the cleft patient as that of the primary lip or palate repair (Cohen 1993). Since the report describing secondary alveolar bone grafting by Boyne and Sands (Boyne 1972), this procedure has become the common method of choice (Turvey 1984; Bergland 1986; Newlands 2000; Hynes 2003).

The optimal timing of bone graft placement remains controversial. Boyne and Sands (Boyne 1976) have used chronological nomenclature in alveolar bone grafting to avoid confusion in this concept: 1) primary bone grafting: when bone grafting is performed in children younger than 2 years of age; 2) early secondary bone grafting: to be applied in patients between 2 and 5 years old; and 3) secondary bone grafting: when procedures are undertaken in patients greater than 5 years of age.

Before the 1970s, primary alveolar bone grafting was commonly carried out until its adverse developmental effects on maxillary growth, severe crossbite, and poor alveolar morphology with unerupted or unsupported teeth were emphasized by Koberg (Koberg 1973) and Ross (Ross 1987). Early secondary bone grafting resulted in improved orofacial development but this was not always ideal (Johanson 1961).

The general steps for secondary alveolar bone grafting are as follows. Firstly, mucoperiosteal flaps on the palate and vestibular surfaces of the maxillary segments to widely expose the alveolar bony defect are made. Meanwhile, the graft materials either autogenous bone or bone substitute are prepared or harvested. The nasal mucosa is firstly closed to repair the nasal floor. It is then pushed upwards and the bony wall is exposed. Bone or bone substitute is then packed into the defect, filling the alveolar defect completely. The palatal flaps are then released for primary closure of the oral layer. Often a finger flap is utilized from the vestibule and rotated over the alveolus. Lastly, all the flaps are sutured together to close the oral layer over the graft in the cleft site (Bergland 1986).

How the intervention might work

Secondary alveolar bone grafting may bring cleft patients several benefits.

1. It gives bony support to the teeth proximal to the cleft and greatly enhances the follow-up orthodontic treatment (Waite 1980; Bertz 1981; Turvey 1984).
2. It gives a bony base for eruption of teeth in the line of the cleft and this prevents drifting of proximal teeth into the cleft and their premature loss (Boyne 1972; Jolleys 1972; Turvey 1984).
3. It provides union to the maxillary arch and re-establishes alveolar bone contour (Skoog 1967; Pickrell 1968; Boyne 1972; Turvey 1984; Enemark 1985).
4. It provides support to arch width and minimizes collapse of the maxillary arch (Pickrell 1968; Epstein 1970; Bertz 1981).
5. It stabilizes the maxillary segments for the maintenance of the dentition and mastication (Skoog 1967; Pickrell 1968; Waite 1980; Turvey 1984; Enemark 1985; Bergland 1986).
6. It reduces notching of the alveolar ridge (Bergland 1986).
7. It eliminates oronasal fistulae to improve the oral hygiene (Pickrell 1968; Boyne 1972; Waite 1980; Bertz 1981; Turvey 1984; Enemark 1985).
8. It may improve facial appearance through improving facial symmetry, providing alar base support, and improving nasolabial contour (Pickrell 1968; Waite 1980; Bertz 1981; Turvey 1984).

Conversely, secondary alveolar bone grafting may cause:

1. increased incidence of canine impaction (Bergland 1986; Trindade 2005);
2. donor site morbidity (Hughes 2002; Swan 2006);
3. reduced anterior-posterior and/or vertical maxillary growth (Ross 1987).

Why it is important to do this review

Although secondary alveolar bone grafting has been widely accepted by professionals within cleft care, there is still controversy as to: (i) the age at which secondary bone grafting should be performed (Bergland 1986); (ii) the type of bone graft and the site from which the donor bone will be harvested (Freihofer 1993); and (iii) whether orthodontic treatment prior to grafting influences outcome (Long 1995; Kindelan 1999). Furthermore, the Clinical Standards Advisory Group (CSAG) reported that only 58% of children had a successful graft in the UK (Sandy 1998). Some of these failures were related to not being grafted at the optimal age or ethnicity (Williams 2001).

Poor outcome and the existing controversies of secondary bone grafting indicate that there is a need to evaluate the existing evidence for this procedure and identify best practice and further areas for good quality primary research.

OBJECTIVES

To compare the effectiveness and safety of different secondary bone grafting methods (timing, source of graft and technique).

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled clinical trials (RCTs) were included.

Types of participants

Inclusion criteria

1. Patients with the diagnosis of unilateral cleft lip and/or palate and bilateral cleft lip and/or palate involving the alveolar process. This included complete or incomplete alveolar cleft types and cleft types involving a Simonart band.
2. Patients greater than 5 years of age.

Exclusion criteria

1. Edentulous premaxilla.
2. Atypical or non-described cleft diagnoses.
3. With associated syndromic conditions.

Types of interventions

Any form of secondary alveolar bone grafting; when this operation was undertaken in patients greater than 5 years of age. Comparisons included variations in timing, donor sites, bone substitutes and technique.

Types of outcome measures

Primary outcomes

Bone graft healing including both the alveolar ridge and augmentation of the nasal alar base.

1. Radiographic assessment of bone graft healing made by the observers through the 2D and 3D images, such as the grading scales for 2D images and the volumetric assessment in the grafted area including interalveolar septum height/width, height of nasal floor support for alar base.
2. Clinical assessment of bone graft healing made by the observers through the intraoral inspection and palpation such as the grading scales of bone graft healing.

Secondary outcomes

1. Morbidity of donor site.
2. The successful rate of insertion of an implant or integration of denture in the alveolar cleft region.
3. The rate of tooth in the line of the alveolar cleft eruption.
4. Gingival health.
5. Quality of life after the surgery e.g. postoperative pain, number of participants underwent the procedure as outpatient, length of hospital stay, etc.
6. Adverse events of the secondary bone grafting.

Search methods for identification of studies

There was no language or time restriction for searching and including eligible studies.

Electronic searches

Search strategies were developed for each database to identify studies in conjunction with the Cochrane Oral Health Group Trials Search Co-ordinator. These were based on the search strategy developed for MEDLINE (OVID) but revised for each individual database. The MEDLINE search strategy used a combination of controlled vocabulary and free text terms and was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins 2011). The following electronic databases were searched for relevant studies.

- Cochrane Oral Health Group's Trials Register (to 11 February 2011) (Appendix 1).
- Cochrane Central Register of Controlled Trials via The Cochrane Library (CENTRAL, to 11 February 2011) (Appendix 2).
- MEDLINE via OVID (1950 - 11 February 2011) (Appendix 3).
- EMBASE via OVID (1980 - 11 February 2011) (Appendix 4).
- Chinese Biomedical Literature Database (CBM, 1978 - 15 February 2011, in Chinese)

Also, WHO International Clinical Trials Registry Platform (11 February 2011) was searched to find relevant ongoing trials.

The first four databases were searched by Cochrane Oral Heath Group Trials Search Co-ordinator, Anne Littlewood, on 11 February 2011 and the rest were searched by review authors on 15 February 2011.

Searching other resources

Conference proceedings and abstracts from the Meeting of the American Cleft Palate - Craniofacial Association were searched (2004 - 11 February 2011). A search of the Internet via google (www.google.com.hk) using the key words secondary alveolar bone grafting was also undertaken. Manufacturers and first authors of included trial reports were contacted to identify any unpublished or ongoing clinical trials and to clarify data as necessary. Reference lists of included studies were screened for further trials. We have handsearched the Chinese journals within the relevant fields. We also examined the reference lists of potential clinical trials and the review authors' personal database of trial reports in an attempt to identify any additional studies or those not identified in the searches. We have also contacted authors of previous publications in the field and requested information on any unpublished and ongoing trials.

Handsearching was done by a handsearching group (8 members) in February 2011. Chinese journals within relevant fields were handsearched:

- *Chinese Journal of Implantology* (1996 to February 2011)
- *Journal of Stomatology* (1981 to February 2011)
- *Chinese Journal of Implantology* (1996 to February 2011)
- *West China Journal of Stomatology* (1983 to February 2011)
- *Journal of Clinical Stomatology* (1985 to February 2011)
- *Journal of Comprehensive Stomatology* (1985 to February 2011)
- *Journal of Modern Stomatology* (1987 to February 2011)
- *Chinese Journal of Stomatology* (1953 to February 2011)
- *Journal of Maxillofacial Surgery* (1991 to February 2011)
- *Shanghai Journal of Stomatology* (1992 to February 2011)
- *Chinese Journal of Dental Material and Devices* (1992 to February 2011)
- *Beijing Journal of Stomatology* (1993 to February 2011).

Also, references of included studies were included in further handsearching of the relevant journals in all languages.

Data collection and analysis

Selection of studies

The titles and abstracts (when available) of all studies resulting from the search were independently assessed by two review authors by scanning the titles, abstracts and the key words of the studies in the search results. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, were obtained. The full text copies were assessed independently by two review authors and any disagreement on the eligibility of included studies was resolved through discussion, and by a third review author if necessary. Studies that did not match the inclusion criteria were excluded and eliminated from further review and their details and reasons for their exclusion were noted in the 'Characteristics of excluded studies' table. The review authors were not blinded to author(s), institution or site of publication. Agreement was assessed using the Kappa statistics.

The following screening exclusion criteria were used.

1. Types of participants: aged below 5 years old.
2. Types of interventions: did not receive any form of secondary alveolar bone grafting.
3. Types of outcome measures: no outcomes related to secondary bone grafting.
4. Types of studies: studies other than RCTs.

Any study which met all of the inclusion criteria and did not meet any of the exclusion criteria were included. Authors of the studies which met exclusion criteria (1) and did not meet (2) to (4) of the exclusion criteria were contacted by letters or emails and asked for details of any participants older than 5 years old. Authors of the studies which only met exclusion criterion (3) and did not meet the other exclusion criteria were contacted by emails to ask for other outcomes not reported in the study. If they did not reply within 3 months, the study was assigned to the awaiting list.

Data extraction and management

Two review authors independently extracted data from the included studies with a self-designed table. Contents of the data extraction included: details of the study setting, characteristics of the study samples, graft sources, treatment names and usage of the interventions, and the outcomes. If stated, the sources of funding of any of the included studies was recorded. Disagreement on data extraction was resolved by discussion.

We present the extracted data from the included studies in a 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Assessment of the risk of bias in the included studies was undertaken independently and in duplicate by two review authors. Disagreements were resolved by discussion or the involvement of a third review author. It was carried out using The Cochrane Collaboration's tool for assessing risk of bias and a 'Risk of bias' table was completed for each study as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 (Higgins 2011).

The following domains were assessed as 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias:

1. Sequence generation
2. Allocation concealment
3. Blinding (of participants, personnel and outcome assessors)
4. Incomplete outcome data addressed
5. Free of selective outcome reporting
6. Free of other sources of bias.

The study authors were contacted to seek clarification when there was uncertainty over the data. These assessments are reported for each individual study in the 'Risk of bias' table under the 'Characteristics of included studies'.

Measures of treatment effect

Dichotomous data

For dichotomous data, risk ratios (RR) and 95% confidence intervals (CI) were estimated.

Continuous data

For continuous outcomes, they were pooled as weighted mean differences (WMD), when trials used the same scale. For continuous outcomes using different scales, the standardized mean difference (SMD) was used. Continuous data presented as endpoint according to the availability of data from primary studies (Schünemann 2011). We also made available the 95% CI around the estimate effects. Only the data at the trial end point was used in the analysis.

If the dichotomous data of one trial presented the same meaning of the continuous data in another trial, they were combined with the instructions mentioned in the Handbook.

Unit of analysis issues

The analysis of studies with non-standard designs would be considered in each study if:

- groups of individuals were randomised together to the same intervention (e.g. cluster-randomised trials);
- individuals undergo more than one intervention (e.g. in a cross-over trial, or simultaneous treatment of multiple sites on each individual);
- there were multiple observations for the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).

Dealing with missing data

For missing data (for example, publication bias, outcome not measured, lack of intention-to-treat (ITT) analysis, attrition from the study) the following strategies would be adopted.

- Whenever possible, contact the original investigators to request missing data.
- Make explicit the assumptions of any methods used to cope with missing data: for example, that the data are assumed missing at random, or that missing values were assumed to have a particular value such as a poor outcome.
- Perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made.

- Address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Also, missing statistics such as standard deviation (SD), changed mean and SD would be calculated using the guidance of the Handbook.

Assessment of heterogeneity

Heterogeneity was assessed using the Chi^2 test in conjunction with the I^2 statistic. A useful statistic for quantifying inconsistency is I^2 = [(Q - df)/Q] x 100%, where Q is the Chi^2 statistic and df is its degrees of freedom. Significance for the Chi^2 test was set at $P < 0.10$ due to the low power of this test (Deeks 2011). Substantial heterogeneity was considered if the I^2 statistic showed a value greater than 50%. When significant heterogeneity was present, an attempt was made to explain the differences based on the clinical characteristics of the included studies.

Assessment of reporting biases

To assess publication bias, data would have been plotted on a funnel graph in The Cochrane Collaboration's review writing software, RevMan, if there were more than ten studies involved in one outcome.

Data synthesis

In the absence of significant heterogeneity ($I^2 \leq 50\%$, $P \geq 0.10$), a fixed-effect model was used. However, if significant heterogeneity was demonstrated ($I^2 > 50\%$, $P < 0.10$), a random-effects model was used for analysis. Where available, the analyses were based on ITT data from the individual studies. The data from included trials were combined in a meta-analysis if they were sufficiently homogeneous, both clinically and statistically. Data were only pooled when there were studies of similar participants, interventions and outcomes.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses would be conducted to explore the influence of study characteristics such as the types of cleft, size of cleft, orthodontic history, technique and source of bone for transplant on the meta-analysis outcome.

Sensitivity analysis

Sensitivity analyses would be used to assess all included studies, in relation to the different levels of methodological quality (e.g. 'Low risk' of bias or 'High risk' of bias), and clinical heterogeneity (Deeks 2011). Also, sensitive analysis was conducted with a different model effect, ITT analysis (worst-case scenario' analysis) or excluding studies which caused significant heterogeneity.

RESULTS

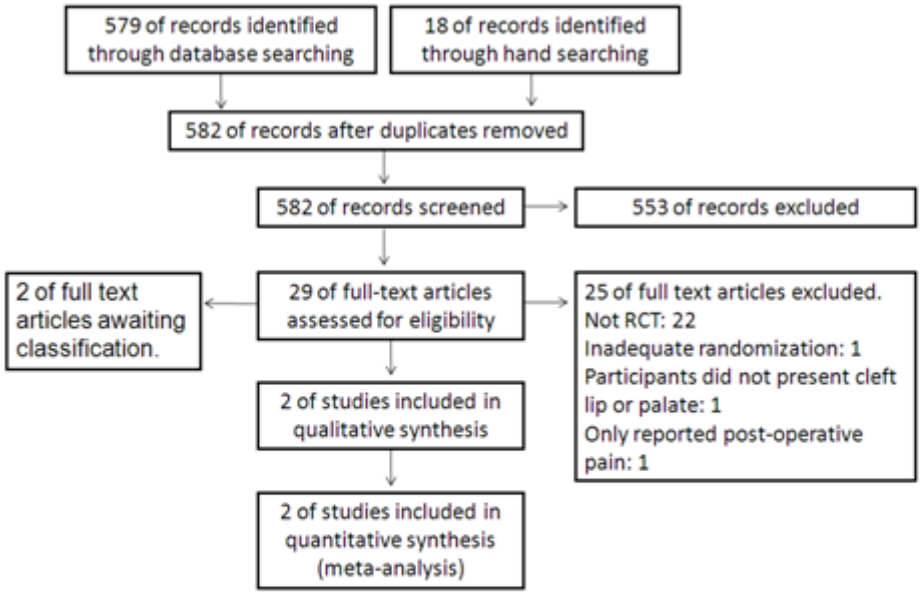
Description of studies

See 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

After the search strategies, 582 publications were identified, of which 553 were excluded after reviewing the titles and abstracts. Of the remaining 29 publications, the full articles were obtained. After screening the full articles, 25 studies were excluded. Therefore, two randomized controlled trials (RCTs) (Segura-Castillo 2005; Dickinson 2008) fulfilled all the criteria for inclusion and two RCTs (Peled 2005; Thuaksuban 2010) are awaiting classification. For details of the studies examined and reasons for inclusion or exclusion please see 'Characteristics of included studies' and 'Characteristics of excluded studies' tables. The process of study identification is presented in Figure 1.

Figure 1. Flow diagram of study inclusion.



Included studies

(*See* 'Characteristics of included studies' table.)

From the searches, the following two RCTs were identified.

1. Traditional iliac bone graft versus alternatives to bone graft

Dickinson 2008: A parallel randomized controlled trial from the University of California, Los Angeles Medical Center and Oliveview Medical Center. The investigators included skeletally mature unilateral cleft lip–cleft palate patients with an alveolar cleft defect and excluded the participants if they had previous alveolar surgery (i.e. failed bone graft or gingivoperiosteoplasty), were still growing, had a contraindication to BMP-2 treatment (i.e. history of neoplasm), or had incomplete records. The mean age of the participants was 16.1 years. The 21 participants were randomly divided, 9 in intervention group and 12 in control group. The intervention group received the InFuse bone graft (Sofamor-Danek, Memphis, Tenn.) impregnated with rhBMP-2 and the control group received traditional iliac crest cancellous graft. The result as reported from the study showed that BMP-2 experimental procedure offered improved bone healing and decreased postoperative pain.

2. Traditional iliac bone graft versus traditional iliac bone graft plus artificial materials

Segura-Castillo 2005: A parallel randomized controlled single-blind trial included 27 participants aged between 7 to 16 with unilateral or bilateral cleft lip and palate from the Department of Pediatric Reconstructive Surgery of the Children's Hospital of the Western Medical Center of the Mexican Institute of Social Security in Guadalajara, Jalisco. They were randomly divided into intervention group (n = 13) which received traditional iliac bone grafting with fibrin glue applied to the bone graft, and a control group (n = 14) which only received traditional iliac bone grafting. Participants were followed up for at least 3 months and the study reported that fibrin glue significantly diminished bone resorption, allowing improved graft integration and quality.

Excluded studies

(*See* 'Characteristics of excluded studies' table for further details.) From the search strategies, besides the included and awaiting studies, there were 18 additional articles or abstracts identified for which the full copies were obtained. These studies were excluded based on the inclusion and exclusion criteria. Although the reasons for exclusion for each study varied, the main points were deficiency of randomisation, no comparison group, or irrelevant research to this systematic review.

Risk of bias in included studies

See 'Characteristics of included studies' table, Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

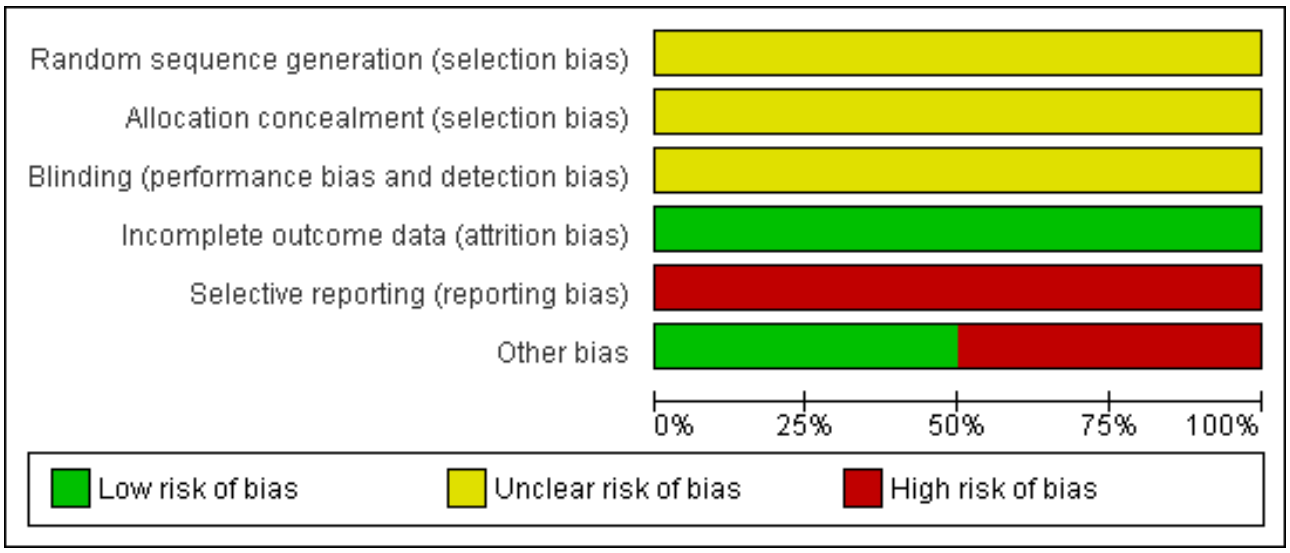
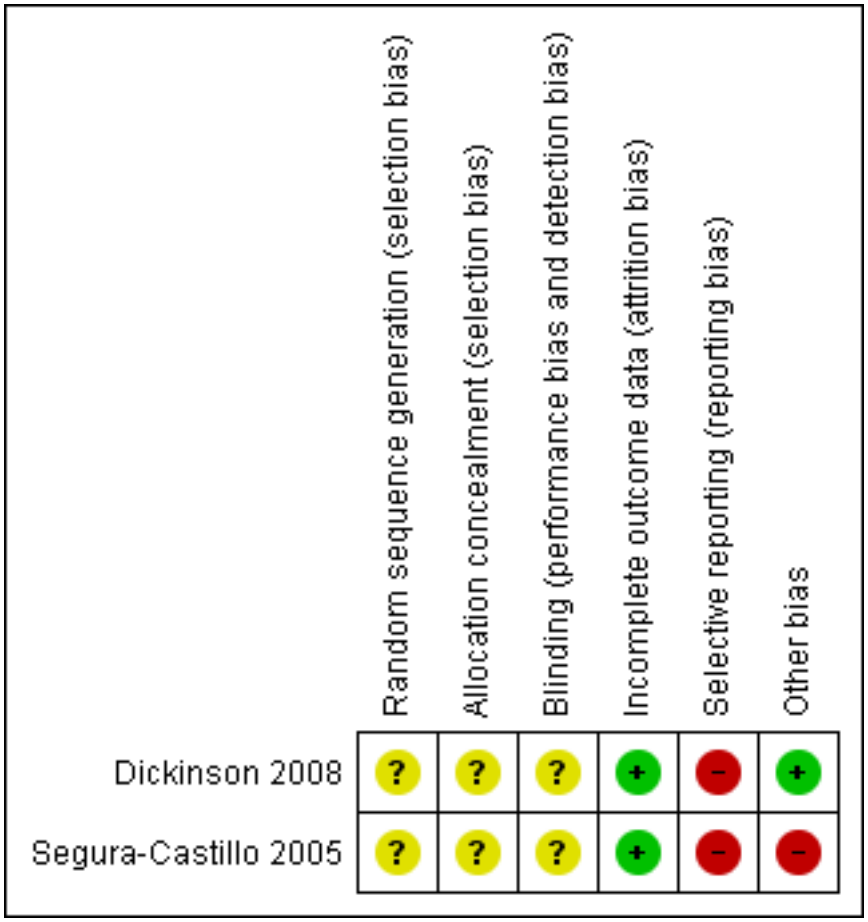


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Both studies are assessed as being at high risk of bias.

Allocation

Adequate sequence generation: Both of the studies mentioned random allocation but neither mentioned the detail of the sequence generation. Thus, the sequence generation was not clear.

Allocation concealment: Neither of the included studies had clearly described the allocation concealment.

Blinding

Segura-Castillo 2005 was single-blinded, but the authors did not mention who was blinded to the therapy.

Dickinson 2008 mentioned that these defects were outlined using the Image program (National Institutes of Health, Bethesda, Md.) by three blinded assessors but the investigator did not mention whether the surgeon or participants were blinded, so blinding was also considered to be unknown.

Incomplete outcome data

From both of the studies, there were no reported drop outs.

Selective reporting

Firstly, neither of the included studies mentioned a previous published protocol. Secondly, in Dickinson 2008, some of the variables mentioned in 'materials and methods' were not fully reported in 'results'. Thirdly, in Segura-Castillo 2005, some results were wrongly printed in the text and could not be used for the meta-analysis. Finally, neither study clearly stated whether the value behind "±" was a standard error (SE) or standard deviation (SD).

Other potential sources of bias

In Segura-Castillo 2005, the authors reported that the orthodontic maxillary expansion differed between different participants but this was not compared, and also did not mention the baseline status such as the difficulty of the surgery or the age, therefore there might be confounding bias. For Dickinson 2008, we could not identify any other sources of bias from the published study.

Effects of interventions

As both of the studies did not clearly state whether the value behind "±" was SE or SD, we have tried to check all the data provided with the supposing that it was SD or SE with the help of the statistical software package, STATA, and we found that those numbers were SD in both studies. So all the statistics used below were the data extracted and used in this systematic review if not specially explained.

Part 1. Effect of traditional iliac bone graft versus alternatives to bone graft (Comparison 1).

As mentioned in Included studies, one study compared traditional iliac bone graft with alternatives to bone graft (Dickinson 2008).

Traditional iliac bone graft versus artificial bone graft materials (+rhBMP-2).

Dickinson 2008 compared traditional iliac graft (control group, n = 12) with InFuse bone graft (Sofamor-Danek, Memphis, Tenn., a kind of collagen matrix) impregnated with rhBMP-2 (intervention group, n = 9). The bone healing was assessed by the clinically assessed variables and the radiological evaluation, and quality of life after surgery reflected by donor-site pain, length of hospital stay and complications.

Two clinically assessed variables (alveolar ridge healing and nasal alar base augmentation) were recorded, but the results did not clearly mention the exact time point (6 weeks or 1 year) when these were recorded. The results were recorded as a four-point grading system from 0 to 3 (0 = complete loss of graft to 25% take; 1 = 25 to 50% graft take; 2 = 50 to 75% graft take; and 3 = 75 to 100% graft take). The reported results showed that BMP-2 group (n = 9) had a score 0.9 point higher when compared to the iliac grafting group (n = 12) (mean difference (MD) -0.90; 95% confidence interval (CI) -1.16 to -0.64). For nasal alar base augmentation, examiners again graded patients from 0 to 3 (0 = minimum or no change from preoperative alar base position; 1 = 25 to 50% improvement; 2 = 50 to 75% improvement; and 3 = 75 to 100% improvement). After follow-up, the mean value of nasal alar base augmentation was 2.2 in the BMP-2 group (n = 9) compared with 2.0 in the iliac grafting group (n = 12), with no significance between the two groups (MD -0.20; 95% CI -0.41 to 0.01). *See* Analysis 1.1.

Radiological evaluations including Panorex, three-dimensional CT scan and periapical films of the teeth adjacent to the cleft were gained preoperatively and at follow-up (1 year). The radiographic evaluations were also recorded by a four-point grading system. The results showed that the artificial bone graft materials group had better bone healing and enhanced mineralization compared with traditional iliac bone graft group (Panorex (MD -0.90; 95% CI -1.39 to -0.41); three dimensional CT scan (MD -0.90; 95% CI -1.39 to -0.41); periapical film (MD -0.60; 95% CI -0.90 to -0.30)). *See* Analysis 1.2.

As the traditional graft group was derived from iliac bone of the participants, most of the participants had donor site pain. All of the participants presented with donor site pain at day 1 post operation and 11 of the 12 participants in the traditional group reported such pain 6 months after the operation. The mean length of stay in the hospital was 1.4 days longer for the participants of the traditional group (mean = 1.8 days, all on inpatient basis) compared to that of artificial material group (mean = 0.4 day) (MD 1.40; 95% CI 0.88 to 1.92). Seven of the participants in the artificial material group were discharged on the day of surgery compared to no participants in traditional group (risk ratio (RR) 0.05; 95% CI 0.00 to 0.80). *See* Analysis 1.3 and Analysis 1.4.

For the postoperative complications, of the 12 participants of traditional iliac graft group, 5 were reported with partial loss of graft and 3 with persistent oronasal fistula compared with no complications in artificial material group (oronasal fistula (RR 5.38; 95% CI 0.31 to 92.73); loss of the graft (RR 8.46; 95% CI 0.53 to 135.74)). The artificial material group had one reported prolonged wound healing episode but the authors did not describe whether there were any participants in the traditional group with a similar problem. *See* Analysis 1.5.

Part 2. Effect of traditional iliac bone graft versus traditional iliac bone graft plus artificial materials (Comparison 2).

One study reported some variables comparing traditional iliac bone grafting with traditional iliac bone grafting plus artificial materials (Segura-Castillo 2005).

Traditional iliac bone graft versus traditional iliac bone graft plus fibrin glue.

Segura-Castillo 2005 compared traditional iliac bone grafting (control group, n = 14) with traditional iliac bone grafting plus fibrin glue (intervention group, n = 13). Radiological assessment and complications were adopted to reflect the bone healing of the grafting.

All the radiological assessments were based on the tomography scans. The average amount of graft resorption reported varied from 62.25% in the control group to 29.72% in the intervention group. The mean coronal bone volume was reported as 42.62 cm^3 greater in the intervention group (64.32 cm^3) when compared with the control group (21.70 cm^3) (MD -42.62; 95% CI -64.25 to -20.99), and mean coronal bone density was 150.89 HU less in the control group (245.68 HU) than intervention group (396.57 HU) (MD -150.89; 95% CI -298.33 to -3.45). *See* Analysis 2.1.

Postoperative complications were reported, there were no infections of the wound and three dehiscences in the control group compared with one infection of the wound and one dehiscence in the intervention group (infection in wound (RR 0.31; 95% CI 0.01 to 7.02); dehiscence (RR 2.79; 95% CI 0.33 to 23.52)) respectively. *See* Analysis 2.2.

DISCUSSION

Summary of main results

This systematic review included 2 randomized controlled trials (RCTs) focusing on the effectiveness and safety of traditional secondary bone grafting with autogenous bone alone or in combination with other bone replacement products in treating an alveolar cleft defect in children with cleft lip and/or palate. Both included RCTs had chosen iliac bone as the donor site material of the secondary bone grafting in the control group. As both of the studies have high risk of bias, the results from the analysis should be treated with some caution.

The clinical evaluation reported in the trials showed improved alveolar ridge healing but no difference in nasal alar base augmentation when assessing the artificial graft, InFuse bone graft (Sofamor-Danek, Memphis, Tenn.) impregnated with rhBMP-2.

When evaluated by CT or other radiological assessments, both studies demonstrate improved outcomes with the use of artifical bone or autogenous iliac bone with additional material, such as fibrin glue.

Postoperative complications, which also reflected the bone healing, showed some small clinical differences with improved outcomes of the artificial group although these were not statistically significant (partial loss of graft: risk ratio (RR) 8.46; 95% confidence interval (CI) 0.53 to 135.74) (persistent oronasal fistula: RR 5.38; 95% CI 0.31 to 92.73), this clinical significance may be better reflected in further studies. The procedure utilising fibrin glue still requires removal of bony tissue from the donor, as in the traditional alveolar bone group, hence the postoperative complications were similar. The main benefit of using artificial materials instead of autogenous bone, from the one study, appears to be the reduction of hospital stay reported due to reduced donor site morbidity.

Overall completeness and applicability of evidence

The outcomes presented suggest possibilities for future research but not currently clinical practice. The evidence from the outcomes reported are inconclusive, with some aspects suggesting an improved outcome, i.e. volumetric assessment from CT, but others suggesting no difference in outcome, i.e. defect height or width reduction. The artificial material investigated could be utilised as an alternative to iliac crest bone, as this had a similar outcome with greatly reduced donor site morbidity and hospital stay, but further research is required before it could be recommended. If human iliac bone is to be used as a graft material, the addition of the artificial material investigated in one trial does not appear to affect the outcome when assessed by radiographic parameters. The use of adjuncts to harvested autogenic bone also requires further research to clarify the benefits to patients and clinicians.

This systematic review has not been able to report all the objectives described in the protocol. Many of the studies assessing artificial materials were not RCTs. Furthermore, no RCTs were found to study the optimal timing and the sequence of orthodontic treatment with secondary bone grafting surgery.

The current limited volume of evidence, which is associated with potential high risk of bias, is not conclusive in demonstrating improved clinical outcomes. Further trials are required before definitive conclusions and recommendations can be made with regard to secondary alveolar bone grafting in children with cleft lip and/or palate.

Quality of the evidence

The included studies had the following methodological defects to some extent. Firstly, both of the studies did not describe the sequence generation, although they claimed that the groups in their trials were all randomly allocated and this may have introduced some selection bias. Secondly, the included studies did not mention the allocation concealment method, and neither of them clearly stated how blinding was used during the trial. Thirdly, selective data reporting and other bias still existed, with both of the studies not fully reporting the data outlined in the method sections (such as the standard deviation or 95% CI of the data).
Finally, only one RCT had reported whether ethical approval and the use of informed consent from the participants had been utilised (Segura-Castillo 2005). The other trial did not mention either of these. Figure 2 and Figure 3 show that the risk of bias for the included studies suggests some caution when interpreting the outcome of the meta-analysis in this systematic review.

Potential biases in the review process

Within the process of conducting the systematic review, there may still be some biases. Firstly, when searching, we have searched six databases, but it is likely that those databases do not cover all the published, unpublished and ongoing studies, which may have led to a search bias within the study. Also extensive handsearching was only conducted for studies published in Chinese. English language studies may have been excluded as not all of the relevant publications were handsearched for all years, unless references were identified by other studies. Secondly, bias may arise from the included studies themselves. Both of the included studies had, to some extent, a risk of bias such as the undescribed randomisation, allocation concealment, inadequate blinding, etc, which may contribute to some further bias in the review process.

Agreements and disagreements with other studies or reviews

Five related reviews were found.

Witsenburg 1985: *The reconstruction of anterior residual bone defects in patients with cleft lip, alveolus and palate. A review* published in the *Journal of Maxillofacial Surgery* in 1985. As this review was published in the 1980s when artificial materials were not widely introduced to this area, it concluded that autogenous bone appeared to be, by that time, the best graft material but disagreement existed on the viability of autogenous bone from different donor sites.

Brattstrom 1989: *The influence of bone grafting age on dental abnormalities and alveolar bone height in patients with unilateral cleft lip and palate* published in the *European Journal of Orthodontics* in 1989. It concluded that the primary grafting group (bone grafted prior to one year of age) had fewer supernumerary teeth in the cleft area and a lower frequency of missing and severely malformed central incisors than the other groups. The early secondary graft group (bone grafted after eruption of the permanent incisors) showed the highest frequency of normal lateral incisors and the most favourable alveolar bone height in the cleft area. The secondary graft group (bone grafted after eruption of the canines) showed the highest frequency of missing teeth outside the cleft area. Early secondary bone grafting, after eruption of the permanent incisors and before eruption of the canines, was reported as preferable.

Handoll 2008: *Bone grafts and bone substitutes for treating distal radial fractures in adults* published in the *Cochrane Database of Systematic Reviews* in 2008. This is a Cochrane systematic review from the Cochrane Bone, Joint and Muscle Trauma Group. There are clinical conditions that require regeneration or implantation of bone besides alveolar clefts. In this systematic review, 10 RCTs (874 participants) have been included. However, no definite conclusions could be drawn from bone grafts/bone substitutes versus conventional treatment because of the small and underpowered trials included.

Board 2009: *Processed versus fresh frozen bone for impaction bone grafting in revision hip arthroplasty* published in the *Cochrane Database of Systematic Reviews* in 2009 from the Cochrane Musculoskeletal Group. The objective of this review was to determine the clinical effectiveness of processed bone in comparison to fresh frozen (unprocessed) bone. Unfortunately, no published RCTs were identified meeting the eligibility criteria.

Goudy 2009: *Secondary alveolar bone grafting: outcomes, revisions, and new applications* published in the *Cleft Palate-Craniofacial Journal* in 2009. In this study, the researchers identified 103 patients who had undergone secondary bone grafting in the past 20 years. During the last 3 years of this study, demineralized bone matrix (DBM) was used in conjunction with secondary bone grafting routinely. The reported conclusion showed that the use of DBM did not significantly decrease the need for revision surgery, or increase the complication rate. These study results agree with findings of our review to some extent.

Therefore, there appears to be a lack of high quality RCTs through the surgical specialities which utilise bone grafting techniques.

AUTHORS' CONCLUSIONS

Implications for practice

Two small randomized controlled trials (RCTs) assessed as being at high risk of bias were included in this review, each trial comparing different interventions. One trial compared an artificial grafting material impregnated with rhBMP-2 with traditional iliac grafting, and the other trial compared traditional iliac grafting plus fibrin glue with traditional iliac graft. Although some significant differences were found, these are unreliable and not highlighted here. We are unable to conclude that either of these new interventions are superior to the traditional iliac grafting.

Implications for research

More RCTs on this topic are still needed, especially those studies investigating new artificial materials, optimal timing of secondary alveolar bone grafting and the sequence of the orthodontic treatment with secondary alveolar bone grafting surgery. RCTs on this topic should report clear methods conforming to CONSORT guidelines and utilise uniform variables of outcome.

- E (Evidence): The present evidence helped us to judge the advantages and disadvantages of different types of secondary bone grafting but the sample was too small to form a high test efficacy and also the quality was not sufficiently high to allow for any conclusions to be stated about preferred techniques or materials.
- P (Population): Whether the participants have cleft lip and/or palate should be mentioned. Participants' age should be controlled to a small range, as the different age of participants may affect the outcome. More studies should be undertaken in wider populations based in Africa, Easten Asia, Europe and South America. Studies using artificial materials could include some participants who had failed a previous bone grafting to test the usage of such materials in this clinical scenario. The samples should be increased and established using prior sample size calculations perhaps using multiple trial sites.
- I (Intervention): Existing materials should be included in well conducted clinical trials if they have been shown to be effective in preliminary studies. New artificial materials could be introduced in the future which might lead to improved outcomes.
- C (Comparison): Studies should compare new surgical techniques and new artificial materials with those techniques and artificial materials which have been established as current practice.
- O (Outcome): Objective measures which have been demonstrated to be valid and reliable measures, such as the alveolar cleft volumetric assessments with 3D CT cone beam scanning, should be utilised in future studies. The extent that 2D radiographic assessments correlate with these 3D assessments should also be clarified to allow for comparison with existing and future trial data using both methods. Consideration should also be made when these assessments are carried out. Both short term, (immediate to 6 months postoperatively) and long term (> 6 months) should be considered when reporting outcomes for alveolar bone grafting. This relates to the suggested benefits of this procedure which may not be evident immediately after surgery and requires time after the procedure, i.e. the eruption of permanent teeth through the previous alveolar cleft defect or

placement of a dental implant, before these can be adequately assessed.

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CHARACTERISTICS OF STUDIES

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

Dickinson 2008

Methods	Study design: parallel randomized controlled trial. Time frame: not reported. Duration of the study: not reported.

Dickinson 2008 *(Continued)*

	Stratification: no. Sample size calculation: not reported.
Participants	Setting: University of California, Los Angeles Medical Center and Oliveview Medical Center. Inclusion criteria: skeletally mature unilateral cleft lip–cleft palate patients with an alveolar cleft were included. Exclusion criteria: participants were excluded from the study if they had previous alveolar surgery (i.e. failed bone graft or gingivoperiosteoplasty), were still growing, had a contraindication to BMP-2 treatment (i.e. history of neoplasm), or had incomplete records. Age: mean = 16.1. Sex: male 9, female 12. Country: USA. Participants type: skeletally mature unilateral cleft lip–cleft palate patients with an alveolar cleft. Total recruited: 21: 9 in intervention group and 12 in control group.
Interventions	Intervention group: the InFuse bone graft (Sofamor-Danek, Memphis, Tenn.), which is a collagen matrix impregnated with rhBMP-2 were grafted. Control group: traditional iliac crest graft.
Outcomes	Complications; alveolar ridge healing (four-point grading system) (preoperative, 6 weeks and 1 year after the surgery); nasal alar base augmentation (four-point grading system) (preoperative, 6 weeks and 1 year after the surgery); panoramic view results (four-point grading system) (preoperative and 6 months after the surgery); three-dimensional computed tomographic scan results (four-point grading system) (preoperative and 6 months after the surgery); periapical films results (preoperative and 6 months after the surgery); volume of bone filled in alveolar cleft (preoperative and 6 months after the surgery); length of hospital stay; donor site pain intensity and frequency (VAS) (day 1, day 7, week 3, week 6, month 3, and month 6); number of participants as outpatient; length of stay in hospital; cost of surgery.
Notes	Funding: the author claimed that none of authors has any financial interest in companies producing or distributing products used for this study, and this study was supported by a Bernard G. Sarnat award in craniofacial biology. Author contacted: further information was requested from the authors but there has been no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients undergoing alveolar cleft repair were divided into two random groups". Comment: probably done, but the detail of the sequence generation was not clear.
Allocation concealment (selection bias)	Unclear risk	Comment: unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "These defects were outlined using the Image program (National Institutes of Health, Bethesda, Md.) by three blinded reviewers".

Dickinson 2008 *(Continued)*

		Comment: still unclear. Although the reviewers of CT were blinded, whether the physical examiner and the participants were blinded to the treatment was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate.
Selective reporting (reporting bias)	High risk	In 'materials and methods', author reported the physical examination preoperatively, 6 weeks and 1 year after the surgery, but the result of only one time point of the postoperative examination was reported. In 'materials and methods', author reported the examination of pain was done on day 1, day 7, week 3, week 6, month 3, and month 6, but in 'results' pain at month 3 was not reported. Standard deviation of pain was not reported.
Other bias	Low risk	No other bias could be found.

Segura-Castillo 2005

Methods	Study design: parallel randomized, controlled, single-blind trial. Time frame: March 2001 to April 2003. Duration of the study: for one participant, the trial took at least 3 months and it took 25 months to finish the trial. Stratification: no. Sample size calculation: not reported.
Participants	Setting: Department of Pediatric Reconstructive Surgery of the Children's Hospital of the Western Medical Center of the Mexican Institute of Social Security in Guadalajara, Jalisco. Inclusion criteria: participants with alveolar cleft were included. Exclusion criteria: not reported. Age: mean = 10.7, range = 7 ~ 16. Sex: male 16, female 11. Country: Mexico. Participants type: 16 patients had unilateral cleft lip and palate, and 11 patients had bilateral cleft lip and palate. Total recruited: 27: 13 in intervention group and 14 in control group.
Interventions	Intervention group: iliac bone grafting + fibrin glue applied to the bone graft + antibiotics and analgesics. Control group: iliac bone grafting + antibiotics and analgesics.
Outcomes	Graft volume and grade of resorption (pre-operation, 3 months postoperatively), bone density and quality (3 months postoperatively), and postoperative complications (3 months).
Notes	Funding: not mentioned. Author contacted: further information was requested from the authors but there has been no reply.

Segura-Castillo 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned at random to one of two groups". Comment: probably done, but the detail of the sequence generation was not clear.
Allocation concealment (selection bias)	Unclear risk	The allocation concealment was not mentioned.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "We designed a randomised, controlled, single-blind clinical trial". Comment: the author did not mention whether the participants or the assessors were blinded to the treatment, so whether the blinding was adequate was unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate.
Selective reporting (reporting bias)	High risk	The outcome of the bone density and quality was wrongly printed.
Other bias	High risk	Quote: "Most patients received preoperative orthodontic maxillary expansion". Comment: the orthodontic maxillary expansion was not compared so there may be existing confounding bias.

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

Study	Reason for exclusion
Bianchi 2004	Not on this topic. Participants did not have cleft lip or palate.
Dawson 1996	RCT. However, this study compared postoperative pain control using ketorolac after the same surgery, which is grafting of clefts with fresh, autologous bone obtained from the anterior iliac crest.
Enemark 1988	Not RCT.
Epker 2009	Not RCT. Atlas of the secondary bone grafting surgery.
Gesch 2006	Not RCT.
Gimbel 2007	Not RCT. Participants were divided into the groups based on randomization and physician preference.
Koole 1989	Not RCT, comparative study.
Loh 1988	Not RCT.
Morselli 2009	Not RCT. No control group.

Study	Reason for exclusion
Oberoi 2009	Not RCT. No control group.
Ozawa 2007	Not RCT.
Power 2009	Not RCT. Case report.
Ramstad 1997	Not RCT, comparative study.
Rawashdeh 2007	Not RCT.
Sadove 1990	Inadequate randomization, CCT not RCT. Alternative schedule was used for randomization.
Sindet-Pedersen 1990	Not RCT, comparative study.
Sivarajasingam 2001	Not RCT, comparative study.
Steinbacher 2009	Not RCT. No comparison.

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

Peled 2005

Methods	Study design: parallel randomized controlled trial. Time frame: not reported. Duration of the study: for one participant, the trial took 2 to 6 years (mean = 3.1). Stratification: no. Sample size calculation: not reported.
Participants	Setting: not mentioned. Inclusion criteria: participants that had unilateral cleft palate and had primary closure of the soft tissues at infancy were included. Exclusion criteria: not reported. Age: mean = 12.3, SD = 2.2, range = 9 ~ 17. Sex: not mentioned. Country: not mentioned. Participants type: unilateral cleft palate. Total recruited: 15. The number of each group was not reported.
Interventions	Intervention group 1: presurgical orthodontics and scaling + ePTFE membrane reinforced with titanium rods (Gore-Tex) grafting, the membranes were retrieved under local anaesthesia 3 to 5 months post-treatment + antibiotics (Amoxicillin 30 mg/kg per day) for 1 week and rinse with chlorhexidine 0.2% for 3 months + quarterly plaque removal and prophylaxis. Intervention group 2: presurgical orthodontics and scaling + autogenous iliac bone and resorbable polylactic-polyglycolic acid membrane (Resolut XT) grafting + antibiotics (Amoxicillin 30 mg/kg per day) for 1 week and rinse with chlorhexidine 0.2% for 3 months + quarterly plaque removal and prophylaxis.

Peled 2005 *(Continued)*

	Control group: presurgical orthodontics and scaling + autogenous iliac bone grafting + antibiotics (Amoxicillin 30 mg/kg per day) for 1 week and rinse with chlorhexidine 0.2% for 3 months + quarterly plaque removal and prophylaxis.
Outcomes	Complications; defects (height, width) (pretreatment and 2 to 6 years later); defect's area (height × width, in square millimetres) (pretreatment and 2 to 6 years later); eruption of canine teeth next to the cleft defect.
Notes	Funding: not mentioned. Author contacted: it is unclear how many subjects are in each of the 3 treatment groups. As there are only 15 subjects in total, it is important that this is correct for the data analysis. Theoretically, the number of each groups could be calculated from the data supplied by the published article, but we found that there were some significant errors in the published data so that the exact number of participants in each group could not be calculated. The exact number of participants and clarification of the data in the article have been requested from the authors.

Thuaksuban 2010

Methods	Study design: parallel randomized controlled trial. Time frame: November 2004 to June 2007. Duration of the study: for each participant, it took 2 years. Stratification: no. Sample size calculation: not reported.
Participants	Setting: Dental Hospital, Prince of Songkla University. Inclusion criteria: ASA class I patients, aged 9 to 12 years, with residual alveolar clefts were included in the study. Exclusion criteria: patients who had bleeding disorders, bone and metabolic diseases, and were not available for 2-year follow-up were excluded from the study. Age: mean = 10.2, SD = 1.7. Sex: male 10, female 20.
Interventions	Intervention group: autogenous iliac bone grafting mixed with DBB (MTEC, Pathumthani, Thailand), with a particle size of 0.25 mm in the ratio of 1:1 by volume + analgesics (acetaminophen and meperidine) + antibiotics (intravenous cephalosporin) + orthodontic treatment 6 months later. Control group: autogenous iliac bone grafting + analgesics (acetaminophen and meperidine) + antibiotics (intravenous cephalosporin) + orthodontic treatment 6 months later. Note: the mean autogenous bone graft volume used in intervention group could be reduced by adding an equal volume of DBB.
Outcomes	First 7 days after operation: duration of hospital stay (day); time taken to walk again, with and without assistance; and postoperative pain level (using a 10 cm visual analogue scale). Two years postoperatively: wound healing, complications, tooth eruption. Changes to the bone graft quantities-bone graft height (assessed by intraoral radiograph 3 days postoperative and 1, 3, 6, 12, 18 and 24 months postoperatively).

Thuaksuban 2010 *(Continued)*

Notes	Funding: a grant for academic research from the Prince of Songkla University, Hatyai, Songkhla, Thailand. Author contacted: it is unclear whether all the participants had cleft lip or palate and the results were illustrated in a figure format. Therefore we require the exact data to do the meta-analysis. An email on these issues has been sent to the original authors to get answers, but up to now, there has been no reply.

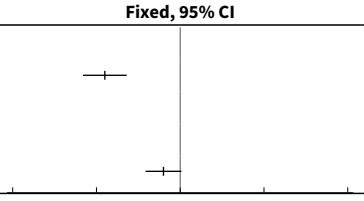
DATA AND ANALYSES

Comparison 1. Effects of traditional iliac bone grafting versus grafting using artificial materials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical assessment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Alveolar healing	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Alar base augmentation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Radiographic assessment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Panorex scan	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Three-Dimensional CT scan	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Periapical film	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Length of hospital stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Number of participants discharged on the same day as surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Postoperative complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Oronasal fistulae	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Loss of bone graft	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Effects of traditional iliac bone grafting versus grafting using artificial materials, Outcome 1 Clinical assessment.

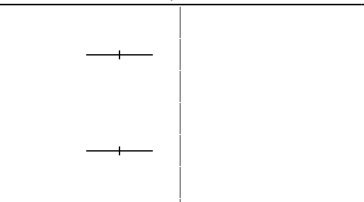
Study or subgroup	Traditional iliac bone grafting		Artificial graft		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.1.1 Alveolar healing						
Dickinson 2008	12	1.9 (0.4)	9	2.8 (0.2)		-0.9[-1.16,-0.64]
1.1.2 Alar base augmentation						
Dickinson 2008	12	2 (0.3)	9	2.2 (0.2)		-0.2[-0.41,0.01]



Favours artificial group — Favours traditional group

Analysis 1.2. Comparison 1 Effects of traditional iliac bone grafting versus grafting using artificial materials, Outcome 2 Radiographic assessment.

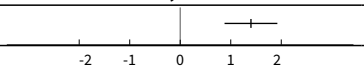
Study or subgroup	Traditional iliac bone grafting		Artificial graft		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.2.1 Panorex scan						
Dickinson 2008	12	2 (0.8)	9	2.9 (0.3)		-0.9[-1.39,-0.41]
1.2.2 Three-Dimensional CT scan						
Dickinson 2008	12	2 (0.8)	9	2.9 (0.3)		-0.9[-1.39,-0.41]
1.2.3 Periapical film						
Dickinson 2008	12	2.8 (0.4)	9	3.4 (0.3)		-0.6[-0.9,-0.3]



Favours artificial group — Favours traditional group

Analysis 1.3. Comparison 1 Effects of traditional iliac bone grafting versus grafting using artificial materials, Outcome 3 Length of hospital stay.

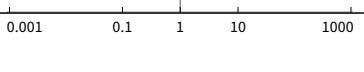
Study or subgroup	Traditional iliac bone grafting		Artificial graft		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Dickinson 2008	12	1.8 (0.8)	9	0.4 (0.4)		1.4[0.88,1.92]



Favours traditional group — Favours artificial group

Analysis 1.4. Comparison 1 Effects of traditional iliac bone grafting versus grafting using artificial materials, Outcome 4 Number of participants discharged on the same day as surgery.

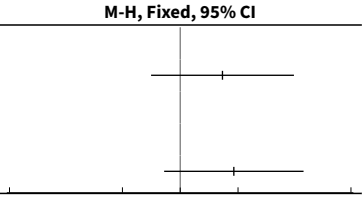
Study or subgroup	Traditional iliac bone grafting	Artificial graft	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Dickinson 2008	0/12	7/9		0.05[0,0.8]



Favours artificial grouo — Favours traditional group

Analysis 1.5. Comparison 1 Effects of traditional iliac bone grafting versus grafting using artificial materials, Outcome 5 Postoperative complications.

Study or subgroup	Traditional iliac bone grafting n/N	Artificial graft n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Oronasal fistulae				
Dickinson 2008	3/12	0/9		5.38[0.31,92.73]
1.5.2 Loss of bone graft				
Dickinson 2008	5/12	0/9		8.46[0.53,135.74]

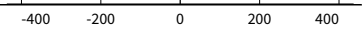


Comparison 2. Effect of traditional iliac bone grafting with traditional iliac bone grafting plus artificial materials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Radiographic assessment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Coronal bone volume	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Coronal bone density	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Postoperative complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Infection in wound	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Dehiscence	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

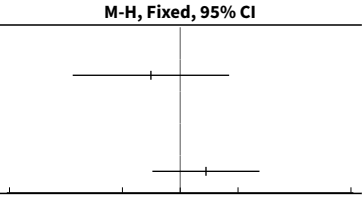
Analysis 2.1. Comparison 2 Effect of traditional iliac bone grafting with traditional iliac bone grafting plus artificial materials, Outcome 1 Radiographic assessment.

Study or subgroup	Trad. iliac bone grafting N	Trad. iliac bone grafting Mean(SD)	Trad. iliac bone grafting + artificial materials N	Trad. iliac bone grafting + artificial materials Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.1.1 Coronal bone volume						
Segura-Castillo 2005	14	21.7 (22)	13	64.3 (33.7)		-42.62[-64.25,-20.99]
2.1.2 Coronal bone density						
Segura-Castillo 2005	14	245.7 (147.7)	13	396.6 (230.9)		-150.89[-298.33,-3.45]



Analysis 2.2. Comparison 2 Effect of traditional iliac bone grafting with traditional iliac bone grafting plus artificial materials, Outcome 2 Postoperative complications.

Study or subgroup	Trad. iliac bone grafting n/N	Trad. iliac bone grafting + artificial materials n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Infection in wound				
Segura-Castillo 2005	0/14	1/13		0.31[0.01,7.02]
2.2.2 Dehiscence				
Segura-Castillo 2005	3/14	1/13		2.79[0.33,23.52]



APPENDICES

Appendix 1. OHG TRIALS REGISTER SEARCH STRATEGY

(("cleft lip*" or "cleft palat*" or "alveolar cleft*" or (mouth? AND abnorm*) or (mouth AND defect*) or (mouth AND malform*) or (maxilla* AND abnorm*) or (maxilla* AND defect*) or (maxilla* AND malform*) or (jaw AND abnorm*) or (jaw AND defect*) or (jaw? AND malform*)) AND ((bone* or bony* or osseous* or osteal* or osteoplast*) AND (graft* or surg* or reconstruct* or restor* or implant* or augment* or repair*)))

Appendix 2. CENTRAL via The Cochrane Library Search Strategy

#1 MeSH descriptor CLEFT PALATE this term only

#2 MeSH descriptor CLEFT LIP this term only

#3 ((cleft* in All Text near/4 lip in All Text) or (cleft* in All Text near/4 palate in All Text))

#4 ((alveolar in All Text near/6 cleft in All Text) or (maxilla* in All Text near/6 cleft in All Text) or (gum* in All Text near/6 cleft in All Text) or (jaw* in All Text near/6 cleft in All Text) or (palat* in All Text near/6 cleft in All Text) or (lip* in All Text near/6 cleft in All Text) or (alveolar in All Text near/6 defect* in All Text) or (maxilla* in All Text near/6 defect* in All Text) or (gum* in All Text near/6 defect* in All Text) or (jaw* in All Text near/6 defect* in All Text) or (palat* in All Text near/6 defect* in All Text) or (lip* in All Text near/6 defect* in All Text) or (alveolar in All Text near/6 malform* in All Text) or (maxilla* in All Text near/6 malform* in All Text) or (gum* in All Text near/6 malform* in All Text) or (jaw* in All Text near/6 malform* in All Text) or (palat* in All Text near/6 malform* in All Text) or (lip* in All Text near/6 malform* in All Text) or (alveolar in All Text near/6 abnorm* in All Text) or (maxilla* in All Text near/6 abnorm* in All Text) or (gum* in All Text near/6 abnorm* in All Text) or (jaw* in All Text near/6 abnorm* in All Text) or (palat* in All Text near/6 abnorm* in All Text) or (lip* in All Text near/6 abnorm* in All Text))

#5 (#1 or #2 or #3 or #4)

#6 MeSH descriptor BONE TRANSPLANTATION explode all trees

#7 ((bone* in All Text near/6 graft* in All Text) or (bone* in All Text near/6 surg* in All Text) or (bone* in All Text near/6 reconstruct* in All Text) or (bone* in All Text near/6 restor* in All Text) or (bone* in All Text near/6 implant* in All Text) or (bone* in All Text near/6 augment* in All Text) or (bone* in All Text near/6 repair* in All Text))

#8 ((bony in All Text near/6 graft* in All Text) or (bony in All Text near/6 surg* in All Text) or (bony in All Text near/6 reconstruct* in All Text) or (bony in All Text near/6 restor* in All Text) or (bony in All Text near/6 implant* in All Text) or (bony in All Text near/6 augment* in All Text) or (bony in All Text near/6 repair* in All Text))

#9 ((osseous* in All Text near/6 graft* in All Text) or (osseous* in All Text near/6 surg* in All Text) or (osseous* in All Text near/6 reconstruct* in All Text) or (osseous* in All Text near/6 restor* in All Text) or (osseous* in All Text near/6 implant* in All Text) or (osseous* in All Text near/6 augment* in All Text) or (osseous* in All Text near/6 repair* in All Text))

#10 ((osteal* in All Text near/6 graft* in All Text) or (osteal* in All Text near/6 surg* in All Text) or (osteal* in All Text near/6 reconstruct* in All Text) or (osteal* in All Text near/6 restor* in All Text) or (osteal* in All Text near/6 implant* in All Text) or (osteal* in All Text near/6 augment* in All Text) or (osteal* in All Text near/6 repair* in All Text))

#11 osteoplast* in All Text

#12 (#6 or #7 or #8 or #9 or #10 or #11)

#13 (#5 and #12)

Appendix 3. MEDLINE via OVID SEARCH STRATEGY

1. CLEFT PALATE/
2. CLEFT LIP/
3. (cleft$ adj4 (lip or palate)).mp.
4. ((alveolar or maxilla$ or gum$ or jaw$ or palat$ or lip$) adj6 (cleft$ or defect$ or malform$ or abnorm$)).mp.
5. or/1-4
6. exp BONE TRANSPLANTATION/
7. ((bone$ or bony or osseous$ or osteal$) adj6 (graft$ or surg$ or reconstruct$ or restor$ or implant$ or augment$ or repair$)).mp.
8. osteoplast$.mp.
9. or/6-8
10. 5 and 9

Cochrane Search filter for MEDLINE via OVID

Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of The Cochrane Handbook for Systematic Reviews of InterventionsVersion 5.0.2 [updated September 2009].

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. EMBASE via OVID SEARCH STRATEGY

1. CLEFT PALATE/
2. CLEFT LIP/
3. (cleft$ adj4 (lip or palate)).mp.
4. ((alveolar or maxilla$ or gum$ or jaw$ or palat$ or lip$) adj6 (cleft$ or defect$ or malform$ or abnorm$)).mp.
5. or/1-4
6. exp BONE TRANSPLANTATION/
7. ((bone$ or bony or osseous$ or osteal$) adj6 (graft$ or surg$ or reconstruct$ or restor$ or implant$ or augment$ or repair$)).mp.
8. osteoplast$.mp.
9. or/6-8
10. 5 and 9

Filter for EMBASE via OVID

The above subject search was linked to the following Filter for EMBASE via OVID.

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ 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. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

CONTRIBUTIONS OF AUTHORS

- Jing Guo (JG) and Jianwei Chen (JWC) conceived the review and they proposed this clinical question and registered the title with the Cochrane Oral Health Group.
- JG and Qifeng Zhang (QFZ) designed the review.
- JG and QFZ did data collection for the review.
- JG and QFZ designed search strategies.
- JG and Chunjie Li (CJL) undertook searches.
- JG and CJL screened search results.
- JG organized retrieval of papers.
- JG and CJL screened retrieved papers against eligibility criteria.
- JG and CJL appraised quality of papers.
- JG and CJL extracted data from papers.
- JG and CJL wrote to authors of papers for additional information.
- Shujuan Zou (SJZ) and Gang Wu (GW) provided additional data about papers.
- CJL and Haikun Hu (HH) did data management for the review.
- CJL and HH entered data into RevMan.
- JG and CJL did analysis of data.
- JG and CJL did interpretation of data.
- Qingsong Ye (QSY) provided a methodological perspective.
- SJZ and GW provided a clinical perspective.
- JG and CJL wrote the review.
- Scott Deacon (SAD), SJZ and GW provided general advice on the review.
- SAD revised this review.

DECLARATIONS OF INTEREST

None of the identified review authors have any financial interests that would present a conflict.

SOURCES OF SUPPORT

Internal sources

- West China College of Stomatology, Sichuan University, China.
- Chinese Cochrane Center, China.

External sources

- Cochrane Oral Health Group, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We have revised the primary and secondary outcomes to make them more precise.
2. We added quality of life after the surgery into the secondary outcomes.

3. In the part of Selection of studies, in those studies which met the inclusion criteria except that they had some participants aged below 5 years old, we contacted the authors by email or letters to ask for the data of those participants older than 5 years.
4. WHO International Clinical Trials Registry Platform and CBM were searched electronically, which was not proposed in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Alveolar Process [*surgery]; Alveolar Ridge Augmentation [methods]; Bone Morphogenetic Protein 2 [therapeutic use]; Bone Transplantation [*methods]; Cleft Lip [*surgery]; Cleft Palate [*surgery]; Fibrin Tissue Adhesive [therapeutic use]; Ilium [transplantation]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans