A meta-analysis of alveolar

by Indri Lakhsmi Putri

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Review Article

A meta-analysis of alveolar bone grafting using bone substitutes in cleft lip and palate patients

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Abstract

In individuals with cleft lip and palate (CLP), an alveolar bone graft (ABG) is carried out for alveolar cleft closure. Several sources for ABG include autologous bone, xenologous bone, and alloplastic substitutes. Autologous bone has been the preferred source for ABG. Alloplastic substitutes might serve as an alternative. This study aimed to compare the outcomes between autologous and alloplastic as sources for ABG. This study made use of eight web databases. Randomized control trials (RCTs) and non-RCTs were included. CLP patients with alveolar cleft with imaging studies, computed tomography (CT scan) and/or cone beam CT scan, and bone graft volume within 6–12 months postintervention were selected. Bone graft volume within 6–12 months postintervention was assessed. Three studies met the inclusion criteria. After 6–12 months of follow-up, there were no statistically significant differences in bone graft volume between autologous and alloplastic bone grafts (fixed-effect model estimate value = 0.21; confidence interval − 0.301–0.730; P = 0.414). The limitations include small research sample sizes, a high likelihood of bias among included studies, and different alloplastic materials from each included study. Autologous and alloplastic bone grafts showed similar effectiveness in alveolar bone grafting. Further clinical trial studies with bigger sample sizes and similar interventions are needed as evidence for future reviews.

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Introduction

Alveolar cleft is a bony defect in the alveolar region that occurs in people with cleft lip and palate (CLP). Alveolar cleft is reported to present in three out of four CLP patients. To restore both function and esthetics to the defect, repair of the alveolar cleft with an alveolar bone graft (ABG) needed to be done [1]. Primary ABG is performed at an early age, but secondary ABG is typically performed later (between the ages of 7 and 12) [2,3]. Several donors can be used for alveolar bone grafting; some of which are donors from autologous bone (autograft), xenogenous bone (xenograft), or allogenic bone substitutes (alloplastic graft) [4].

All of the graft materials above have been used in the repair of alveolar clefts for many years. However, grafting with autologous bone has been the preferred method, due to the osteogenic cells and osteoinductive factors the donor had for new bone formation [5,6]. Autologous bone grafts can be obtained from different donor sites. It can be obtained from the ilium and/or tibia (cancellous bone) or the calvarium and/or mandibular symphysis (corticocancellous bone) [7]. The major concern of autograft is the harvesting of the bone, which requires a second operative method that could cause inconveniences to the patient, from increased operation and hospitalization time to morbidity of the donor site.

Throughout recent years, other graft materials have been developed to fix the issues of autologous bone grafts. Some materials like hydroxyapatite (HA) and xenogeneic grafts such as bovine bone graft and demineralized bone graft have been used clinically as bone substitutes for alveolar bone grafting [5,8,9]. The advantage of using an alloplastic graft material is there is no need to harvest bone from the donor. These materials have osteoconductive properties that could be effective for filling the alveolar clefts; however, they might not have the ability to produce new bone cells to properly heal the

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defect [10]. Some might even use growth factors like platelet-rich plasma (PRP) in combination with alloplastic materials to promote bone healing [11]. Alloplastic bone graft with bone substitutes might be an alternative or a better solution for alveolar bone grafting.

This study aimed to compare the outcome of different methods of ABG, between autologous bone graft and alloplastic substitute graft.

Methods

This investigation followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Guidelines checklist as shown in Figure 1. The protocol was registered at PROSPERO, the international prospective register of systematic reviews under the number CRD42023401860. The patients or problems, interventions, comparisons, and outcomes procedure were used to help define the study selection criteria.

Eligibility criteria

Types of studies

Randomized control trials (RCT) and non-RCTs were included in this study. Case reports, case series, case–control, and reviews were excluded from this study.

Types of participants

CLP patients with alveolar cleft who had imaging studies, computed tomography (CT scan) and/or cone beam CT (CBCT scan), and bone graft volume within 6–12 months postintervention were included. Exclusion criteria were patients with noncongenital alveolar defect.

Types of outcomes

The main outcome was bone graft volume measured using CT and/or CBCT scan within 6–12 months postintervention.

Search methodology

Only studies in English were included in this study. The authors conducted a search across different web databases. The online databases used were PubMed, Cochrane, EBSCOhost, ScienceDirect, Web of Science, ProQuest, Scopus, and ClinicalTrials.gov. Aside from that, we also investigated for gray literature on Preprint and MedRxiv. The keywords used to search the online databases used the Medical Subject Headings (MeSH) terms. Each database used a combination of MeSH terms "cleft lip," "cleft lip palate," "cleft palate," "alveolar cleft," "alveolar cleft repair," "alveolar bone graft," "bone substitutes," "autograft," and "alloplastic" in combination with Boolean terms such as "AND" and "OR." The full description is listed in Supplementary Table 1.

Study selection

All papers from each database were then assembled using Mendeley and further evaluated by reviewing the title and abstract in relation to the inclusion criteria and removing any duplicate studies. The full-text copies of the remaining studies were then assessed and used for this study. In this stage, all studies that did not meet the inclusion criteria were excluded.

Data extraction process

Data were gathered from the studies that were included. The data retrieved included research setting characteristics, demographic descriptions, graft sources and materials, and intervention results. The authors extracted the data individually, and the collected data will be collated and evaluated. This process was done between January 2023 and April 2023.

Risk of bias in individual studies

The risk of bias in the included studies was made according to the type of study. The Jadad scale was used for RCT studies. The Jadad scale uses 5 points to determine the risk of bias in the study. The parameters are: (1) described as randomized; (2) described as double-blinded; (3) description of withdrawals; (4) randomization method described and appropriate; and (5) double-blinding methods described and appropriate. The total scores ranged from 0 to 5 (poor to good quality).

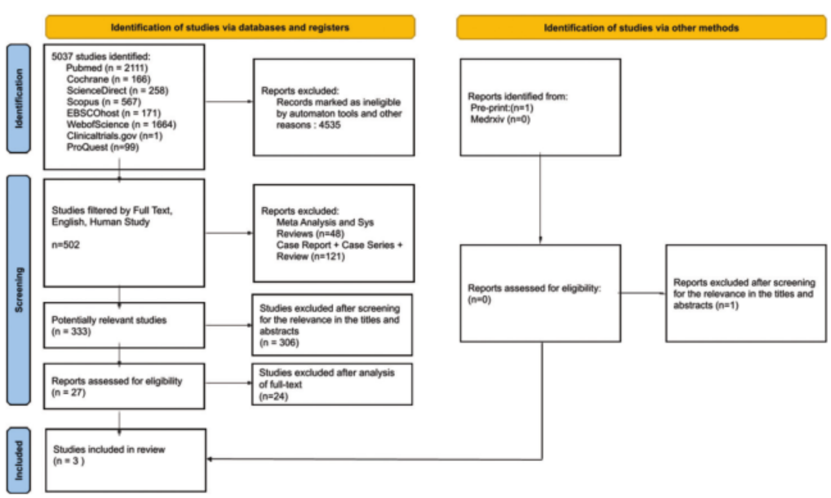

Figure 1: The Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart

Summary measures

The meta-analysis was carried out using Jamovi software, a "3rd generation" statistical spreadsheet. For descriptive data (bone volume), mean, standard deviation, and sample size were reported. $P < 0.05$ was considered statistically significant. Heterogeneity was calculated by I^2 or *Tau*. In the included studies, the fixed-effect method was employed in instances of low heterogeneity, whereas the random-effect method was employed in instances of high heterogeneity.

Results

Study selection

After the online search, 5037 studies were identified; of which 4535 were excluded after using the filter "Full Text, English, and Human Studies" from the database's automated search engine. We found one related gray literature, but we excluded it. The remaining 502 studies were then further excluded by excluding other meta-analyses, systematic reviews, reviews, case reports, case series, and case–control studies. The remaining 333 studies were then filtered based on their titles and abstracts. After excluding 306 papers, the full texts of the remaining 27 research were acquired. After reviewing the full texts, 21 studies were eliminated. Consequently, only six studies fulfilled the criteria; out of these studies, there were four RCTs and two non-RCTs. A second screening of the six studies was done to determine the data's suitability for the meta-analysis. From this, three studies were excluded. The final count of studies that passed all the inclusion criteria was three RCT studies. The details of the studies and the exclusion criteria are shown in Figure 1 and Table 1 [1,12,13].

Study characteristics

There were 61 individuals with alveolar cleft included in the study; 30 patients underwent autologous alveolar bone grafting, while 31 patients underwent alveolar bone grafting using bone substitutes. The autologous bone graft used was harvested from the cancellous iliac bone in two studies and mandibular symphysis in one study. The bone substitutes used were a demineralized bone graft in 10 patients, bioabsorbable HA/collagen complex (HA/Col) in 11 patients, and bovine bone graft (Bio-Oss; Geistlich Pharma AG) with PRP in 10 patients. The three studies selected were conducted in India, Japan, and Brazil. Table 2 shows the characteristics of the included studies.

All of the studies were assessed using the Jadad scale with one study being good quality, whereas the other two studies being poor quality. Details of the Jadad scale assessment are described in Table 3.

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Shen *et al*., 2022 [12]	The only included non-RCT study (no comparison)
Kibe *et al*., 2021 [13]	No information about the SD was found
Mossaad *et al*., 2019 [1]	No information about bone graft volume

RCT: Randomized control trials, SD: Standard deviation

Synthesis of results

The systematic review included three RCTs [5,8,9]. All three trials compared the efficacy of autologous and alloplastic ABG in CLP patients. Out of these three studies, two studies used cancellous iliac bone graft as the autologous donor site and one study used mandibular symphysis. The alloplastic materials used were different for each study. Kumar *et al.* used demineralized bone graft, Sakamoto *et al.* used HA/Col, whereas Bezerra *et al.* used Bio-Oss; Geistlich Pharma AG with PRP for the graft material. For all investigations, the radiologic assessment was done to determine the volume of the ABG. A three-dimensional CT scan was used as a method for evaluation, allowing the volume of the bone graft to be determined [14].

Bone graft volume

Kumar *et al.* measured the volume of the bone graft after 6 months [9]. Autologous and alloplastic bone grafts presented similar results in terms of volume. Sakamoto *et al.* and Bezerra *et al.* measured the volume of the bone graft after 12 months [5,8]. The heterogeneity test using the *Tau* method shows that it has low heterogeneity with an $I^2 < 70\%$ and a *Tau* significancy <0.05; therefore, the fixed-effect model (FEM) was used. The estimated value of the FEM is 0.21, and the confidence interval [CI] is between − 0.30 and 0.73 with $P = 0.414$ ($P > 0.05$). After 6–12 months of follow-up, there were no statistically significant differences in bone graft volume between autologous and alloplastic grafts (FEM estimate value = 0.21; CI − 0.301–0.730; $P = 0.414$) [Figure 2].

Discussion

The systematic review included three RCTs; all of which compared the efficacy of autologous and alloplastic bone grafting in alveolar cleft patients after 6 months and/or 1 year of follow-up.

The main results of the included studies suggest that using alloplastic materials for alveolar bone grafting showed similar results to autologous bone grafting [5,8,9]. According to Kumar *et al.*, alveolar bone grafting with bovine-derived bovine-derived demineralized bone matrix (DMBM) was volumetrically comparable to iliac crest bone grafting but not statistically significant [9]. Sakamoto *et al.*'s work has shown that HA/Col may be employed as an alternate graft material for ABGs [8]. Bezerra *et al.* also discovered that combining

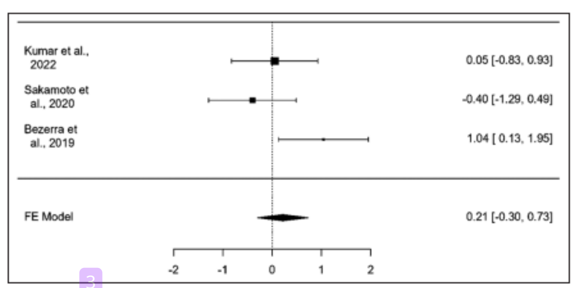

Figure 2: Comparison of bone graft volume between the autologous bone graft and alloplastic bone graft after 6 to 12 months postintervention. FE: Fixed effect

Table 2: Characteristics of included studies

Study ID	Setting	Total sample	Study groups	Outcome
Kumar, MDS *et al.*, 2022 [9]	Unit of oral and maxillofacial surgery, Oral Health Science Center, Postgraduate Institute of Medical Education and Research, Chandigarh	20 patients with UCLP	Intervention group: SABG using DMBM Control group: SABG using iliac crest bone graft	Outcomes were assessed at 2 weeks, 6 months, and then after a mean follow-up period of 63 months. Volumetric analysis of the grafted bone in the alveolar cleft site was done through CBCT using Cavalieri's principle and modified assessment tool. Clinical assessment was performed in terms of pain, swelling, duration of hospital stay, cost of surgery, alar base symmetry, and donor-site morbidity associated with iliac crest harvesting
Sakamoto MD *et al.*, 2020 [8]	Department of plastic and reconstructive surgery, Keio University School of Medicine, Shinjuku, Tokyo, Japan	21 patients with unilateral cleft lips and alveolar clefts	Intervention group: ABG using HA/Col Control group: ABG using cancellous iliac bone graft	The alveolar cleft and bone volumes were measured by computer-aided engineering. Preoperative data and mirror-reversed data were obtained; the difference in volume between the original and mirror-reversed data was determined as the cleft volume. The differences in volume between preoperative and postoperative data were defined as the 1-month and 12-month volumes
Bezerra DDS, MSc, *et al.*, 2019 [5]	University Hospital of Sergipe, Aracaju, Brazil	20 individuals met the inclusion criteria and accepted to participate in the study	Intervention group: ABG using bovine bone graft (Bio-Oss; Geistlich Pharma AG) with PRP Control group: ABG using autologous bone graft	Following the allocation procedure, CBCT scans of the maxillary arch were taken and converted into 3D models for all patients at the following two time points: preoperatively and 1 year following the surgical procedure

3D: Three dimensional, DMBM: Demineralized bone matrix, HA/Col: Bioabsorbable hydroxyapatite and collagen complex, CBCT: Cone-beam computed tomography, PRP: Plasma-rich plasma, ABG: Alveolar bone graft, UCLP: Unilateral cleft lip and palate, SABG: Secondary alveolar bone grafting

Table 3: Jadad scale assessment

Study ID	Type of study	Jadad score	Described as randomized	Described as double-blinded	Description of withdrawals	Randomization method described and appropriate	Double-blinding methods described and appropriate
Kumar *et al.*, 2022 [9]	RCT	5	1	1	1	1	1
Sakamoto *et al.*, 2020 [8]	RCT	2	1	-	-	1	-
Bezerra *et al.*, 2019 [5]	RCT	2	1	-	-	1	-

RCT: Randomized control trial

Bio-Oss with PRP yielded results equivalent to autologous bone grafts [5].

This study found no statistically significant difference between autologous bone grafting and alloplastic bone grafting by bone graft volume 6–12 months after surgery. It means these two methods showed similar effectiveness for alveolar clefts viewing only from bone graft volume. However, there are several clinical differences that are very distinct between these two methods, one of them being donor-site morbidity [15].

Autologous bone grafting requires a donor or graft source to be utilized. There are a handful of graft sources for ABG, including cortical and cancellous bone [16]. The iliac crest and mandibular symphysis were used for the autograft in the included study [5,8,9]. Studies show that there are several potential drawbacks to this, such as longer surgical time, donor site scarring, postoperative pain, recovery time, and the potential for nerve injuries [15,17-19]. However, multiple-study evaluations showed some similarities regarding operation time and complications. Studies from Shen *et al.*, Kumar *et al.*, and Sakamoto *et al.* indicated that the surgical time between autologous and alloplastic bone grafting showed no significant difference with a range of 84–150 min [1,9,11]. The length of stay from multiple studies also showed that there is no significant difference, ranging from 5 to 8 days [8,9,12]. This suggests that using a nonautologous bone source like alloplastic material could serve as an alternative for alveolar bone grafting to avoid donor-site morbidity.

This study found no statistically significant difference between autologous bone grafting and alloplastic bone grafting in terms of postoperative bone graft volume. To further determine how alloplastic material usage compares to autograft, there are other aspects that should be put into consideration. There are other outcome measures that are not included in this study, like resorption rate. Shen *et al.* compared autograft to BMP2 loaded calcium phosphate cement (BMP2 CPC), whereas Mossaad *et al.* employed nano calcium hydroxyapatite with collagen membrane and bone marrow stem cells extract with PRP growth factor [1,12]. The bone resorption rate of BMP2-CPC and hydroxyapatite is superior for bone grafting than autologous bone grafts, with a significant difference at 3 and 6 months postoperative [1,19-21].

From a clinical standpoint across the included studies, autologous and alloplastic alveolar bone grafting showed similar results without statistically significant differences. However, there is one parameter that showed a significant difference. One of the results discussed in the study by Kumar *et al*. is the average cost of surgery. The average cost of surgery for the two methods showed a significant difference. Surgery using alloplastic material costs almost double that of autologous graft [9].

Limitations

The review conclusions should be viewed cautiously, due to several limitations of this study. The first one is due to the number of included studies for the analysis. Aside from that, the sample size of each RCT study included was limited. Due to this, the studies were limited to using different time frames within 6–12 months in the meta-analysis. The limited number of included studies also limits the ability to do a publication bias assessment. Therefore, further prospective RCTs with a bigger sample size and comparable pre- and postinterventions are needed to serve as additional data as a way to determine the best ABG source for CLP patients.

Another issue is the likelihood of bias in each involved study. From the Jadad scale, it is determined that one study has a full score of 5 (good quality), whereas the other two studies have a lower score of 2, respectively (poor quality). These two studies were not described as double-blinded, and there was no description for the withdrawals from the initial study sample. Due to the lack of scientific quality in these two included investigations, there is a potential for bias throughout the analysis.

Eventually, all of the RCTs that were analyzed in this study used different materials for alloplastic bone grafting. Kumar *et al*. used demineralized bone matrix (DMBM), Sakamoto *et al*. used bioabsorbable HA/Col, while Bezerra *et al*. used bovine bone graft (Bio Oss; Geistlich Pharma AG) with PRP [5,8,9]. The inconsistency in material might contribute to a variation in results. Therefore, extended studies using the same alloplastic materials are needed as additional evidence for further reviews.

Conclusion

There are no significant differences between autologous and alloplastic bone grafting. This absence shows that by assessing the bone graft volume, these two methods showed similar effectiveness for alveolar clefts. Further clinical trial studies with a bigger sample size and similar interventions are needed to serve as evidence for future reviews.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgment

We would like to express our gratitude to all the authors of the studies included in this meta analysis and systematic review for their contributions to the field of study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

Supplementary Table 1: Database

	Database	Jumlah
	PubMed	
#1	(cleft lip palate) OR (cleft lip) OR (cleft palate) OR	42,147
	(cleft lip palate unilateral) OR (cleft lip palate bilateral) OR (cleft lip unilateral) OR (cleft palate unilateral) OR (cleft lip bilateral) OR (cleft palate bilateral) OR (CLP) OR (cleft lip repair) OR (alveolar cleft) OR (alveolar cleft repair)	
#2	((alveolar bone graft*) OR (alveolar bone graft) OR (alveolar bone repair) OR (alveolar bone repair*) OR (alveolar cleft repair) OR (alveolar cleft repair*)) OR ((bone substitute) OR (bone substitute*) OR (hydroxyapatite) OR (tricalcium phosphate) OR (calcium sulfate) OR (autograft) OR (autograft*) OR (alloplast*))	167,664
#3	#1 AND #2	2070
	Cochrane	
#1	(cleft lip palate) OR (cleft lip) OR (cleft palate) OR	1449
	(cleft lip palate unilateral) OR (cleft lip palate bilateral) OR (cleft lip unilateral) OR (cleft palate unilateral) OR (cleft lip bilateral) OR (cleft palate bilateral) OR (CLP) OR (cleft lip repair) OR (alveolar cleft) OR (alveolar cleft repair)	
#2	(((alveolar bone graft*) OR (alveolar bone grafting))	6023
	OR (alveolar bone repair*)) OR (alveolar cleft repair*)) OR ((bone substitute*) OR (hydroxyapatite) OR (tricalcium phosphate) OR (calcium sulfate) OR (autograft*) OR (alloplast*))	
#3	#1 AND #2	166
	ScienceDirect	
	(cleft lip palate OR cleft lip) AND ((alveolar bone graft OR alveolar bone repair) AND (bone substitute OR hydroxyapatite OR tricalcium phosphate OR calcium sulfate OR autograft))	255
	Scopus	
	(ALL(“cleft lip palate”) OR ALL(“cleft lip”) OR ALL(“cleft palate”) OR ALL(“cleft lip palate unilateral” OR ALL(“cleft lip palate bilateral”) OR ALL(“cleft lip unilateral”) OR ALL(“cleft palate unilateral”) OR ALL(“cleft lip bilateral”) OR ALL(“cleft palate bilateral OR ALL(“CLP”) OR ALL(“cleft lip repair”) OR ALL(“alveolar cleft”) OR ALL(“alveolar cleft repair”)) AND ((ALL(“alveolar bone graft*”) OR ALL(“alveolar bone graft”) OR ALL(“alveolar bone repair*”) OR ALL(“alveolar cleft repair*”)) AND (ALL(“bone substitute*”) OR ALL(“hydroxyapatite”) OR ALL(“tricalcium phosphate”) OR ALL(“calcium sulfate”) OR ALL(“autograft”) OR ALL(“alloplast*”))))”)	567
	ClinicalTrials.gov	
	Cleft lip palate+alveolar cleft+alveolar bone graft	12
	EBSCOhost	
	TX ((cleft lip palate) OR (cleft lip) OR (cleft palate) OR (cleft lip palate unilateral) OR (cleft lip palate bilateral) OR (cleft lip unilateral) OR (cleft palate unilateral) OR (cleft lip bilateral) OR (cleft palate bilateral) OR (CLP) OR (cleft lip repair) OR (alveolar cleft) OR (alveolar cle repair)) AND TX (((alveolar bone graft*) OR (alveolar bone grafting) OR (alveolar bone repair*) OR (alveolar cleft repair*)) AND ((bone substitute*) OR (hydroxyapatite) OR (tricalcium phosphate) OR (calcium sulfate) OR (autograft) OR (alloplast*))) f	171
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	all (hydroxyapatite) OR all (tricalcium phosphate) OR all (calcium sulfate) OR all (autograft*) OR all (alloplast*)))	
	Web of Science	
#1	(((((((((((ALL=(cleft lip palate)) OR ALL=(cleft lip)) OR ALL=(cleft palate)) OR ALL=(cleft lip palate unilateral)) OR ALL=(cleft lip palate bilateral)) OR ALL=(cleft lip unilateral)) OR ALL=(cleft lip bilateral)) OR ALL=(cleft palate unilateral)) OR ALL=(cleft palate bilateral)) OR ALL=(CLP)) OR ALL=(cleft lip repair)) OR ALL=(alveolar cleft)) OR ALL=(alveolar cleft repair)	40,192
#2	((((((((ALL=(alveolar bone graft)) OR ALL=(alveolar bone graft*)) OR ALL=(alveolar bone repair*)) OR ALL=(alveolar cleft repair*)) OR ALL=(bone substitute*)) OR ALL=(hydroxyapatite)) OR ALL=(tricalcium phosphate)) OR ALL=(calcium sulfate)) OR ALL=(autograft*)) OR ALL=(alloplast*)	129,445
#3	#1 AND #2	1664

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