Effectiveness of Secondary Alveolar Bone Graft on Canine Eruption: Systematic Review

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Abstract

There are controversies related to the effects of bone grafts on tooth eruption and impaction in patients with cleft lip and palate. The aim of this systematic review was to evaluate the effectiveness of bone grafting on eruption of canines in patients with unilateral cleft lip and palate (UCLP). An electronic search was conducted in six electronic databases and gray literature, without limitations on year of publication or language. The primary outcome was the increase in rate of canine eruption; the secondary outcomes were success of the bone graft, canine impaction due to agenesis of the lateral incisor, and effect of orthodontic treatment before and after bone grafting. The risk of bias was analyzed by means of the tool Cochrane risk of bias in nonrandomized controlled trials (NRCTs) of interventions (ROBINS-I). The certainty of the evidence was assessed for outcomes reported through a narrative synthesis using grading of recommendations, assessment, development and evaluation (GRADE) approach. Four NRCTs were included, with a total of 360 patients, 283 UCLP and 77 bilateral cleft lip and palate (BCLP). The studies reported association between the increase in the rate of tooth eruption and bone graft with very low certainty of evidence, and greater experience of surgical success, with low certainty of evidence. The majority of the studies found an association between increase in the rate of canine impaction and agenesis of the lateral incisor, with very low certainty of evidence. There was very low certainty of the efficacy of secondary alveolar bone grafting for increasing the rates of eruption and reducing impaction of the maxillary canine.

Keywords
- cleft palate
- alveolar bone grafting
- tooth eruption
- systematic review

Introduction

Cleft lip with or without cleft palate and cleft palate are common craniofacial deformities in human beings.[1] Patients with clefts involving the palate generally need bone grafts at different stages of life, in order to re-establish the growth and development of the face and allow the evolution of normal occlusion, [2] especially the canines commonly involved in the morphogenesis of cleft palate.[3]

Among these grafts, the primary type is used before patients complete 1 year of age; the early secondary type is performed before eruption of the permanent canine,

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and the late secondary, after eruption of the permanent canine.[3,4] Successful bone grafting has been related to the patient's age at the time of surgery, gender, stage of eruption of permanent canine adjacent to the cleft, size of cleft, development of postoperative infection, and orthodontic treatment.[2,5,6]

Pre and postsurgery orthodontic treatment may play an important role in allowing space in the dental arch for the requirements of the graft and for suiting the teeth in the rehabilitation of patients with clefts.[2,7,8] Some studies [9,10] have reported that secondary bone grafting may increase the intraosseous retention of the maxillary canines, while others [11,12] have demonstrated that the bone graft works as a guide for the eruption of these teeth.[3,7,13,14]

In conjunction, the literature has shown controversies in relation to the real effects of bone grafting, and its influence on eruption of the canine in adolescent patients with clefts.[3,7,11-14] In view of the absence of systematic reviews about the topic up to now, the aim of the authors of this review was to evaluate the body of scientific evidence of the efficacy of secondary alveolar bone grafting on eruption of the permanent canine in patients with clefts.

Materials and Methods

Focus Question

This systematic review was conducted in order to answer the following clinical question: Is there any scientific evidence of the efficacy of secondary alveolar bone graft surgery has in patients with unilateral clefts for increasing the rate of eruption of the maxillary canine in the cleft area when compared with the control or to patients who were not submitted to surgery? The population, intervention, control, and outcomes (PICO) question and eligibility criteria are detailed in ►**Table 1**.

This systematic review was conducted in accordance with the items of reference for the evaluation of articles in systematic reviews and meta-analysis (*preferred reporting items for systematic review and meta-analysis [PRISMA]*).[15]

Search Strategy

An electronic search was conducted in the following databases up until November 2020, without limitation on year of publication or language: PubMed (Medline), Scopus, Web of Science, Medline Complete (EBSCO), Cochrane (Database for Systematic Review, CENTRAL, and Protocols), and gray literature through Trials Central and Clinical Trials. A manual search was conducted in specific periodicals of the area (*The Cleft Palate-Craniofacial Journal*, *Plastic and Reconstructive Surgery*) and in the list of references of the articles selected.[15,16] The search strategies are described in ►**Table 2**.

Eligibility Criteria of the Articles

Two researchers (R.G.B. and R.L.S.) independently selected the abstracts, titles and complete texts, according to the eligibility criteria (►**Table 1**). Discrepancies were decided by discussion and consensus.[17] In the event of divergences between the two evaluators, who could not reach consensus, a third evaluator (S.S.N.) was consulted.

Table 1 Criteria (PICOS, inclusion and exclusion) for selecting the studies

PICOS		
Participant (P)	Patients with cleft lip and palate, and mean age between 7 and 14 years	
Intervention (I)	Secondary alveolar graft surgery in the cleft region	
Comparison (C)	Not submitted to surgery	
Outcomes (O)	Primary outcome:	Increased rate of canine eruption
	Secondary outcome:	Successful bone graft Canine impacted due to agenesis of the lateral incisor. Effect of orthodontic treatment before and after bone graft surgery
Study (S)	Nonrandomized controlled trials (NRCTs)	
Criteria		
Inclusion	Report the dental condition, canine eruption and impaction, presence of agenesis and orthodontic treatment indication of patients with unilateral cleft lip and palate, who received secondary bone graft before eruption of the canine.	
Exclusion	Patients making use of systemic medication and those with systemic diseases. Patients who have not received bone graft prior to eruption of canine, who did not have eruption of canine evaluated, considering its intraosseous angulation/position. Studies reporting bone graft with history of trauma or fistulas. Case reports, case series, studies with number of participants < 65, studies with animals, corticotomy, osteogenic distraction, in vitro studies, reviews of the literature and editorials.	

Quality and Risk of Bias Assessment

Two independent reviewers evaluated the risk of bias of the studies included by using the Cochrane risk of bias in nonrandomized controlled trials (NRCTs) of interventions (ROBINS-I) guidelines.[18]

The domains evaluated by ROBINS-I were: (1) bias due to a confusion; (2) bias in selection of the study participants; (3) bias in classification of the interventions; (4) bias due to deviations from the intended intervention; (5) bias due to lack of data; (6) bias in measurement of the results; (7) bias in selection of the result reported. The general risk of bias of the individual studies was classified as being low (if all the domains were considered to have low risk of bias), moderate (if one or more domains showed moderate risk of bias), serious (if one or more domains showed serious risk of bias), or critical (if one or more domains showed critical risk of bias).

Data Extraction and Data Analysis

Two independent reviewers extracted data. Disagreements were solved by discussion until a consensus was reached.

Table 2 Database and research method

Database	Search Strategy
Pubmed (Medline) Web of Science (Clarivate Analytics) Medline Complete (EBSCO) Cochrane (Database for Systematic Reviews, CENTRAL, Trials, Protocols)	((orthodontics [MeSH Terms] OR orthodontic OR "orthodontic patients" OR "orthodontic treatment" OR "cleft palate" [MeSH Terms] OR "cleft lip-palate" OR "alveolar cleft") AND ("alveolar bone grafting" [MeSH Terms] OR "bone graft" OR "bone grafting") AND ("tooth eruption" [MeSH Terms] OR "dental eruption" OR "teeth eruption" OR "root resorption" [MeSH Terms] OR "tooth movement" OR "teeth movement" OR efficacy OR complications [MeSH Terms]))
Scopus (Elsevier)	TITLE-ABS-KEY (orthodontics [MeSH Terms] OR orthodontic OR "orthodontic patients" OR "orthodontic treatment" OR "cleft palate" [MeSH Terms] OR "cleft lip-palate" OR "alveolar cleft") AND TITLE-ABS-KEY ("alveolar bone grafting" [MeSH Terms] OR "bone graft" OR "bone grafting") AND TITLE-ABS-KEY("tooth eruption" [MeSH Terms] OR "dental eruption" OR "teeth eruption" OR "root resorption" [MeSH Terms] OR "tooth movement" OR "teeth movement" OR efficacy OR complications [MeSH Terms])
Trials Central	((orthodontics [MeSH Terms]))
Clinical Trials	((orthodontics [MeSH Terms]) AND (alveolarbonegrafting [MeSH Terms] OR bone grafta))

The primary outcome was increase in the rate of canine eruption. The secondary outcomes were success of bone graft, canine impaction due to agenesis of the lateral incisor, and effect of orthodontic treatment before and after bone grafting.

The was a high level of heterogeneity in data reported by studies, thus it was not possible to pool data for a meta-analysis. A narrative synthesis was planned instead. For reporting the outcomes, a summary of findings (SoF) table was built for each outcome according to grading of recommendations, assessment, development and evaluation (GRADE) pro. We followed the GRADE approach when using ROBINS-I to assess the certainty of the evidence for narrative synthesis.[19,20] Using ROBINS-I, the certainty of the evidence began with high, and it could be further rated up by magnitude of the effect, dose response, and effect of residual confounders.[20]

Results

Selection of Studies

After triage of the titles and abstracts of 750 articles, 66 potentially eligible articles were selected for full text analysis; of these, 04 NRCTs.[3,7,13,14] were included (►**Fig. 1**). RCTs were not found for the addressed criteria. The characteristics of studies are described in ►**Table 3** and the outcomes in ►**Table 4**.

Characteristics of Studies

The studies evaluated a total of 360 patients, of whom 283 patients had unilateral cleft lip and palate (UCLP) and 77 had bilateral cleft lip and palate (BCLP), with mean age ranging between 7 and 13.7 years. The studies were conducted between 2007 and 2018 in Canada,[3] Brazil,[7] Italy,[13] and Sweden.[14]

All the studies[3,7,13,14] evaluated the position of the vertical angulation of the canine, one[13] study evaluated the long axis of the canine in relation to the occlusal plane, two[3,14] evaluated it in relation to the median sagittal plane, and the other,[7] in relation to the bicondylar line. The lateral position of the canine in relation to the lateral incisor was evaluated by only one[3] study, and its height, in relation to the occlusal plane by the other study.[7]

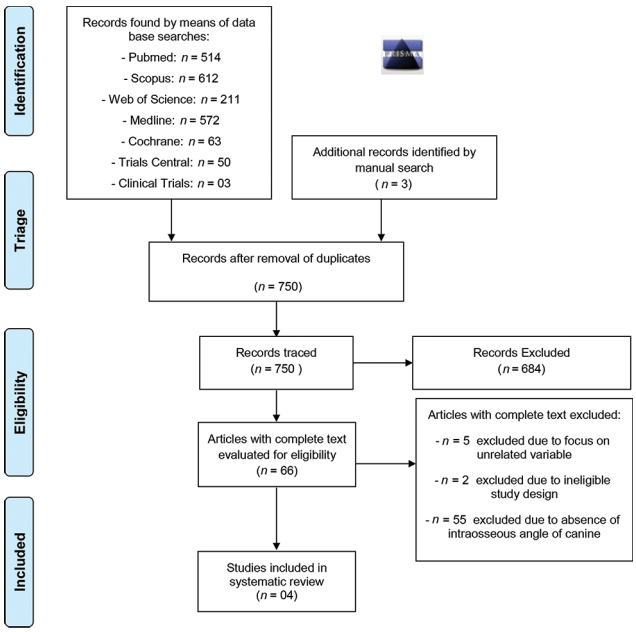

Fig. 1 Flow diagram showing evidence of synthesis of systematic review in accordance with preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines

As control, two[3,13] studies made paired evaluations of patients with BCLP, one[13] study used the analysis of Bergland for the graft, and both[3,13] used predefined angulation for the canine, and the split mouth system for the patients with UCLP.[3,13]Two other studies[7,14] used the split mouth system for all the patients with UCLP.

Risk of Bias

All[3,7,13,14] the studies showed serious risk of bias due to confounding factors, and two [13,14] studies had serious risk of bias due to missing data and bias in selection of the result reported. All [3,7,13,14] the studies had critical risk of bias due to measurement of outcomes. The overall bias of studies[3,7,13,14] was of critical risk (►**Fig. 2**).

Table 3 Characteristics of studies included

Study design, description of participants, and interventions included				
Study/year	**Meazzini et al[13]**	**Russell et al[3]**	**Westerlund et al[14]**	**Holz et al[7]**
Sample size (F/M)	116	101	68 (19/49)	75 (24/51)
UCLP/BCLP	87 UCLP/29 BCLP	53 UCLP/48 BCLP	68 UCLP	75 UCLP
Age of participants (min/max)	9.8 ± 4 y (4y–20y)	7y - early graft (5y - 8y 9m) 13y 7m - late graft (9y 3m - 16y 9m)	7y (6y-8y)	9.8 ± 0.7y
Evaluation Method: grafts/canine	Bergland (Type I, II, III, IV) / Types: 1(< 15º), 2 (15-45º) and 3 (> 45º) in relation to OP	NR/vertical position: normal (< 45º), at risk (> 45º) in relation to MSP of 90º; Lateral: normal (distal position), at risk (mesial position) to midplane of root of LI	NR/angulation of canine: intersection of its long axis with the MSP	NR/mesiodistal angulation: intersection between its long axis and the bicondylar line; Height of canine: tip of cusp perpendicular to OP
Prior Condition: Graft / Canine	Type I (71.7%); II (23.5%); III (4.8%); IV (0%) / Type 1 (37.5%); 2 (56.9%); 3 (5.6%)	NR/early graft: abnormal vertical position 58% and abnormal lateral 19%; Late graft: abnormal vertical position 48% and abnormal lateral 13%.	NR/impacted canine 20.6%; angulation of canine cleft side: 27º and noncleft side: 15.6º (p = 0.001) Cleft side: pre-eruptive angle of impacted canines 34.4º and in spontaneous eruption 25.5º (p < 0.05)	NR/(T1) late mixed dentition: canine with 1/4–2/3 of root before graft placement; Cleft side: angulation t1 (67.85º); height T1 (–11.58 mm); Noncleft side: angulation T1 (79.48º); height T1 (–7.74 mm);
Presence of LI	LI Absent: (116P): 49.6% UCLP (87P): 50.6% BCLP (29P): 46.5%	LI Absent: Canine in abnormal vertical position 72% and abnormal Lateral 22%; LI present: Canine in abnormal vertical position 43% and abnormal lateral 26%.	LI absent on cleft side: 48.5% and noncleft side: 4.4%	Absence LI reported
Intervention bone graft; Age (variation) / Orthodontics	Gingival alveoloplasty; 33.9 m (18 to 63 m) /NR	Iliac crest; Early graft < or = 9 y; Late graft > 9 y/without orthodontic treatment	NR/7y (6 y–8 y)/ orthodontic treatment performed	Graft with rhBMP-2/ 9.8± 0,7y / Orthodontic treatment: 90% RME before performing graft (T1)
Control	Paired evaluation (BCLP) and nonoperated Side (UCLP)	Paired evaluation (BCLP) and nonoperated side (UCLP)	Nonoperated side	Nonoperated side

Abbreviations: BCLP, unilateral cleft lip and palate; F, Female; LI**,** lateral incisor; M, male; Max, maximum; Min, minimum; MSP, median sagittal plane; NR, not reported; OP, occlusal plane; RME, rapid maxillary expansion; UCLP, unilateral cleft lip and palate.

Results of Studies Included

Increased Rate of Canine Eruption

The SoF in ►**Table 5** describes the outcomes and the certainty of the evidence using GRADE approach for narrative synthesis. All the studies[3,7,13,14] reported improvement in angulation of the canine after bone grafting, which favored canine eruption (►**Tables 3**-**4**), with very low certainty of evidence (►**Table 5**). In a prior manner, the angulation of canine eruption before bone graft surgery was considered a risk for impaction by all[3,7,13,14] the studies, and only one[7] study clearly described the stage of root formation in 1/4 to 2/3 of the root of the canine on the cleft side before the bone graft.

One[13] study reported that the rate of canine eruption was strongly correlated with its previous inclination (Fisher, p < 0.00); the angulation of the canine on the noncleft side ranged from 15.9º (p < 0.001)[14] to 86.6º (p < 0.001),[7] values with significant difference in relation to the cleft side. Canine impaction on the noncleft side ranged from 1.3% (86.6º) (p < 0.001)[7] and 2.9% (30º) (p < 0.05)[14] to 25% (> 45º).[3] One[13] study did not clearly report about the frequency of canine impaction on the noncleft side. Only one[14] study clearly reported that canine impaction increased by 50% after reoperation of the bone graft.

Success of Bone Graft

In general, all[3,7,13,14] the studies reported success of the bone graft (►**Table 4**) with low certainty of evidence (►**Table 5**). After follow-up, the condition of the graft was considered a success in all the individuals in two[3,7] studies, and successful in 93.7% of patients in one[13] study. Only two [13,14] studies reported rates of bone graft failures; however, the rates were low, 11.8%[14] and 6.3%,[13] indicating that bone grafting procedures were successful in the large majority of cases.

All[3,7,13,14] the studies performed 2D radiographic follow-up examinations, with initial and final panoramic r-X examinations; however, with wide sample [13,14] and temporal variation in[3,7,13,14] the examinations performed. No study used 3D examinations. The initial and final r-X examinations, respectively, were performed on an average at 4.9 y and 12.5 y (partial sample = 76),[13] 7 y (partial sample = 59) and 10 y (partial sample = 41)[14], 6.2 y and 8.10 y (early graft) and 12.8 y and 14.4 y (late graft),[3] and 9.8 y (T1)–T2 (3–12 m after T1) and T3 > 13 m after T1 (mean time of follow-up 33m).[7]

Canine Impacted due to Agenesis of the Lateral Incisor

Three studies clearly reported canine impaction due to agenesis of the lateral incisor, with conflicting results.[3,7,13] Two[3,7] studies reported association between the rate of canine impaction and agenesis of the lateral incisor, while another[13] study did not find this association (►**Tables 3**-**4**), with very low certainty of the evidence (►**Table 5**). Agenesis of the lateral incisor generated distinct canine impaction in the patients with UCLP, ranging from 72.2%,[7] 68% of the vertical position and/or abnormal lateral position[3], of up to 20%.[13] Non impaction was 33.3% ($p = 0.006$) in one[7] study, and 80% in the other.[13] One[3] study reported that the noncleft side also demonstrated some type of abnormal position of the canine, 54%, vertical and/or lateral.

Effect of Orthodontic Treatment before and after Bone Graft Surgery

Two studies reported the effect of orthodontic treatment before and after the bone graft. [7,13] In general, one [7] study reported association between rapid maxillary expansion (RME) and gain of space in the maxilla and improved response of tooth eruption before the bone graft, while the other[13] study did not obtain this association (►**Tables 3**-**4**), with very low certainty of the evidence (►**Table 5**). In the pregraft period, only one[7] study clearly reported the type of orthodontic treatment performed, which was RME in 90% of the patients. In the postgraft period, one study[13], with a

Table 4 Outcome of studies included

Characteristics of interventions and details of outcomes				
Study/year	**Meazzini et al[13]**	**Russell et al[3]**	**Westerlund et al[14]**	**Holz et al[7]**
Radiographic follow-up: time interval(s); 2D, 3D	(76P): initial r-X: 4.9 ±1.8y and final r-X: 12.5± 4.9 y; panoramic r-X	initial r-X: 10 m before early graft, and 11m before late graft. Post-graft r-X: 2 y 8 m after early graft, and 1 y 8 m after late graft; panoramic r-X	initial r-X (59P): 7 y (6 y–8 y); final r-X (41P): 10 y (9y–11y); in both time intervals (32P)/panoramic r-X	r-X: before (T1), 3–12 m postgraft (T2), > 13 m postgraft (T3)/panoramic r-X/ mean time of follow-up: 33 m
Condition of graft	Unchanged 68.4%; Improved 25.3%; Worsened 6.3%	Success	Failure 11.8%	Success
Position of canine (rate of eruption)	Unchanged 36,8%; Improved 40%; Worsened 23.2% (45P permanent dentition–UCLP: 80% eruption; 15.5% retention; 4.5% surgical exposure) Eruption was strongly correlated with the previous inclination (Fisher, $p < 0.00$)	Early graft: abnormal vertical position 44% and abnormal lateral 28%; Late graft: abnormal vertical position 13% and abnormal lateral 30%.	Angulation: Cleft side 31.9º and noncleft side 15.9º ($p < 0.001$); Pre-eruptive angulation on cleft side: 38.7º (impacted canines) and 30º (spontaneous eruption) ($p < 0.05$); Impacted canines: cleft side 17.6% and noncleft side 2.9%; impaction (↑ 50%) with reoperation of the graft (mean: 12 y)	Cleft side: angulation T2 (65.62º) T3 (74.42º) ($p < 0.001$); height T2 (–7.05 mm) T3 (–1.67 mm) ($p < 0.001$); T3: impaction (24%) and eruption (76%) Noncleft side: angulation T2 (82.63º) T3 (86.62º) ($p < 0.001$); height: T2 (–2.63 mm) T3 (–1.92 mm) ($p < 0.001$); T3: Impaction (1.3%) and eruption (98.7%)
Position of canine versus LI	Subgroup 45P UCLP: 36P canine erupted (LI absent: 55.5% and LI present: 44.4%); 7P canine retained (LI absent: 42,8% and LI present: 57.1%); 2P surgical exposure (LI absent: 100% and LI present: 0%);	LI absent: abnormal vertical position 36% and abnormal lateral 32%. LI present: abnormal vertical position 36% and abnormal lateral 18%.	NR	LI Absent: impaction of canine (72.2%) and nonimpaction (33.3%) ($p = 0.006$)
Postgraft orthodontic treatment /type and time	Subgroup 45P Permanent dentition, UCLP: 100% of orthodontic treatment, 70% underwent orthopedic expansion/NR	NR	Orthodontic treatment performed/NR	(T2) without orthodontic treatment, (T3) 28% fixed partial orthodontic treatment for correction of LI rotation

(*continued*)

Table 4 (*continued*)

Characteristics of interventions and details of outcomes				
Study/year	**Meazzini et al[13]**	**Russell et al[3]**	**Westerlund et al[14]**	**Holz et al[7]**
Conclusion	Early secondary gingival alveoloplasty appeared to allow adequate ossification in both the nasal and alveolar regions. Permanent tooth eruption occurred at a normal rate. Early secondary gingival alveoloplasty may be adopted to reduce the number of surgical interventions (without the need for secondary bone graft) without the need for invasive pre-surgical orthopedic treatment. To the contrary, patients submitted to early secondary gingival alveoloplasty appeared to exhibit a higher incidence of canine retention and need for orthopedic maxillary expansion.	Patients with complete alveolar clefts had a significantly changed canine position during eruption and had an increased risk of canine impaction in comparison with a population of patients without clefts. Both the time of bone grafting and presence of lateral incisors were factors capable of influencing the risk of canine impaction. Bone grafting must be planned in accordance with maxillofacial and dental development, considering the eruption and periodontal health of the teeth adjacent to the cleft.	The prevalence of impaction was ten times higher in comparison with that in the general population. The factors associated with canine impaction are a pre-eruptive inclination of >30º and re-operation of the bone transplant.	The risks of canine impaction on the cleft side in patients with UCLP are associated with the increase in mesiodistal inclination (≤ 68º). Agenesis of the maxillary lateral incisor on the cleft side is an indicator of early risk for canine impaction. Mesial displacement and superimposition on neighboring incisors could not clearly predict impaction on the cleft side in patients with UCLP.

Abbreviations: LI, lateral incisor; NR, not reported; P, patients; UCLP, unilateral cleft lip and palate.

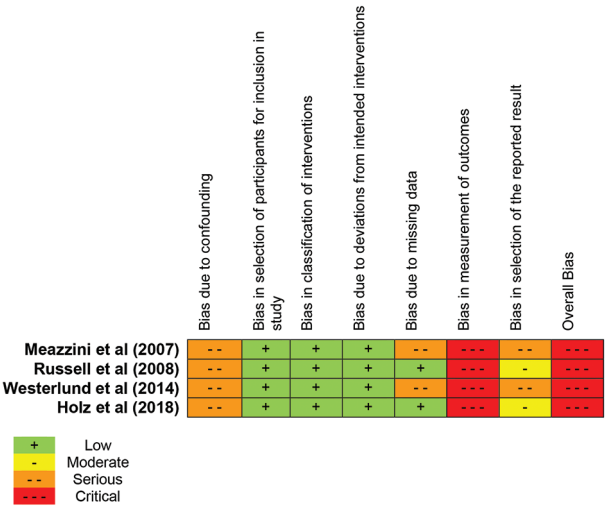

Fig. 2 Risk of bias through risk of bias in nonrandomized studies of interventions (ROBINS-I).

subgroup of 45 patients at the stage of permanent dentition were treated with orthodontic movement and 70% of the patients were submitted to RME. In another study[7], 28% of the patients were submitted to orthodontic treatment with partial fixed appliances for rotational correction of the lateral incisor. In both studies, the treatments were performed after the period of canine eruption.[7,13]

Certainty of the Evidence

The certainty of the evidence was very low or low due to problems of risk of bias, inconsistency, indirectness, imprecision, and publication bias (►**Table 5**). The evidence was rated up due to large effect.

Discussion

There was very low evidence of patients with cleft lip and palate being able to benefit from bone graft surgery for eruption of the canine teeth.

With regard to the outcome, involving successful bone graft, different types of grafts were reported, which contributed to the heterogeneity of the estimates. The rhBMP-2 (morphogenetic bone proteins) were used in one[7] study and may have influenced bone healing[7,21] and favored tooth eruption. Complications such as reoperation procedures performed due to failure of the bone grafts reported[13,14] elevated the risk of canine impaction, due to the additional surgery that deteriorated a site that was already overloaded with inherited and environmental limitations[14]. Although the studies [3,7,13,14] reported successful bone grafting and tooth eruption with panoramic radiography, [22] there was wide methodological variability of the studies and potential influence of the evaluator on the results. In this sense, 3D analyses must be encouraged as a method for evaluating the results of canine eruption, and recently-formed bone [23] 6 months post-surgery with cortical bone maturation.[24]

Table 5 Summary of findings (SoF) table according to the grades of recommendations, assessment, development, and evaluation (GRADE) approach to narrative synthesis

Certainty assessment									
N. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other factors: great magnitude effect**	**Impact**	**Certainty**
Increased rate of canine eruption									
4[a]	NRCTs	Very serious[d]	Not serious	Not serious	Not serious	Strongly suspected [h]	Large effect [i]	All studies reported association between increase in rate of tooth eruption and bone graft. The individuals who received bone grafts before canine eruption had less experience of tooth impaction	Very low
Successful bone graft									
4[a]	NRCTs	Very serious[d]	Not serious	Not serious	Not serious	Strongly suspected [h]	Very large effect [i]	All studies reported greater experience of successful surgery. Two studies experienced unsuccessful surgery with need for reoperation	Low
Canine impacted due to agenesis of the lateral incisor									
3[b]	NRCTs	Very serious[d]	Very serious [e]	Not serious	Serious [g]	Strongly suspected [h]	Large effect [i]	The majority of the studies (2 out of 3) found association between the rate of canine impaction and agenesis of the lateral incisor. One study found that agenesis was not associated with tooth impaction	Very low
Effect of orthodontic treatment before and after bone graft surgery									
2[c]	NRCTs	Very serious[d]	Very serious [e]	Serious [f]	Serious [g]	Strongly suspected [h]	Large effect [i]	One study found that individuals submitted to RME before bone graft had greater gain of space in the maxilla and better response of tooth eruption. One study reporter higher level of experience of gain in space of the maxilla and response of tooth eruption with postgraft RME	Very low

Abbreviations: NRCTs, nonrandomized controlled trials; RME, rapid maxillary expansion.
[a] 4 studies: 3, 7, 13, 14.
[b] 3 studies: 3, 7, 13.
[c] 2 study: 7.13.
[d] All the studies included showed risk of bias; they were NRCTs with great problems in relation to the effect of confounders, selection of participants, lack of blinding, reproducibility, and bias in selection of the result.
[e] There was inconsistency in the estimates of the studies: two estimates were more in favor of eruption with agenesis and 1 estimative favored impaction with agenesis. One estimate favored RME before bone grafting.
[f] The evidence came from studies with only two types of orthodontic treatments that were applicable to cleft lip and palate, limiting the applicability to other orthodontic treatments.
[g] Based on the ideal size of the information (OIS), the number of events was lower than 300 for the dichotomous variable.
[h] Suspicion of publication bias due to possible estimates not published which may not have been statistically significant.
The outcomes demonstrated the effect of great magnitude for the estimates: large RR~50% and very large RR~80%.

The 3D examination may increase the interexaminer reliability, improve reproducibility of the method[25], enable digitization of small regions for precise diagnosis, and have low dose irradiated in reduced images[26] of the cleft.

Cleft lip and palate arise from the absence of fusion between the primary palate, secondary uni- or bilateral maxillary and palatine processes, affect the upper lip and extend up to the sulcus between the canine and lateral incisor

(LI), commonly generating agenesis and tooth impactions, even attaining the maxilla and nose in the eighth week of gestation.[3,27] As from this gestational phase, absence of the LI over the course of time appears to be a factor that reduces the potential of verticalization of the canines and spontaneous eruption,[3,14] with 68% more risk of impaction versus 6% on the noncleft side[3], and predictive of impaction in 81% of the individuals.[7] For other[13,27] studies, the presence of LI did not appear to be so relevant in the orientation of canine eruption.

In the outcome, rate of canine eruption, mesiodistal inclination appeared to be predictive of canine retention.[13] Some studies have suggested that mesiodistal inclination of the canine > 30^0 in 7 to 10 years may increase the probability of impaction,[3,14,27,28] when compared with the medium angle of 22°[29] of impacted canines in patients without clefts. Although other authors[30] have not found this association, in the studies evaluated, the cleft side showed canines that were more angulated[3,7,13,14] and more distant from the occlusal plane[7]. In the postgraft period, the position of the canine became more vertical in the majority of the individuals[3,7,13,14] and the neoformed bone frequently allowed spontaneous migration and eruption of the canine on the cleft side.[7,31-33] The studies[3,7,13,14] were not sufficiently clear about whether the follow-up of the canine corresponded to the period of rhizogenesis and active eruption, commonly occurring from 9 to 12 years; and only two studies reported follow-up for periods longer than 36 months.[13,14]

The outcome, orthodontic treatment success, combined orthodontics with the surgical approaches as a common procedure in UCLP and BCLP. Along this line, expansion of the maxillary arch before bone grafting has been recommended in many clinical discussions, but not supported in the literature as being necessary to increase the space in the area of the cleft and promote canine eruption.[3] Only one[7] study was clear about the orthodontic treatment performed prior to bone grafting, RME in 90% of the individuals. As an alternative approach, post bone-grafting expansion would minimize the size of the cleft defect. Two[3,13] studies considered postbone grafting the adequate time for performing the two treatments, using maxillary expansion and fixed orthodontic appliances. To sum up, it was not sufficiently clear whether there would be a significant difference in canine eruption if expansion of the arch were performed pre- or postbone grafting.[31,32] Although this study addressed as comparison (C) in PICO question the side not submitted to surgery for patients with UCLP, the descriptive results demonstrated for BCLP suggest a behavior similar to the cleft side of patients with UCLP, with analogous outcomes.

The certainty of the evidence was low to very low. In general, all studies had critical risk of bias, due to confunding, bias on account of missing data, bias in measurement of the outcome and selection of the result reported. There was imprecision for some outcomes due to limited number of studies and this consequently limited the sample size and number of events. We also found inconsistency in results with conflicting data and limited applicability of the types of orthodontic treatments that could improve the rates of canine eruption. Although we thoroughly searched several electronic databases, gray literature and performed a manual search, we suspected a selection reporting bias in trials that did not publishing negative outcomes. We rated up the certainty of the evidence, since some studies reported effect estimates of large effect.

Strengths and Limitations

This study had limitations. There were a limited number of studies included, which led to the effect of imprecision of the data input on the results. Meta-analysis was not possible due to the great heterogeneity of data reported among studies. However, as a strong point, we used the GRADE approach to report the certainty of the evidence for narrative synthesis when ROBINS-I was used for risk of bias.[19] The GRADE approach for narrative synthesis can avoid misleading conclusions and be more conservative for interpretation of the results.[19,34] This systematic view was conducted with strict methodological rigor.

Implications for Research

Controlled clinical trials (RCTs) with clinical and radiographic methodologies such as standardization of the severity of the cleft, blinding of the professionals (the outcome evaluator should not be the surgeon, and should not have knowledge of the patient's previous history), performing sample calculation, evaluating the level of rhizogenesis of the canine, and time of follow-up longer than 3 years, in order to evaluate the influence of bone grafting and agenesis of the lateral incisor on the eruption of the canine, are necessary and would offer more information in the long term. However, due to the particularities of patients with cleft lip and palate, factors such as age, patient expectations, surgical options, and orthodontic planning may make it difficult to conduct RCTs. Therefore, future high-quality, nonrandomized observational studies may allow significant outcomes to be obtained.

Possible sources of bias must be controlled, such as the insertion of sufficiently clear protocols for surgical and orthodontic treatment, 3D measurement instruments of recently-formed bone and tooth eruption, and longer periods of follow-up. Further studies must also investigate the esthetic satisfaction and quality of life of patients submitted to the different treatment modalities.

Conclusions

There is low to very low certainty of evidence:

- Of the efficacy of the secondary bone graft for patients with cleft lip and palate.
- Secondary alveolar bone grafting favored the increase in rates of eruption and diminished impaction of maxillary canines.
- On the effect of grafting on the rate of canine impaction and agenesis of the lateral incisor.
- On the efficacy of orthodontic treatment before bone grafting to promote greater gain of space in the maxilla and improve the response of tooth eruption.

Conflict of Interest
None declared.

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