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Review

Early or delayed palatoplasty in complete unilateral cleft lip and palate patients? A systematic review of the effects on maxillary growth

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ABSTRACT

The aim of this study was to review the effects of early and late hard palate repair on maxillary growth. PubMed, Scopus, Web of Science, LILACS, Cochrane Library CENTRAL databases, OpenGrey, Google Scholar, and Clinical Trials were searched using a PICO strategy, with terms related to unilateral cleft lip and palate (UCLP) and timing of repair. Methodological quality evaluation was carried out using the Fowkes and Fulton guidelines, and quality (or certainty) of evidence and strength of recommendations were evaluated using GRADE (grading of recommendations, assessment, development and evaluation). Five retrospective and non-randomized studies were included in the study. Folkes and Fulton assessment showed a high risk of bias in all articles and very low levels of certainty (GRADE). The results showed conflicting findings for comparisons of the effects of timing of repair of hard palate in UCLP. Two studies presented better maxillary growth in a group operated on later (18 months after birth), two presented no differences between the results, and another presented better results in the group operated on earlier than 18 months of age. At this point, it cannot be proven or refuted that postponing hard palate surgery brings benefits for maxillary growth. Studies included in this review did not show similar conclusions. Randomized clinical trials present some ethical issues that make them difficult to perform.

1. Introduction

Patients with cleft lip and palate who have undergone a standard surgical protocol tend to exhibit significant maxillary hypoplasia (Ross, 1987; Mars and Houston, 1990; Normando et al., 1992; Filho et al., 1996). Therefore, the search for a treatment protocol that minimizes the facial growth impairment caused by surgery is a necessity.

Several surgical protocols have been presented, using different techniques and surgical timings — early or late, and have been evaluated in terms of benefits to maxillary growth. While some researchers have stated that maxillary growth benefits when the hard palate surgery is performed later, having observed a more anterior position of the maxilla (Friede and Enemark, 2001; Liao et al., 2010; Bakri et al., 2014), others have reported that early surgical treatment does not cause impairment in the sagittal or vertical growth of maxilla when compared with individuals treated later (Holland et al., 2007; Pradel et al., 2009; Zemann et al., 2011; Mikoya et al., 2015). Despite this divergence of opinions regarding the effect of surgical timing on maxillary growth, patients treated in only one surgical stage in the first year of life have shown better development of speech and facial growth when compared with patients treated in two stages, one

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of them being postponed (Daskalogiannakis et al., 2006; Holland et al., 2007; Pradel et al., 2009).

In a systematic review proposed by Liao and Mars (2006), which sought to evaluate the optimal timing for palate repair in terms of facial growth, the results were inconclusive. However, this systematic review assessed unilateral and bilateral clefts, which were analyzed regardless of the timing of surgery for hard and soft palate closure. In addition, the studies in this paper showed great heterogeneity in terms of interval times between surgeries, and involved small samples and short-term follow-ups.

Our systematic review aimed to evaluate the optimal timing of palatoplasty in terms of maxillary growth in patients with complete unilateral cleft lip and palate.

2. Materials and methods

2.1. Protocol and Record

The systematic review was recorded in PROSPERO, under the protocol CRD42016033183, in accordance with the recommendations of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) and following Moher's guidelines (Moher et al., 2009).

2.2. Search Strategy and Eligibility Criteria

A systematic search was performed for studies that evaluated children with unilateral complete cleft lip and palate (P) subjected to early palatoplasty, with hard palate surgery carried out before 18 months (I), compared with children subjected to late palatoplasty, with hard palate surgery carried out after 18 months (C), with the aim of assessing, through cephalometric radiographs in lateral norm, the differences in the maxillary growth among the groups (O).

The search was performed in the following databases: PubMed, Scopus, Web of Science, LILACS, The Cochrane Library, CENTRAL, OpenGrey, Google Scholar, and Clinical Trials until June 2018, without language or year restrictions.

MeSH and/or free terms were used in all the databases, following individual search rules, relating to children with unilateral complete cleft lip and palate, non-syndromic, and operated early and late. Boolean terms (OR, AND, and NO) were used to combine the searches in all databases.

The research was conducted by two separate evaluators (KRS and ARW), using the same words and in compliance with the same rules. The results obtained were stored in a single database (EndNote X7; Thomson Reuters, Philadelphia, USA). Duplicate results were removed and the titles and abstracts were analyzed by the evaluators in accordance with the inclusion and exclusion criteria of the PICO strategy. A third evaluator (PBL) decided on the disagreement cases. Upon completion and after the study selection, a manual search was carried out to identify new studies within the eligibility criteria.

For the final selection, the following inclusion criteria were evaluated: patients with complete unilateral cleft lip, alveolus and palate; non-syndromic; with maxillary growth evaluated by cephalometric analysis; and with surgical interventions — hard palate surgery performed before the 18th month of life for the early group, or delayed hard palate surgery performed after 18 months for the late group; and lip and soft palate surgery performed up to 12 months for both groups. The following were excluded: textbooks, editorials, case reports, case series, review articles, opinion articles, studies on animals, technical articles, and guides (Fig. 1).

2.3. Data Extraction and Quality Assessment

From the final selection, a collation of individual articles was generated using the following data: author, year, country, study design, study objective, source of samples, sample size, age range, identification of groups, lip surgery, surgical technique, results, and statistical analysis (Table 1).

A search for additional data relating to articles, in cases of absence of information or questions related to risks of bias, was conducted by sending e-mails to the authors twice over two consecutive weeks.

The articles that met all inclusion criteria were evaluated in relation to methodological quality and risk of bias, according to the guidelines proposed by Fowkes and Fulton (1991), and adapted according to Penoni et al. (2017). Critical evaluation of the verification guidelines was performed using the following characteristics: type of appropriate study; representativeness of the sample; the presence of an acceptable control group; quality of measurements and results; and integrity and confounding factors. According to the guidelines, a quality was assigned to each question: (0) for no problem assigned, (+) for a minor problem, and (++) for a bigger problem, and (NA) when the issue was not applicable to the type of study (Supplementary Table 2).

2.4. Risks of Bias

After careful evaluation of the quality of the studies, an analysis was performed for the risk of bias using the functions 'biased results', 'serious confounding factors', and 'occurrence of chance' (Fowkes and Fulton, 1991; Penoni et al., 2017). For determining the value of the studies, three questions were asked: Are the results erroneously biased in a certain direction? Are there some serious confusion or other distortion influences? Is it likely that the results have occurred by chance? If the three questions were answered with a NO, the methodology was considered sound.

2.5. Level of Evidence

An evaluation was made regarding the degree of scientific evidence of the included studies using the GRADE (grading of recommendations, assessment, development and evaluation) tool (Balshem et al., 2011). The studies were evaluated according to their design, risk of bias, consistency, directness, and precision.

3. Results

3.1. Selection of Studies

318 articles were found among the databases investigated, with the following breakdown: 151 articles from PubMed, 85 from Scopus, 30 from Cochrane Library, 30 from CENTRAL, 21 from Web of Science, and one from Google Scholar. No articles were found in the other databases within the searches made. After the duplication removals (67), 251 articles remained that had their titles and abstracts assessed in accordance with the inclusion and exclusion criteria. From this initial reading, over 226 articles were removed that did not meet the criteria, leaving only 25 articles. Of these 25, after a more careful reading, including the methodology, 23 were excluded: five because they were literature reviews, one because it was a personal opinion article, and 17 because they did not meet the required difference between early and late timing (Rudolph, 1978; Wada et al., 1990; Joos, 1995; Kramer et al., 1996; Friede et al., 1999; Friede and Enemark, 2001; Nollet et al., 2005; Friede, 2007; Stein et al., 2007; De Mey et al., 2009; Pradel et al., 2009; Liao et al., 2010; Gundlach et al., 2013; Ganesh et al., 2015;

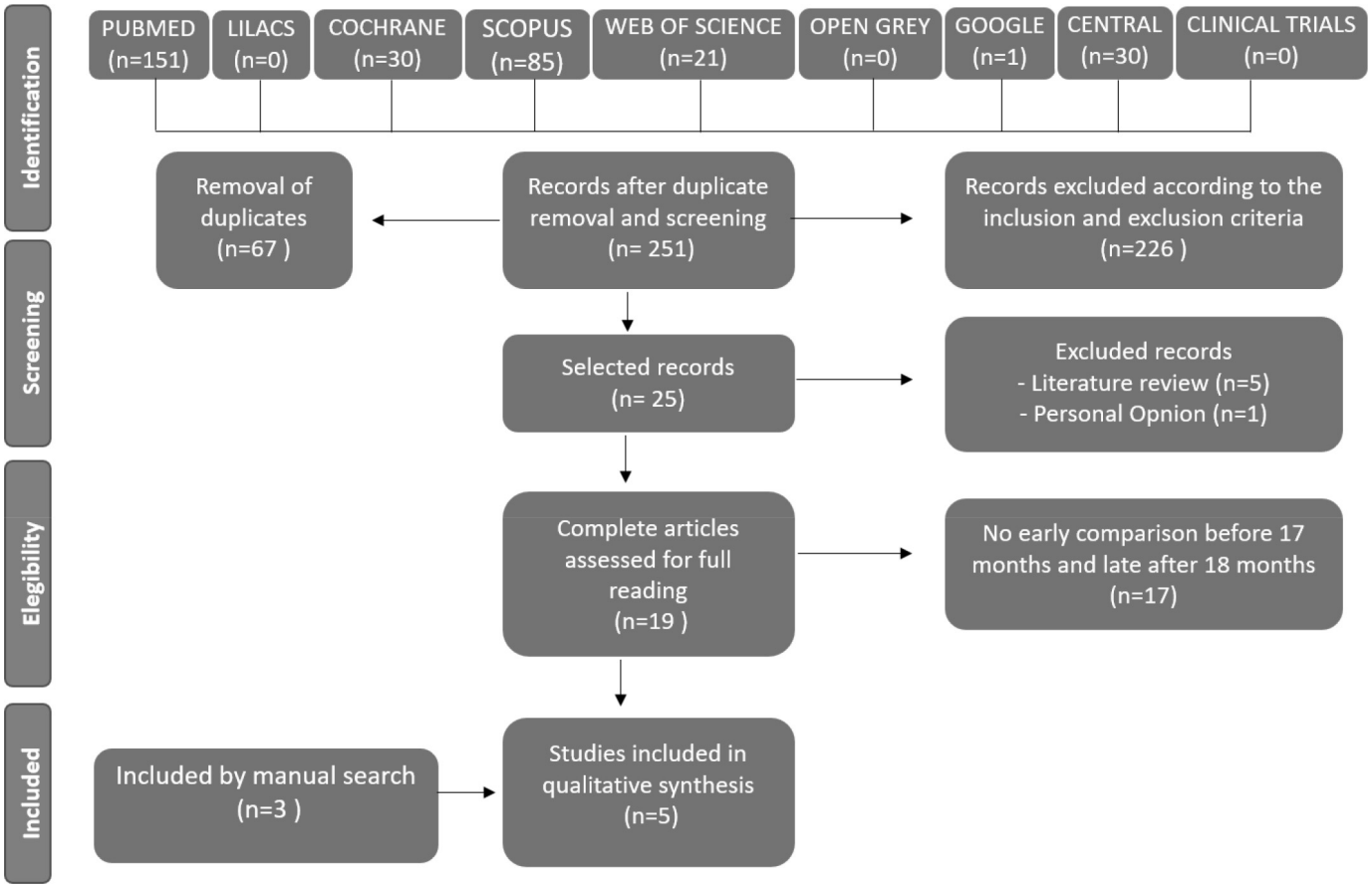

Fig. 1. Flow chart showing the number of records identified and removed at each stage of the review, according to the PRISMA statement.

Mikoya et al., 2015; Stancheva et al., 2015; Xu et al., 2015), leaving only two papers read in full (Holland et al., 2007; Yamanishi et al., 2011). At this point, three more articles were included (Daskalogiannakis et al., 2006; Zemann et al., 2011; Bakri et al., 2014), resulting from a manual search through the references of the selected articles (Fig. 1). After a qualitative synthesis, the five articles for the final study were retained. These were summarized and described in the data analysis (Table 1).

3.2. Characteristics of the included articles

The five articles included in this review were all observational studies, with complete unilateral cleft lip and palate (UCLP). These papers followed the surgical repair timings stipulated by this research: early group before 18 months of life and late group from 18 months. In addition to the comparison of craniofacial growth, two articles assessed speech development (Holland et al., 2007; Yamanishi et al., 2011).

The authors used different surgical techniques in the process of cleft repair. For lip repair, the following were used: modified Millard technique (Daskalogiannakis et al., 2006; Yamanishi et al., 2011), Millard rotation-advancement (Zemann et al., 2011), Tennison-Randall technique (Zemann et al., 2011), and vomer flaps (Bakri et al., 2014). One article did not specify the technique employed for lip correction (Holland et al., 2007). The palate repair techniques were as follows: modified Furlow (Yamanishi et al., 2011), Wardill-Kilner pushback (Yamanishi et al., 2011; Bakri et al., 2014), Veau technique (Zemann et al., 2011), intravelar veloplasty with simultaneous mucoperiosteal and alveolus closure (Holland et al., 2007; Zemann et al., 2011), Schweckendiek technique/modified Von Langenbeck (Daskalogiannakis et al., 2006; Holland et al., 2007), and soft palate closure with vomer flap and closure of residual hard palate in the mixed dentition, but without reporting how this technique was done (Bakri et al., 2014). The mean patient age at the time of surgery timing varied according to the surgical protocol: lips from 16 to 18 weeks (Daskalogiannakis et al., 2006), 2 months (Bakri et al., 2014), 3 months (Daskalogiannakis et al., 2006; Yamanishi et al., 2011; Zemann et al., 2011) to 6 months (Zemann et al., 2011); early palatoplasty from 9 months (Bakri et al., 2014) to 12–17 months (Daskalogiannakis et al., 2006; Holland et al., 2007; Zemann et al., 2011; Yamanishi et al., 2011); and late palatoplasty from 18 months (Yamanishi et al., 2011), 2.5 years (Zemann et al., 2011), 7 years (Holland et al., 2007), and 8–10 years (Daskalogiannakis et al., 2006; Bakri et al., 2014). All studies evaluated maxillary growth through cephalometric analysis. Three performed cephalometric analysis in the medium-term follow-up, but before the end of the growth, ranging from 4 years (Yamanishi et al., 2011) to 10 years of follow-up Zemann et al. (2011); Bakri et al. (2014). Two studies carried out long-term follow up after the end of growth (Daskalogiannakis et al., 2006; Holland et al., 2007).

3.3. Result of Individual Studies

Of the five studies, two resulted in improvements in maxillary growth in the later operation group. Yamanishi et al. (2011) showed that the anteroposterior length of the maxilla (ANS–ptm') was greater in the group with hard palate treated at 18 months

Table 1
Data extraction from included articles.

Author, year; country; study design	Objectives of the study	Sample				Lip surgery/lip surgical technique	Surgical technique for palatoplasty	Results	Statistical analysis
		Source of sample	Sample size	Age range	Identification of groups/surgical timing				
Daskalogiannakis et al. (2006); Canada; cohort study	Identify differences in craniofacial morphology of two populations with UCLP treated under different protocols, at 5, 10, and 18 years follow-up	Cleft Center of the University of Nijmegen, Netherlands, and the Cleft Lip and Palate Program, Hospital for Sick Children, Toronto, Canada	38	Toronto group, 12−15 months (soft and hard palate); Nijimegen group, 12 months (soft palate) and 9 years (hard palate)	Toronto group, early one-stage palatoplasty; Nijimegen group, late two-stage palatoplasty	Toronto group, 16 −18 weeks/Millard technique; Nijimegen group, 3−4 months/ Millard technique	Toronto group, modified von Langenbeck; Nijimegen group, modified von Langenbeck	At T3 the SNA angle was higher in the Toronto group. No differences were seen in the maxillary measurements. The patients in the Toronto group had significantly larger mandibles at all three times registrations.	Repeated-measures analysis of variance
Holland et al. (2007); USA; cohort study	Compare the closure of the hard palate, in a single phase, with the late closure and its effects on speech and maxillary growth	Pittsburgh University	82	0−84 months: G1, 12 months (soft palate) and 84 months (hard palate); G2, 12 months (hard palate and soft palate)	G1, late two-stage palatoplasty; G2, early one-stage palatoplasty	Does not report technique/timing	G1, Schweckendiek technique; G2, modified von Langenbeck palatoplasty and intravelar veloplasty	Class III malocclusion: G1, 66%; G2, 31% ($p < 0.05$) SNA: G1, 74.8°; G2, 78.2° ($p < 0.05$) ANB: G1, 2.4; G2, 1.1 ($p < 0.05$) Need for Le Fort I: G1, 42%; G2, 24% ($p < 0.05$)	Mann−Whitney test Fischer's exact test Independent t-test
Yamanishi et al. (2011); Japan; cohort study	Evaluate maxillofacial growth and speech development in children with CUCLP treated with palatoplasty in one stage and two stages	Osaka Medical Center and Research Institute, Japan	72	0−18 months: ETS, 12 months (soft palate) and 18 months (hard palate); PB, 12 months (hard palate and soft palate)	ETS, late two-stage palatoplasty; PB, early one-stage palatoplasty	3 months/modified Millard	ETS, modified Furlow/ z-plasty; PB, Wardill-Kilner/push-back	N-SNA: ETS, 2.5; PB, 0.26 ($p < 0.05$) ANS-Ptm: ETS, 46.7; PB, 43.6 ($p < 0.05$) Anterior facial height: ETS, 43.3; PB, 40.1 ($p < 0.05$)	Student t test, not paired Fisher's exact test Unidirectional variance analysis Averages and standard deviation
Zemann et al. (2011); Austria; cohort study	Compare the sagittal facial growth of children with CUCLP treated with different surgical protocols; evaluated at 4 years and reassessed at 10 years of age	University Medical Center Ljubjana, Slovenia and Medical University of Graz, Austria	54	3−30 months: G1, 12 months (soft and hard palate); G2, 12 months (soft palate) and 30 months (hard palate)	G1, early one-stage palatoplasty; G2, late two-stage palatoplasty	G1, 3 months/ Millard's advancement and spin; G2, 6 months/ Tennison-Randall technique	G1, Veau technique; G2, intravelar veloplasty with simultaneous mucoperiosteal and alveolar closure	No statistical differences between the mean values of the angles analyzed — SNA, SNB, SNPg, and ANB.	Student t test Kolmogorov −Smirnov test Bonferroni test
Bakri et al. (2014); Switzerland; cohort study	Compare vertical maxillary growth in patients with UCLP treated with two different surgical protocols.	University of Gothenburgh	92	2 months to 10 years: G1, 9 months (soft and hard palate); G2, 7 months (soft palate) and 8−10 years hard palate	W-K, early one-stage palatoplasty; DHCP, late two-stage palatoplasty	2 months/Vomer tabs	G1, Wardill-Kilner/ push-back; G2, Vomer flap and bone graft	n-sp': W-K, 43.98; DHCP, 45.41 ($p < 0.05$) NL-is: W-K, 24.89; DHCP, 26.33 ($p < 0.05$) Overbite: W-K, 1.74; DHCP, 3.18 ($p < 0.001$) NSL/NL: W-K, 9.07; DHCP, 10.67 ($p < 0.05$)	Method error: Dahlberg formula Student t test

G1: group 1; G2: group 2; *p*: *p-value*; SNA: sela-nasio-point angle A; SNB: sela-nasio-point angle B; ANB: angle point A-nasio-point B; ETS: early two-stage palatoplasty; PB: one-stage Wardill-Kilner push-back palatoplasty; N-SNA: distance from the projection of the N point on the palatal plane to the anterior nasal spine; ANS-Ptm: anteroposterior maxillary length; SNPg: sela-nasio Pogonion angle; W-K: Wardill-Kilner; DHCP: delayed hard palate closure; n-sp': upper anterior maxillary height; NL-is: anterior maxillary height; NSL/NL: maxillary inclination.

compared with that treated at 12 months; also, the distance was longer from the anterior nasal spine to the projection of point N in the palatine plane (N′–ANS). Greater anterior facial height (N–N′) was also found in later operation group. The SNA and SNB values showed no statistical differences in spite of linear measurements showing statistically significant gains. The study by Bakri et al. (2014) assessed vertical maxillary gain, showing that the anterior facial height (n–sp'), maxillary anterior height (baseline of the maxilla (NL)–is), overbite, and the maxilla inclination (nasion-sella line (NSL)/NL) had better results in the later operation group, at 8–10 years, compared with the earlier operation group, treated at 9 months.

On the other hand, Daskalogiannakis et al. (2006) and Zemann et al. (2011) found no statistical differences among the treatments, evaluating the sagittal growth between two different centers. In their paper, Daskalogiannakis et al. (2006) showed only differences in mandibular points: SNB larger in the Toronto group (early group, operation at 12–17 months) at T1, T2, and T3 (pT1 = 0.02; pT2 = 0.01 and pT3 = 0.0001 respectively); and mandibular length greater in the Toronto group (early group) in the T2 and T3 follow-up ($p = 0.04$ and $p = 0.0002$, respectively). In T3 (18-year follow-up) the SNA point was also significantly larger in the Toronto sample, by 4.4° ($p = 0.0002$), resulting in no significant difference in the average ANB angle.

The study by Holland et al. (2007) found statistically significant differences in maxillary growth in the early group, operated on at 12 months (soft and hard palate), with a gain in SNA (mean of 74.8° in the early group and 78.2° in the late group) and ANB (mean of 2.4° in the early group and 1.1° in the late group) — higher than those operated on later, at 84 months — and observed that patients treated later presented class III malocclusion with greater frequency (66%) than those treated earlier (31%). Le Fort I surgical advancement of was carried out in 42% of the patients in the later group compared with 24% of those in the early group ($p < 0.05$), where the mean advancement in the later group was 9 mm, compared with 6 mm in the earlier group.

3.4. Risk of Bias

The characteristics of the selected studies were tabulated for qualitative analysis (Table 1). After assessing the quality and risk of bias of the studies, it was observed that in all the selected articles, the methodologies had high susceptibility to risk of bias (Table 2). The confounding factors presented in these studies that introduced this risk of bias were mainly of two aspects: four articles had sample groups treated at different times regarding the timing of protocol used by the study center (Daskalogiannakis et al., 2006; Holland et al., 2007; Yamanishi et al., 2011; Bakri et al., 2014); and two articles made a comparison between two different centers (Daskalogiannakis et al., 2006; Zemann et al., 2011).

3.5. Level of Evidence

The GRADE evaluation showed a very low level of certainty among the two results being assessed — vertical and sagittal maxillary growth. This result can be associated with the risk of bias and the type of included studies. There was no concordance among the papers in terms of optimal moment of intervention for the best effects on sagittal maxillary growth. Among the four studies that

Table 2
Quality evaluation of included studies according to Fowkes and Fulton (1991) and adapted by Penoni et al. (2017).

Guideline	Checklist	Daskalogiannakis et al. (2006)	Holland et al. (2007)	Yamanishi et al. (2011)	Zemann et al. (2011)	Bakri et al. (2014)
Study design appropriate to objectives?	Objective, common design prevalence Cross-sectional Prognosis Cohort					
	Treatment Controlled trial	0	0	0	0	0
Study sample representative?	Source of sample	0	0	0	0	0
	Sampling method	+	+	+	+	+
	Sample size	++	+	+	+	++
	Entry criteria/exclusion	0	0	0	0	0
	Non-respondents	NA	NA	NA	NA	NA
Control group acceptable?	Definition of controls	0	0	0	0	0
	Source of controls	+	0	0	+	0
	Matching/randomization	0	0	0	0	0
	Comparable characteristics	0	0	0	0	0
Quality of measurements and outcomes?	Validity	0	0	0	0	0
	Reproducibility	+	+	0	0	0
	Blindness	++	++	++	++	++
	Quality control	0	++	0	0	0
Completeness	Compliance	NA	NA	NA	NA	NA
	Drop outs	NA	NA	NA	NA	NA
	Deaths	NA	NA	NA	NA	NA
	Missing data	NA	NA	NA	NA	NA
Distorting influences?	Extraneous treatments	0	0	0	0	0
	Contamination	NA	NA	NA	NA	NA
	Changes over time	+	+	+	NA	+
	Confounding factors	+	+	+	+	+
	Distortion reduced by analysis	NA	NA	NA	NA	NA
Summary questions	Bias: Are the results erroneously biased in a certain direction?	Yes	Yes	Yes	Yes	Yes
	Confounding: Are there any serious confusing or other distorting influences?	Yes	Yes	Yes	Yes	Yes
	Chance: Is it likely that the results occurred by chance?	Yes	Yes	Yes	Yes	Yes

0 = no problem, + = minor problem, ++ = major problem, NA = not applicable due to type of study.

assessed sagittal growth, two studies showed no differences between the groups evaluated, with a follow-up at 18 years; one indicated improvements in the later operation group and another in the earlier group. Only one study evaluated the effects on vertical maxillary growth, showing better maxillary growth when the hard palate surgery was postponed. We must reinforce that these results should be carefully considered, because the studies presented very low levels of evidence and high risks of bias (Table 3).

4. Discussion

Systematic reviews represent some of the best sources of scientific evidence in the literature when the primary studies are methodologically well delineated. When researching, strategically and rigorously, studies that assess a certain subject, through the synthesis of information, such revision allows access to information by professionals without experience in selecting and reading relevant scientific articles. Information that defines the most suitable timing for hard palate repair in cleft patients may assist surgeons, generating significant improvements in the quality of life of these patients (Cook et al., 1997).

The systematic search in this study, evaluating the timing of repair surgeries of the hard palate in relation to the effects on maxillary growth, culminated in the selection and analysis of five articles with different results. Upon qualitative analysis of these studies using the Fowkes and Fulton (1991) evaluation guidelines, three questions were posed: Are the results erroneously biased in a certain direction? Are there some serious confusion or other distortion influences? Is it likely that the results have occurred by chance? All were answered with a YES in the end, suggesting that these articles presented methodological deficiencies due to differences in the timings of the protocols used by the same center and/or in multicenter comparisons. The latter generated a great risk of bias, with the possibility of results being mistakenly biased in one direction, of confounding factors capable of influencing the results, and of occurrence of results by chance.

None of the selected articles performed a comparison of operation timings only. They also assessed, for example, different surgical protocols, including varied techniques for lip and palate repair. However, all were divided into groups according to the inclusion and exclusion criteria regarding the proposed methodology. The absence of a standardized protocol regarding the technique and ideal timing of surgery, as well as the surgical stages, made the selection of these studies difficult, and also generated many controversies (Berkowitz, 1996; Shaw et al., 2001; Mossey et al., 2009). In an attempt to standardize the selection criteria, the study included only articles in which comparisons were performed specifically regarding the ideal timing for hard palate surgery, thus standardizing lip and soft palate surgery up to 12 months, regardless of surgical techniques and stages.

The final five articles evaluated maxillary growth through cephalometric measurement. Although cephalometric analysis is commonly used to evaluate facial growth, it has methodological weaknesses that can lead to a variation in measurements, depending on the magnification, radiographic distortion, and the observer's judgment, in addition to its two-dimensional nature (Bongaarts et al., 2008; Pittayapat et al., 2015). The measurements of points and angles analyzed in these studies showed heterogeneity. This, together with the high susceptibility to risk of bias in these studies — different times of intervention among the evaluated groups, and variation in the age of the patients in each study — prevented the achievement of a meta-analysis. Whereas four of the

Table 3
Grading of recommendation, assessment, development, and evaluation (GRADE) (Balshem et al., 2011).

Certainty assessment							Impact	Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Sagittal effects on maxillary growth (follow-up range 4–10 years; assessed with cephalometric analysis)									
4	Observational study	Serious[a],[b]	Not serious	Not serious	Not serious	None	In four studies, 124 patients were treated with early palatoplasty and 122 patients with delayed palatoplasty. They had a follow-up range from 4 to 18 years. Two studies showed no difference between the timings of surgery at 10–18 years follow-up. One study showed better effects for those treated early and the other one showed better effects for those treated latter.	⊕◯◯◯ Very low	Critical
Vertical effects on maxillary growth (follow-up 10 years; assessed with cephalometric analysis)									
1	Observational study	Serious[a]	Not serious	Not serious	Not serious	None	In this study, 46 patients treated with early hard palatoplasty and 46 patients treated with delayed hard palatoplasty had a 10-year follow-up. The results showed greater anterior upper facial height, anterior maxillary height, overbite, and inclination of maxilla in the group treated later, when compared with the group treated earlier.	⊕◯◯◯ Very low	Critical

[a] Daskalogiannakis et al., Holland et al., Yamanishi et al., and Bakri et al. reported different times of intervention between the groups.
[b] Daskalogiannakis et al. and Zemman et al. reported different centers between the groups.

studies (Daskalogiannakis et al., 2006; Holland et al., 2007; Zemann et al., 2011; and Yamanishi et al., 2011) performed the measurements using the SNB, SNA, and ANB angles, as well as some linear measurements, one (Bakri et al., 2014) used linear and angular measurements in the vertical direction (Table 3).

There is still no agreement in the literature about the ideal timing for the intervention of the palate in patients with unilateral cleft lip and palate, in terms of facial growth. Yamanishi et al. (2011) and Bakri et al. (2014), despite stating better values for of maxillary growth in the later operation group, evaluated different points of measurement. Bakri et al. (2014) assessed vertical gain, which showed a less severe deleterious effect of palate surgery in patients for whom treatment was postponed, corroborating previous studies (Swennen et al., 2002; Swennen et al., 2004; Wermker et al., 2012; Xu et al., 2015) and justifying their findings as being not as a consequence of timing, but rather due to the surgical technique proposed. They suggested that this improvement was due to the Wardill-Kilner technique used in the early group, which presented a greater quantity of extensively denuded palatine bone, resulting in scar tissue and negatively affecting maxillary growth in all dimensions (Ross, 1970; Bardach et al., 1984; Ishikawa et al., 1998; Xu et al., 2012). In addition, Yamanishi et al. (2011) suggested that the residual cleft palate in the hard palate, in cases of surgeries that postponed this repair, decreased in width by 0.5–1 mm within a year after soft palate closure, as a result of growth. This, the hard palate can be closed later with minimal interference (Ross, 1987; Friede and Enemark, 2001; Liao et al., 2010; Bakri et al., 2012).

Some studies have reported that maxillary retrusion in operated cleft patients is progressive and worsens during the pubertal growth stage (Hayashi et al., 1976; Ross, 1987; Semb, 1991). The study by Zemann et al. (2011), in which the optimal timing of surgical repair was evaluated in terms of maxillary growth 10 years after the surgical interventions, reported that there were no differences regarding the ideal moment for the palate surgical repair among the compared centers, either at the 6-year or 10-year follow-up. These results corroborate other findings, which also reported no statistical differences in follow-up cephalometric analysis at 18 years of age, showing that, initially, there were differences, but that these were overcome in the course of puberty (Daskalogiannakis et al., 2006; Stein et al., 2007).

Other studies advocate the possibility of surgical palate repair at an earlier stage, where cephalometric values closer to normal in maxillary growth, as well as in speech, have been demonstrated in patients treated between 9 and 12 months (Pradel et al., 2009). These studies are in agreement with the findings by Holland et al. (2007), one of the selected studies in this systematic review, which show a reduced need for maxillary advances or secondary surgical interventions for speech, as well as a lower incidence of oronasal fistulae and velopharyngeal incompetence, in early-operated patients (Holland et al., 2007).

There are many factors, aside from timing of surgery, that can affect the expected results. Possible confounding factors that can also influence facial growth include ethnicity, surgical technique, number of surgical interventions, protocol, cleft size, previous orthodontic treatment, speech development, use of prosthetic devices, and professional experience and skills (Ross, 1987; Shaw et al., 1992; Rorich et al., 1996; Nollet et al., 2005; Daskalogiannakis et al., 2006). Professional experience and skills are probably the factors of greater influence on subsequent facial growth than the timing or choice of technique (Ross, 1987; Shaw et al., 1992).

It is also known that lip repair has a considerable influence on anteroposterior maxillary growth in patients with complete unilateral cleft lip and palate. Lip pressure generated after cheiloplasty causes a restriction in maxillary growth in patients with complete unilateral cleft lip, alveolus and palate, as well as in patients with unilateral cleft lip and alveolus (Normando et al., 1992; Silva et al., 1989).

Regarding the quality of the selected studies, all of them presented problems concerning sample representativeness, possibly due to the retrospective aspects. Studies that are retrospective and nonrandomized can generate a high risk of bias. However, this can be justified by ethical issues regarding the randomization of patients into certain groups, some of which could be deleterious (Bardach et al., 1984; Witzel et al., 1984; Noordhoff et al., 1987; Rorich et al., 1996; Lohmander-Agerskov et al., 1998; Lee & Liao, 2013). In addition, the quality of life of a child, and the family, is enhanced by surgical repair at a earlier age, in terms of functional, aesthetic, psychosocial, and speech issues (Nollet et al., 2008; Oberoi et al., 2008; Bichara et al., 2015).

It is possible to highlight problems with small sample size in some of the selected studies (Yamanishi et al., 2011; Zemann et al., 2011; Holland et al., 2007), who had representative samples, but no reports of sample size calculation or power analysis. The studies by Daskalogiannakis et al. (2006) and Bakri et al. (2014) presented problems regarding the sample dimensioning seemingly not being representative, in addition to not reporting on sample size calculation. In this systematic review, the studies by Daskalogiannakis et al. (2006) and Zemann et al. (2011) presented problems with control group evaluation, due to having samples obtained from two different centers.

Regarding the methodological soundness of the included articles, no study reported the performing of blinding among the examiners. Holland et al. (2007) showed failures in the quality of measures and results, due to the replicability performed with a level close to the limit, and in quality control, for not presenting calibration and/or inter- and intraexaminer agreement.

In relation to distortion influences observed in the papers included in this review, it is possible to highlight four studies that reported surgical repair of the palate among the groups evaluated at different times, and two studies that presented a comparison of groups originating from different centers, with surgeries performed by different surgeons.

A limitation of studies on optimal timing for surgery of the palate is the lack of a reference for what constitutes early or late surgery, due to the great diversity of existing surgical protocols. What some authors consider to be earlier surgery might be deemed later by others. Koberg and Koblin (1973) considered surgeries performed in the first year of the patient's life as early. In our review, hard palate surgery performed up to and including the 17th month after birth was considered as early and any from 18 months onwards as later. In the study conducted by Yamanishi et al. (2011), the group treated in two stages was considered early, with the age of hard palate surgery at 18 months, but according to the criteria used in our review, this group was considered as late.

The ideal timing for palate repair surgery, when early and late surgeries are compared, still requires more reliable scientific evidence. Controlled studies are still scarce, as well as primary studies focused on limiting confounding factors in assessing effects on maxillary growth.

5. Conclusion

The five studies included in this review showed diverse results that, therefore, are inconclusive. At this point, since a low level of evidence and high risk of bias were found, it is not possible to prove or rebut that postponing surgery of the hard palate will bring

benefits in terms of maxillary growth. Clinical studies with a more reliable scientific methodology are therefore necessary.

Ethical approval

Not applicable.

Conflicts of interest

The authors declare no conflicts of interest, and have no financial interests in any products, devices, or drugs mentioned in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.06.017.

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