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Impact of Palate Repair Timing on Speech Outcomes in Children with Cleft Palate: A Systematic Review

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Background: Obtaining successful speech outcomes is one of the primary treatment goals of cleft palate repair. Yet deciding the optimal time to perform surgery has not been well-defined amongst surgeons.

Methods: Four retrospective cohort studies and one RCT were assessed with the primary outcome being speech outcomes. We conducted a systematic search in the following databases: Pubmed, Scopus, Cochrane, and ScienceDirect. Quality of studies were assessed using the Cochrane Risk of Bias tool for retrospective cohort studies.

Results: From the literature search conducted, 179 articles were identified. Two reviewers independently screened titles and abstracts. Out of 179 articles, 16 were included for full text screen and review, 6 were then excluded because they had unsuitable study design and outcomes. With the remaining 10 studies, 5 were excluded because they did not meet our inclusion criteria. Four retrospective cohort studies and one randomized clinical trial were included in the final analysis.

Conclusion: This systematic review demonstrated evidence that late palatoplasty resulted in poorer speech outcomes (e.g. compensatory misarticulation, speech and language delays) in children with cleft palate.

Keywords: Cleft palate; speech; palate repair

INTRODUCTION

Orofacial clefts are one of the most common birth defects, which occur separately or apart of a syndrome.[1] It presents as an abnormal space in the upper lip, alveolus or the palate. Occurrence of isolated cleft palate varies between geographical location, with reported rates ranging from 1 to 25 per 10,000 live births.[2] In cleft palate, there are abnormal fusion between the palatal shelves of the maxillary processes leading to the formation of a cleft in either the hard palate, soft palate, or both.[3] This condition may lead to several issues, such as impairment in suckling resulting in failure to thrive, deafness, gross facial deformity, severe psychological problems, and speech impediment.[3] Therefore, patients with orofacial cleft deformities require timely and age-appropriate treatment to attain both functional and aesthetic well-being.[3]

The intricate relationship between the timing of palate repair and speech outcomes in children with cleft palate presents a complex clinical challenge. One of the primary treatment goals of cleft palate repair is obtaining successful speech outcomes. Yet deciding the optimal time to perform surgery in order to achieve the best speech outcomes have not been well-defined in the medical community. The timing of primary closure for cleft palate repair has been a subject of enduring debate among surgeons and within the medical community.[3]

This contentious issue has elicited varied viewpoints, each supported by a plethora of arguments. Early intervention is advocated by some surgeons to mitigate the potential negative effects of cleft palate on speech development.[3] As speech is a skill acquired through learning, some evidence argues that with an intact anatomical structure, the more advantageous it is for the development of speech.[4] Meanwhile others who advocate for delayed closure procedures, argue that early surgical intervention negatively impacts maxillary development, consequently affecting facial aesthetics and occlusal relationships. Concerns regarding safety, particularly surrounding airway obstruction and anesthesia, are significant factors why some surgeons refrain from performing repairs in younger infants.[4]

Timing of palate repair to achieve optimal speech with minimal facial growth disturbance has been one of the more debated topics in the medical community. It has now been well accepted that speech outcomes are better when soft and hard palate repair is completed prior to speech development. Palate surgery is therefore timed according to a patient's speech development, rather than their chronological age. For most children, this is around 9 to 12 months. Some studies associate late palatoplasty with an increased odds of speech/language delays.[5] While others found no difference in postoperative speech outcome parameters between early and late palatoplasty groups.[6] Therefore, the present study aims to assess the impact of cleft palate repair timing on speech outcomes.

MATERIALS AND METHODS

The procedures for this review were informed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines

(Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009; see Supplemental Material S1 for the PRISMA checklist). This systematic review did not require patient consent or Research Ethics Committee approval.

Search strategy

We identified relevant studies according to the PRISMA Guidelines through electronic searches of Pubmed, Cochrane, Scopus and ScienceDirect. We limited the search to peer-reviewed articles, published in English, and included human participants. The search term used was formed using the PICO framework: a) Population: Children with cleft palate, b) Intervention: Timing of palate repair, c) Comparison: Different timing approaches for palate repair (early vs delayed), d) Outcome: Speech outcomes (e.g. speech intelligibility, articulation, resonance). The search string entered into the search engine was ("cleft palate" OR "palatoplasty") AND ("timing of palate repair" OR "timing of surgery") AND ("early" OR "delayed") AND ("speech outcomes" OR "speech intelligibility" OR "articulation" OR "resonance").

Inclusion and Exclusion Criteria

Literature search was followed by a screening process based on the predetermined inclusion and exclusion criteria. Original studies on timing of palate repair in children with cleft palate within the last 10 years were included. The inclusion criteria for this systematic review were as follows: a) subjects were children with cleft palate, b) studies comparing the timing of palate repair, c) studies reporting at least one quantitative speech outcome measure such as speech intelligibility, articulation, resonance, or other related measures. Studies were excluded if they were not in English, full text articles were not retrievable, were commentaries, letters/correspondences, unpublished manuscripts, reports, dissertations, and theses. In addition to the electronic search, we reviewed the titles and abstracts from studies identified by manually combing through reference lists from relevant literature reviews and included primary studies. From this, we were able to identify additional studies for potential inclusion

Quality Assessment

We evaluated the quality of the included studies based on their respective study designs. We used the Cochrane Risk of Bias (RoB) 2.0 for trial studies and the JBI Critical Appraisal Checklist for retrospective cohort studies.[7,8] In RoB 2.0, the quality of included studies was assessed according to five appraisal elements: randomization process, discrepancies from the planned interventions, data lost, parameters to be measured, and the results chosen to be published. Studies are scored as low risk, some concerns, and high risk according to the corresponding categories. Meanwhile, in JBI Critical Appraisal Checklist, the quality assessment items consist of the similarity of population; validity of exposure, confounding factors, measurements of the outcome, follow-up, and statistical analysis. Authorities next consider the studies if they have been included or excluded and identify more data if needed.[8]

Data Extraction

All reviewers independently screened all of the titles from the search and excluded studies that were irrelevant. Following this, all the reviewers independently screened the titles and abstracts using an eligibility checklist. Potentially eligible texts then went through full-text review and retrieved for final selection. Any discrepancies in the extracted data were discussed by all reviewers. The following data were extracted: (1) general information (author, title, year of publication); (2) study characteristics (study design, number of samples); (3) intervention and setting (timing of palate repair surgery); (4) outcome data (speech outcomes, assessed using a combination of nasometric assessment and Universal Parameters guidelines which assesses hypernasality using four-point scale).

RESULTS

Study selection and included studies' characteristics

The flowchart for the study selection can be seen in Figure 1. The initial literature search yielded 179 results. One article was identified through manual searching from the literature yielded from the initial search. Two reviewers independently screened titles and abstracts. Out of 179 articles, 16 were included for full-text screen and review, 6 were then excluded because they had unsuitable study design and outcomes. With the remaining 10 studies, 5 were excluded because they did not meet our inclusion criteria. Five studies were included in the final analysis. The included studies were retrospective cohort studies conducted in Turkey, Iran, and the United States, and one multicenter randomized clinical trial with a total of 1.089 participants. Timing of speech assessment varies between studies ranging from 6 months up until 5 years after palatoplasty surgery. Evaluation of speech outcome also displayed variation. Two studies measured hypernasality and compensatory misarticulation in postoperative patients. One study focused on nasometric and nasopharyngoscopy measurements, while the other two studies concentrated on assessing speech development, language delays based on language milestones, and articulation errors.

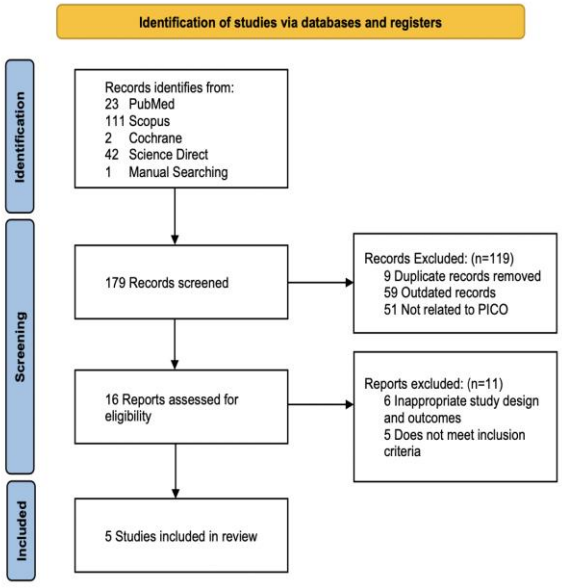

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart on the literature search and screening

RoB Assessment

RoB assessment was conducted through JBI Critical Appraisal Tool for nonrandomized studies and Cochrane RoB 2.0 for randomized studies. Results can be seen in supplementary materials. One randomized study assessed showed a low risk of bias. While with the JBI tool, research population, exposure measurement, process of recruitment, outcome measurement, follow-up period, and statistical analysis was deemed to be clear in four other non-randomized studies, and therefore were eligible for inclusion.

Timing of Surgery

Kara et al. conducted a study comprising 90 patients, segmented into three distinct cohorts based on the timing of surgical intervention for cleft palate repair. Group 1 underwent surgery before reaching 12 months of age; group 2 between 12 and 18 months, and group 3 after 18 months of age.[9] Similarly, Shaffer et al. conducted a study with 232 cleft palate patients who were also segmented into three different cohorts with different timings of surgery – the first group undergoing the surgery before they were 11 months old, the standard group undergoing surgery when they were 11 - 13 months old, and the late group undergoing surgery after they turn 13 months old.[5]

In a separate study, Rezaei P et al. observed and analyzed 180 patients, comprising 102 males and 78 females, which were then divided into two groups with different surgery timing. The 'early' group underwent surgery before they were 13 months old, while the 'late' group underwent surgery after they were 13 months old.[10] In a similar manner, Ettinger et al. conducted a study which observed 29 patients with either isolated submucous cleft palate or syndromic diagnosis, dividing them into two groups, with the first group having the surgery before they were 4 years old, and the latter after they were 4 years old.[6] While a randomized clinical study by Gamble et al split children with cleft palate into two, where the first group went palatoplasty surgery at 6 months old, and the other at 12 months old.[3]

Assessment of Speech Outcomes

Data synthesized of the studies are summarized in Table 2. Measurement of speech outcomes were carried out through assessment of various parameters. Razaei et al found a significantly higher percentage of children producing compensatory misarticulation (CMA) in the late surgery group at 78.9% compared to 63.3% in the early surgery group (P=0.021).[10] The same research group also found a higher percentage of moderate-severe hypernasality in the late surgery group, yet there were no significant difference in the presence of hypernasality in both early and late surgery group post palatoplasty, which stood at 82.6% and 85.5% respectively (P= 0.086).[10] With regards to hypernasality, Ettinger et al. also found similar results where both early and late operative groups showed improvement in mean universal parameters of speech (UPS) hypernasality rating scores following Furlow palatoplasty, however both cohorts demonstrated similar trends. In addition, objective nasometry scores were also measured 6 months after surgery and no significant difference between study groups was present (P=0.12).[6] On the contrary, Kara et al carried out nasometric measurements at 4-6 years of age or at least 1 year post surgery for those with delayed palatal repair and found a significant difference in nasalance nasometry scores in children with late palatal closure (Group 3) when compared with results from children in group 1 and 2 with the the highest nasalance scores found in Group 3.[9]

The other two studies, one by Shaffer et al and the other by Gamble et al had different results. Gamble et al found no difference in articulation status at 3 and 5 years of age in both early and late palatoplasty groups, whilst Shaffer et al found that at 20 months speech evaluation post palatal repair, late palatoplasty was associated with increased odds of speech or language delays compared with early (OR: 8.48, 95% CI: 1.89-38.1; P=0.005) or standard palatoplasty (OR: 3.26, 95% CI: 1.44-4.35; P=0 .005).[3] Meanwhile, at 5 year post palatal repair speech evaluation, language delays were more commonly found in those with late palatoplasty compared with standard palatoplasty (OR: 6.38, 95% CI: 1.07- 38.0; P=0.042).[5]

DISCUSSIONS

Albeit the studies that have been performed to determine the timing for cleft palate repair for the most optimal speech outcomes, this topic remains controversial in various literature.

The three retrospective cohort studies and one RCT included in this systematic review found that poorer speech outcomes were observed in cleft palate patients who had undergone palatoplasty at a later age, albeit using different ways of outcome measurement. One retrospective cohort study reported there were no

significant differences in speech outcomes in their study.

Kara et al. found nasalance scores (hypernasality assessed based on the Universal Parameters for reporting speech outcomes in cleft palate patients) were highest in group 3, which was the group who underwent palatoplasty at an age later than 18 months old.[9] This was supported by the findings in the research conducted by Rezai P et al, who also found a higher percentage of moderate-severe hypernasality in the late surgery group. The same research group also found that those who had palatoplasty at a later age had a higher percentage of compensatory misarticulation (CMA).[10]

Shaffer et al also reported a similar finding, in which their research reported that late palatoplasty was associated with increased odds of speech or language delays compared with early palatoplasty.[10] Gamble et al also reported that there were more canonical babbling present at a greater percentage of children who had the surgery at 6 months old rather than 12 months old, suggesting that speech development was better amongst the population who had earlier palatal repair.[3] The present findings agree with previous studies which found associations between later palatoplasty and speech therapy utilization in toddlers with cleft palate, also studies which found associations between the presence of hypernasality and significantly lower language skills and intelligibility which may be a clinically valuable indicators for a higher likelihood for delays in language and reading skills.[10]

Many studies performed prior to the 2000s also agree with the findings from this present study. These studies suggested that performing the surgery earlier was associated with better speech. Early surgery is associated with better articulation, less compensatory articulation, more normal resonance, and the result is known to require less secondary surgery.[11] Kaplan et al also reported that cleft palate patients in their early surgery group had more normal onset of babbling and speech and language acquisition compared to those in the late surgery group.[12]

Better speech outcomes seen in children who had earlier palatoplasty could be attributable to the fact that the palate repair enables the child to develop speech patterns in a more typical anatomical structure, therefore aiding the natural speech processes development.[10]

Palate repair surgery fixes the opening in the palate, leading to improved function of the velopharyngeal valve, a valve that separates the oral and nasal cavities during speech. A properly functioning velopharyngeal valve is essential for producing sounds without excessive nasal resonance. Early repair ensures that this function develops well avoiding problems with clarity of speech. Previous studies indicated that speech developed before the age of 18 to 24 months, with consonant-vowel sequence emerging between 6 to 9 months of age. Therefore, misarticulations and language development problems can be traced to the chronology of cleft palate treatment and intervention.[13]

Research on this topic predates back until the year 1931, during which Veau was the first author who reported the positive outcomes of performing an early palatal repair on speech outcomes. He found that cleft palate patients who had undergone surgery before they were 12 months old had better quality of speech compared to those who did the surgery between the ages of 2 to 4 years.[14] During the 1970s, Kaplan et al performed two studies which also looked into this – Kaplan proposed the time of palatal repair as 3 to 6 months of age based on the fact that the VPU should be functional by the time the patient is 9 to 12 months old for the production of their first syllables.[12]

Contrary to the findings stated previously, Ettinger et al reported different results, where both early and late operative groups showed improvement in mean universal parameters of speech (UPS) hypernasality rating scores following Furlow palatoplasty, and there were no significant difference with regards to objective nasometry scores between the two study groups. However, they did not advocate for performing the palate repair at a much later age than the recommended age. There are, however, other researchers who did not support the concept of performing palatal repair 'earlier'. This is due to a variety of reasons. Dorf and Peterzon reported that patients who had surgery before they were 12 months old had higher compensatory articulation rates.[11] In addition to that, other opponents of performing 'early' surgery have argued that said surgery could have deleterious effects on midfacial growth.

One of the many limitations of studies on this topic is the lack of consensus on what constitutes 'early' surgery. To this day, this remains a topic of debate. However, since the research performed by Dorf and Curtin in 1982 and by Rohrich et al in 2000, it is widely accepted that palatal repair should be performed before 12 months or 18 months. (Dorf Curtin 1982, Rohrich et al 2000). The American Cleft Palate Craniofacial Association also recommends performing palatoplasty before 18 months of age. (American Cleft Palate Craniofacial Association, 2018), regardless of the technique. It is believed that said period of time is best because speech is learned best during the first two years of life (Webster and Webster, 1977; Kuhl and Meltzoff, 1996).

It should also be accounted for that the development of speech is a multifactorial process, and proper palatal repair is only one of said contributing factors. Other variables which could have an impact on speech outcomes in patients include patient's intelligence, socioeconomic status of the family, cleft width and length, developmental delays, hearing loss and other social variables.[9-11]

Strength and Limitations

This systematic review has several strengths. To our knowledge, this study is the most recent, and the first to review the impact of palate repair timing on speech outcomes in children with cleft palate. In

addition to that, the studies included in this systematic review had low risk of bias, and were done in a variety of study locations.

However, it also has several limitations, including the lack of consensus on what constitutes an 'early' or 'late' surgery. The studies assessed in this systematic review each had different groups of children with cleft palates with different timing of surgery, so comparisons were not precisely apple-to-apple.

CONCLUSION

This systematic review demonstrated evidence that performing palatoplasty at a later age resulted in poorer speech outcomes (e.g. compensatory misarticulation, speech and language delays) in children with cleft palate.

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TABLES FOOTNOTES & CAPTIONS

Table 1. Characteristics of included studies.

Author, Year	Study Population	Study Design	Study Location; Settings	N samples included	Timing of speech assessment	Speech Outcomes Assessment Parameters
Kara et al (2020)[9]	Children with unilateral complete cleft lip and palate (UCCLP) that underwent Bardach's two-flap palatoplasty with intravelar veloplasty.	Retrospective cohort study	Turkey; Hospital	90 patients (46 males; 44 females)	4-6 years of age or at least 1 year post surgery for those with delayed palatal repair.	Nasometric Evaluation
Shaffer et al (2019)[5]	Children with cleft palate (with or without cleft lip) born between April 2005 and April 2015 listed in medical records of the Cleft Craniofacial Clinic of a tertiary care children's hospital that underwent straight line or Furlow palatoplasty.	Retrospective cohort study	USA; hospital	232 patients	24 months and 5 years post surgery	Speech or language delays and disorders
Rezaei et al (2022)[10]	Children with cleft palate listed in medical records of the Isfahan Cleft Care Team (ICCT) between 2011-2015.	Retrospective cohort study	Iran; Hospital	180 patients		Hypernasality, Compensatory misarticulation (CMA), Nasal emission and nasal turbulence
Ettinger et al (2018)[6]	Children with submucous cleft palate with either operative (primary palate repair with Furlow palatoplasty) or nonoperative treatment.	Retrospective cohort study	USA; Hospital	29 patients	6 months after surgery	Hypernasality, Nasometry scores

Gamble et al (2023)[3]	Children with nonsyndromic isolated cleft palates which underwent Sommerlad technique palatoplasty.	Randomized clinical trial	United Kingdom, Denmark, Norway, Sweden and Brazil; Hospital	558 patients	1,3, and 5 years of age	Speech development and articulation errors

Table 2. Outcome of included studies.

Author, Year	N Included Samples (Gender)	Timing of Surgery			Speech Outcomes
		Group 1	Group 2	Group 3	
Kara et al (2020)[9]	90 patients (46 males; 44 females)	< 12 months	12 - 18 months	> 18 months	**Nasometry results:** Highest nasalance scores were recorded in late palatoplasty group (group 3) in all syllables and counting scores There was no significant relationship between group 1 and group 2, there was a statistically significant difference between these two groups compared to group 3.
Shaffer et al (2019)[5]	232 patients	< 11 months	11 - 13 months	> 13 months	**Speech or language delays:** At 20 months speech evaluation, late palatoplasty was associated with increased odds of speech/language delays compared with early (OR: 8.48, 95% CI: 1.89-38.1; P=0.005) or standard palatoplasty (OR: 3.26, 95% CI: 1.44-4.35; P=0 .005). At 5 year speech evaluation, language delays (but not SSPD, speech therapy, or ONF) were more commonly found in those with late palatoplasty compared with standard (OR: 6.38, 95% CI: 1.07-38.0; P=0.042).
Rezaei et al (2022)[10]	180 patients (102 males; 78 females)	< 13 months	> 13 months	N/A	**Hypernasality:** Higher percentage of hypernasality in late surgery group (85.2%) compared to early surgery group (82.6%) with no significant difference between the two (*P= 0.086).*

					Compensatory misarticulation: Significantly higher percentage of children producing CMA in the late surgery group 78.9% compared to early surgery group (63.3%); *P=0.021.*
Ettinger et al (2018)[6]	29 patients (18 males; 11 females)	< 4 years	> 4 years	N/A	**Hypernasality:** Both the early and late operative groups demonstrated improvement in mean UPS hypernasality rating scores following Furlow palatoplasty. **Nasometry:** No significant difference between postoperative nasometry scores between early and late operative groups (P=0.12).
Gamble et al (2023)[3]	558 patients (225 Males, 331 females, 2 not recorded)	6 months	12 months	N/A	**Speech development and articulation errors:** At the age of 1 year, a higher proportion of children in the 6-month (early palatoplasty) group exhibited canonical babbling compared to those in the 12-month (late palatoplasty) group, with a difference of 20.7 percentage points. No significant distinctions between the groups were observed in speech development.

APPENDIX

1.1 JBI Assessment Checklist for Nonrandomized Studies

Retrospective cohort; Kara et al[9]

Signaling Questions	Yes	No	Unclear	Not applicable
Were the two groups similar and recruited from the same population?	Yes			
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes			
Was the exposure measured in a valid and reliable way?	Yes			
Were confounding factors identified?	Yes			
Were strategies to deal with confounding factors stated?	Yes			
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes			
Were the outcomes measured in a valid and reliable way?	Yes			
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes			
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes			
Were strategies to address incomplete follow up utilized?			Unclear	
Was appropriate statistical analysis used?	Yes			
Overall appraisal:	Include			

Retrospective cohort; Ettinger et al[6]

Signaling Questions	Yes	No	Unclear	Not applicable
Were the two groups similar and recruited from the same population?	Yes			

Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes			
Was the exposure measured in a valid and reliable way?	Yes			
Were confounding factors identified?	Yes			
Were strategies to deal with confounding factors stated?	Yes			
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes			
Were the outcomes measured in a valid and reliable way?	Yes			
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes			
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes			
Were strategies to address incomplete follow up utilized?			Unclear	
Was appropriate statistical analysis used?	Yes			
Overall appraisal:	Include			

Retrospective cohort; Shaffer et al[5]

Signaling Questions	Yes	No	Unclear	Not applicable
Were the two groups similar and recruited from the same population?	Yes			
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes			
Was the exposure measured in a valid and reliable way?	Yes			
Were confounding factors identified?	Yes			
Were strategies to deal with confounding factors stated?	Yes			

Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes			
Were the outcomes measured in a valid and reliable way?	Yes			
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes			
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?			Unclear	
Were strategies to address incomplete follow up utilized?			Unclear	
Was appropriate statistical analysis used?	Yes			
Overall appraisal:	Include			

Retrospective cohort; Rezaei et al[10]

Signaling Questions	**Yes**	**No**	**Unclear**	**Not applicable**
Were the two groups similar and recruited from the same population?	Yes			
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes			
Was the exposure measured in a valid and reliable way?	Yes			
Were confounding factors identified?	Yes			
Were strategies to deal with confounding factors stated?	Yes			
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?			Unclear	
Were the outcomes measured in a valid and reliable way?	Yes			
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes			
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?			Unclear	

Were strategies to address incomplete follow up utilized?			Unclear	
Was appropriate statistical analysis used?	Yes			
Overall appraisal:	Include			

1.2 Cochrane Risk of Bias (RoB) Assessment for Randomized Study

Randomized Clinical Trial; Gamble et al[3]

Signalling Questions	Description	Response Option
Bias due to confounding		
Is there potential for confounding of the effect of intervention in this study?	Author have addressed possible confounding factors on the study and try to control it during participants selection	Possibly No
Questions relating to baseline confounding only		
Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Adjustment of confounding factors were analysed through regression	Yes
Questions relating to baseline and time-varying confounding		
Did the authors control for any post-intervention variables that could have been affected by the intervention?	Author did not mention any post intervention variable control	No
Risk of bias judgement	**Low risk of bias**	

Signalling Questions	Description	Response Option
Bias in selection of participants into the study		
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Selection of participants was performed before the intervention was performed.	No
Do start of follow-up and start of intervention coincide for most participants?	Yes, all participants were assessed at 1,3 and 5 years after the intervention	Yes
Risk of bias judgement	**Low risk of bias**	

Signalling Questions	Description	Response Option

Bias in classification of interventions		
Were intervention groups clearly defined?	The intervention group was well defined.Its divided into palatoplasty at 6 months and 12 months	Yes
Was the information used to define intervention groups recorded at the start of the intervention?	Yes, Author explained inclusion and exclusion criteria well. Participants included patients with isolated cleft palates, considered to be medically fit to undergo surgery at 6 months of age, corrected for gestational age, and had one parent or caregiver who was a native speaker of the language (Brazilian, Portuguese, Danish, English, Norwegian, or Swedish).	Yes
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No, it would not be affected	No
Risk of bias judgement	**Low risk of bias**	

Signalling Questions	Description	Response Option
Bias due to deviations from intended interventions		
Were there deviations from the intended intervention beyond what would be expected in usual practice?	There were no deviation or events in which intervention and comparator group deviates from their assigned intervention	No
Risk of bias judgement	**Low risk of bias**	

Signalling Questions	Description	Response Option
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	No, there were some participants with no outcome data	No
5.2 Were participants excluded due to missing data on intervention status?	No participants were not excluded on missing data	No
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No participants were not excluded on missing data	No
Risk of bias judgement	Low risk of bias	

Signalling Questions	Description	Response Option
Bias in measurement of outcomes		
Could the outcome measure have been influenced by knowledge of the intervention received?	Outcomes were measured with a standardized measurement	Possibly No
Were outcome assessors aware of the intervention received by study participants?	Yes assessors are aware of the intervention received	Yes
Were the methods of outcome assessment comparable across intervention groups?	Outcomes were detected equally between intervention groups. With the same definition	Yes
Were any systematic errors in measurement of the outcome related to intervention received?	Since the outcome was well defined, no systematic error were found in measurement of outcomes	Possibly No
Risk of bias judgement	**Low risk of bias**	

Signalling Questions	Description	Response Option
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
multiple outcome *measurements* within the outcome domain?	No multiple measurements were made on an outcome	No
multiple *analyses* of the intervention-outcome relationship?	No multiple multiple analyses of the intervention-outcome relationship were made	No
different subgroups?	The author generated multiple effect estimate for different subgroup however it does not omit the whole proportion of the original cohort	Possibly No
Risk of bias judgement	**Low risk of Bias**	

Overall Bias		
Risk of bias judgement	**Low Risk of Bias**	