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Incidence of Obstructive Sleep Apnea in Non-Syndromic Children Operated with Primary Palatoplasty- A Systematic Review

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Background: Children with cleft palate have both structural and functional anomalies in the upper airway. Several primary palatoplasty techniques exist, such as the two-flap palatoplasty, a straight-line repair, and the double-opposing Z-plasty. Although these changes may worsen upper airway obstruction, thereby inducing or worsening OSA, definitive data pertaining to the true impact of primary palatoplasty on OSA are limited. Materials and Methods: The search was performed in various electronic databases using the search items alone. Data Bases of PubMed, Google scholar, Cochrane and Web of Science were searched for the related topics till December 2022. Only Randomized Control Trials were included. The studies were assessed for eligibility according to inclusion criteria by two independent reviewers. Results: All the studies included were based on the data extraction and analysis of the studies for quality. According to Prado et al, palatoplasty did not cause evident signs of OSA in the sample of children with cleft palate analyzed. Conclusion: The high prevalence of snoring observed in the long term indicate that children with a palatal cleft who undergo surgical repair are at risk for OSA. Future studies should analyze the occurrence of apnea by poly- somnography, which is the gold standard for the diagnosis of sleep breathing disorders.

Keywords: Cleft Palate, Palatoplasty, Obstructive Sleep Apnea.

1. Introduction

Cleft lip and palate (CLP) is the most common congenital craniofacial malformation, occurring in 1:700 births. The clinical manifestations are diverse and may involve, individually or in combination, the upper lip, the alveolar process, and the palate, in different extensions and amplitudes. The literature suggests that the anatomical changes that occur due to the presence of the cleft per se, or as a consequence of the surgeries performed during the

rehabilitation process, lead to reduced upper airway dimensions and, consequently, to a greater risk of sleep-disordered breathing, including obstructive sleep apnea (OSA). Children with craniofacial conditions, such as micrognathia and cleft lip/palate, have been identified as a heterogeneous group at high risk for obstructive sleep apnea (OSA). The mechanism of OSA in children with isolated cleft palate ± cleft lip (ICP) is less clear, but could be due to smaller maxillary and mandibular dimensions. Additionally, changes in the upper airway structure could alter upper airway muscle length-tension relationships due to changes in muscle insertion. In some patients with cleft lip, nasal deformities may also contribute to upper airway obstruction.

Sleep-disordered breathing is on a continuum, with snoring at one end and obstructive sleep apnea at the other, leading to fragmentation of sleep, cardiovascular, and neurocognitive disorders. Apnea (or even hypopnea) is caused by recurrent pharyngeal collapse during sleep, as a result of loss of neuro- muscular compensation, which ensures airway patency in normal conditions (Katz and D'Ambrosio, 2008), or in the presence of congenital skeletal malformations of the upper airway, which reduce internal dimensions (MacLean et al., 2009b). In children with cleft palate, these malformations are observed 5 times more frequently than in children without clefts.

AIM

The aim of this systematic review is to analyse the incidence of obstructive sleep apnea in non-syndromic children operated with primary palatoplasty. By systematically reviewing and analyzing the existing literature on this topic, the review can provide valuable insights into the treatment protocols of primary palatoplasty and its influence on long term sleep disordered breathing.

STRUCTURED QUESTION

Does cleft palate repair procedure increase the risk of obstructive sleep apnea in non syndromic cleft palate children?

NULL HYPOTHESIS

There is no increased incidence of obstructive sleep apnea after primary palatoplasty in non syndromic patients with cleft palate.

2. MATERIALS AND METHODS

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Prior to the start of the review, the methodology was developed based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

PICOS Analysis

Population: Non syndromic children with cleft palate

Intervention: Primary Palatoplasty

Comparison: Airway space

Outcome: Obstructive sleep apnea

Study Design: Randomised controls trials and clinical trials

SEARCH STRATEGY AND ELIGIBILITY

The Data Bases of PubMed, Google scholar, Cochrane and Web of Science were searched for the related topics till December 2022. Articles were selected based on the inclusion criteria, which included all RCTs.

Articles describing Randomized Control Trials (RCTs), clinical trials, were included in this systematic review, while narrative, systematic review, animal studies, and studies published in languages other than English were excluded from this systematic review. The studies were assessed for eligibility according to inclusion criteria by two independent reviewers.

SCREENING AND SELECTION

Two reviewers independently screened the gathered papers, and their level of agreement in terms of making decisions was assessed with a value of 0.81, demonstrating improved agreement between the two reviews. After gathering all the information from the computer search, a screening was conducted, and articles that did not fit our inclusion and exclusion criteria as outlined in the four phases below were deleted. Step 1 involved eliminating publications and citations that were not relevant. One reviewer completed stage 2 by reading the titles and abstracts of all the acquired studies and selecting only those that were pertinent. Every story that lacked statistics and facts was instantly disqualified from our examination. The complete article was received and cross-checked with the second examiner for its consideration in the event that there was any remaining uncertainty.

In order to determine if the articles that were first reviewed in Stage 1 indeed contained information relevant to our review, both examiners double-checked them in Stage 3. Care was made to weed out any unfinished or publications with scant data during this phase. The uncited articles were also taken out.

The publications gathered in Stage 3 were carefully examined, and Stage 4 focused on the research that matched our PICOS data. In our review, certain articles were eliminated.

DATA EXTRACTION

The required data for our review were obtained from the final articles by the first reviewer which was then re-evaluated by the second reviewer. They were tabulated and the data were collected according to the headings as characteristics table and summation table.

- Author,
- year of publication,
- place of study,
- study design,
- Age
- total sample size,

- intervention group,
- control group,
- type of outcome,
- method of outcome assessment,
- Posterior Airway space
- oAHI
- Respiratory Distress index
- author conclusions.

VARIABLE OF INTEREST

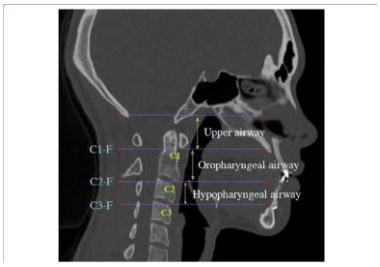
- Posterior Airway Space
- oAHI
- Respiratory Distress Index

	Mild	Moderate	Severe
OI	$4 \leq OI < 8$	$8 \leq OI < 16$	$OI \geq 16$
OSI	$5 \leq OSI < 7.5$	$7.5 \leq OSI < 12.3$	≥ 12.3

OI - oxygenation index, based on the formula: MAP x FiO_2/PaO_2; OSI - oxygen saturation index based on the formula: MAP x $FiO_2/SatO_2$. When $SatO_2$ was used as a criterion for the diagnosis of pARDS, oxygen therapy should be titrated to achieve $SaO_2 \leq 97\%$ for the OSI calculation. In patients undergoing non-invasive ventilation, there is currently no means to stratify the severity of pARDS, which is defined in these cases by an $OI \leq 300$ or $OSI \leq 264$.

AHI score	Description
Mild	AHI score between 5 and 15 events per hour
Moderate	AHI score between 15 and 30 events per hour
Severe	AHI score greater than 30 events per hour

Apnea hypopnea index score [13].



RISK OF BIAS

Risk of Bias was assessed using the RoB 2.0 tool and ROBINS I tool. The risk of bias parameters for each included study were evaluated by two authors. The risk of bias in was assessed according to the description given for the following parameters: random sequence generation; single-operator protocol implementation; the presence of a control group; blinding of the testing machine operator; standardization of the sample preparation; failure mode evaluation; use of the materials following manufacturer's instructions; clarification of the sample size calculation. If the examined parameter was reported by the author, the study received a "YES". On the other hand, if the information was missing, the parameter received a "NO." Risk of bias from each study was classified according to the sum of the "YES"

answers received: 1 to 3 corresponded to a high, 4 to 6 medium, and 7 to 8 to a low risk of bias. The quality of the articles selected were reviewed by two authors and the assessment was in accordance with CONSORT guidelines.

SUMMARY SYNTHESIS

Consequently, we provided a narrative synthesis of the findings, summarizing the key results of each study and identifying any patterns or trends that emerged. Although we were not able to perform a meta-analysis, our narrative synthesis provided a qualitative summary of the available evidence, allowing us to draw meaningful conclusions and inform clinical practice.

3. RESULTS

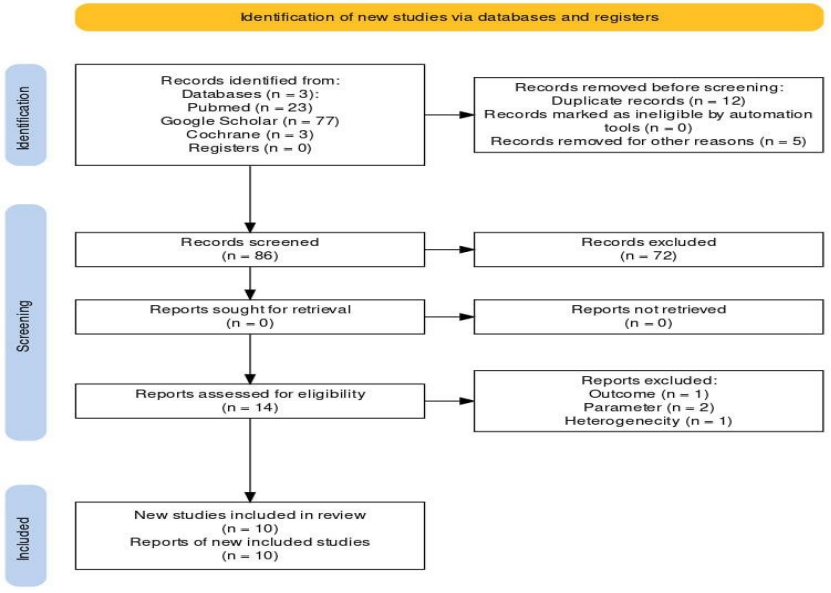
SEARCH RESULTS

A total of 106 articles were obtained from electronic databases and manual search. 12 duplicates were removed and 5 articles were removed due to the incomplete data. 86 records were taken up for the screening process followed by 14 articles selected for assessment. After final screening process, 10 articles were included in this study.

CHARACTERISTICS TABLE

Out of the 10 included articles, 5 studies were retrospective and 5 were prospective studies. All studies included, used the same parameters to describe signs of obstructive sleep apnea. A total of 562 patients were assessed in all these studies with the use of polysomnography as the gold standard of diagnosis. Madrid et al has also used pharayngoplasty as one of the surgical procedure for the treatment of primary cleft palate. All these studies have observed high snoring and disordered breathing as one the common post operative compliaction.

PRISMA FLOWCHART



SUMMARY OF STUDIES INCLUDED

Sr No.	Author and Year	Study Design and Sample Size	Age	Method of evaluation	Mean Value	Outcomes
1.	Campos et al, 2019	Prospective clinical trial N= 21	20-29 years	Polysomnography, AHI Index	Pharyngeal space Non OSA – 145±84 mm^2 OSA - 94±19mm^2	6 patients (29%) presented with OSA
2.	Liao et al, 2002	Prospective trial N= 10	Mean age 5.1 years	Polysomnography	RDI before surgery – 0.4±0.4/hr RDI 1 week after surgery 1.8±0.5/hr	High incidence of mild OSA during early postoperative period. Resolved in 80% ptients 3 months post operatively.
3.	Cielo et al, 2016	Prospective Cohort Study Infants with ICP=15 Micrognathia = 19 Controls = 9	Less than 6 months age	Polysomnograms, Neurodevelopmental testing Cephalometrics.	AHI: -Micrognathia : 20.1 events/hr ICP: 3.2/hr Controls: 3.1/hr	Cephalometric measurements correlated with OSA severity. Neurodevelopment was similar. Micrognathia was associated with OSA compared to controls.
4.	Bergeron et al, 2019	Retrospective case control study. N= 64	Means age 2±2.8 years	Pre surgical and Post surgical Polysomnography .	oAHI: Before surgery – 3.4±3.9 events/hr Post surgery – 5.9±14.5/hr 34.4% had worsening of more than 1 OSA events/hr. And 18.9% had worsening of 5 or more events/hr.	OSA did not develop or worsen following primary palatoplasty. Presence of syndrome is a factor of worsening OSA after palatoplasty.
5.	Rose et al, 2001	Randomised Controlled trial N=43	Mean age : 12.1±3.8 years	Respiratory disturbance index. Apnea index. Mean Oxygen saturation. Minimal oxygen saturation. Desaturation index. Snoring index.	RDI: 2.44±1.29 AI: 0.23±0.21 Mean oxygen saturation: 96.1±0.9 Minimal Oxygen Saturation: 86.4±5.4 Desaturation index: 0.7±0.48 Snoring Index: 3.04±1.19	Cleft palate patients had higher respiratory disturbance index and snoring index. Cleft palate patients having undergone primary closure demonstrate symptoms of nocturnal upper airway obstruction.
6.	Madrid et al, 2010.	Observational cohort study N= 20	Mean age: 15 years	Polysomnography AHI Index	AHI: Pharyngoplasty group: 12.7 Palatoplasty group: 1.35	More incidence of OSA in pharyngoplasty group than palatoplasty group.
7.	MacLean et al, 2008	Cross sectional study N=248	Mean age: 33.4 months	Composite Sleep ad Breathing Research Questionnaire	OSA was present in 31.4%	Pre school children with cleft lip or palate have a risk of OSA 5 times more than that of children without cleft.
8.	Prado et al, 2018	Prospective clinical trial N= 56	Cleft lip: 5 months Cleft palate: 14 months	-Difficuly of breathing -Apnea events -Snoring during sleep		Surgical closure of palate has an obstructive effect on upper airway in short term causing OSA related symptoms. High prevalence of snoring is still observed in long term.

9.	Rose et al, 2002	Cohort study N=53	12.3±3.7 years	Cephalometric analysis AP dimension of pharynx	RDI: -Cleft :2.44 -Non cleft: 0.8 Desaturation index: -Cleft:0.7 -Non Cleft:0.32	Patients with cleft palate had a significant narrow A-P dimension of pharynx , a more downward hyoid position and a longer uvula.
10.	Maclean et al, 2007	Retrospective trial N=62	8 months	Age, gender, syndrome diagnosis, cleft classification and surgical status.	Sleep disordered breathing in 87% children and 28% had severe symptoms.	Children with cleft palate appear to have a significant risk for sleep disordered breathing.

RISK OF BIAS ASSESSMENT

Out of the 10 selected studies, 7 studies had a low risk of bias and 2 studies showed bias in the randomisation process.

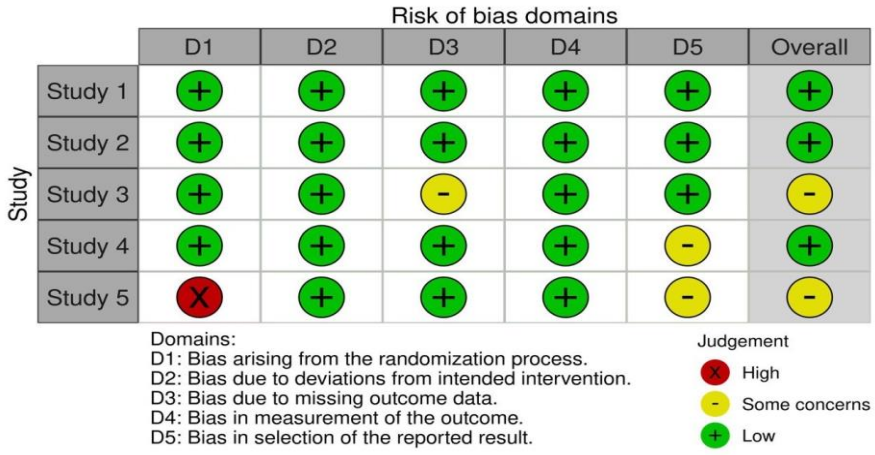


Figure 5 - Risk of Bias Summary

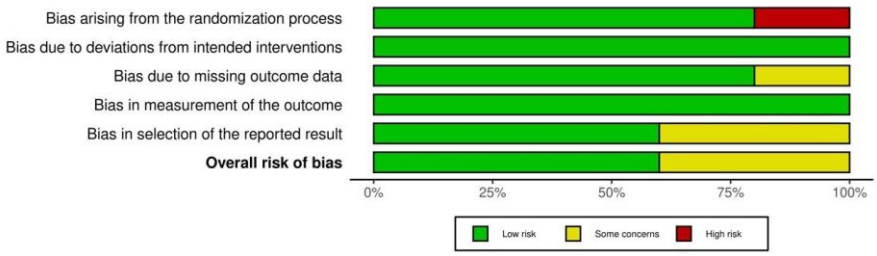


Figure 6 - Risk of Bias Graph

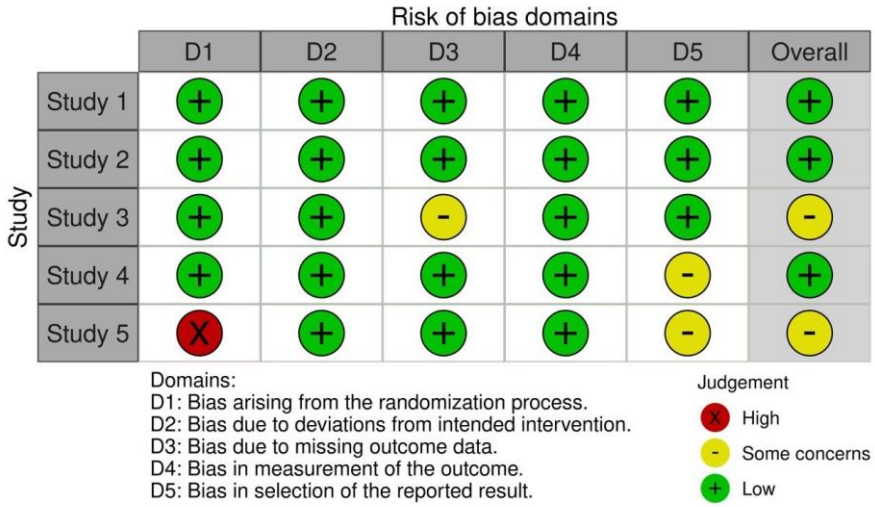


Figure 7 - Risk of Bias Summary

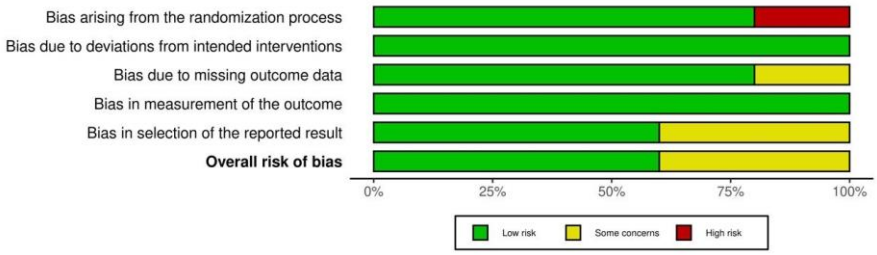


Figure 8 - Risk of Bias Graph

OUTCOME

According to the selected studies, a total of 562 patients were included and the observed desaturation index was only 0.7, and according to Prado et al, only 28% of patients showed severe symptoms of snoring but did not cause evident signs of obstructive sleep apnea. The mean oxygen saturation did not drop more than 96%, and the mean snoring index was 3.04±1.09.

Meta-analysis is a commonly used statistical technique to combine the results of multiple studies in a systematic review, providing a more accurate estimate of the overall effect. However, the ability to perform a meta-analysis depends on the homogeneity of the included studies, with studies needing to be sufficiently similar in terms of study design, patient population, intervention, and outcome measures. In some cases, the lack of homogeneity may be due to differences in study design, patient population, or outcome measures. In other cases, it may be due to differences in the methodology or reporting of the studies themselves. In our systematic review, we encountered two studies on a particular topic that were not sufficiently homogeneous to allow for meta-analysis due to differences in the methodology and outcome

measures.

4. DISCUSSION

According to Campos et al, the airway volume and the oropharyngeal segment, in particular, were significantly smaller in individuals with OSA. The reduced oropharyngeal volume may explain the OSA pathophysiology in this population.

Whereas studies using image analysis of subjects with OSA from the general population show that the velopharynx is the main site of obstruction, the present study shows that the oropharynx is the most affected region in CLP individuals. The authors speculate that a large percentage of these patients had oral breathing, which would explain an increase in the tongue size and the reduction in the airway at the oropharyngeal level.

Ceilo et al : A total of 33 participants were included in the study. There was a greater percentage of total sleep time with PETCO2 > 45 torr in the ICP group than the control group. There were significant improvements from baseline to follow-up testing for three of the five variables in the micrognathia group (AHI, sleep time with saturation below 90% and mean transcutaneous CO2) and for the AHI in the ICP group. In conclusion, this study has shown that in infants with micrognathia and midface hypoplasia are significant risk factors for OSA whereas isolated cleft palate does not appear to contribute substantially. Another important finding is that OSA improves with growth in infants with ICP before the cleft palate is repaired.

According to Bergeron et al. Overall, OSA did not develop or worsen following primary palatoplasty. However, the oAHI increased by 5 or more events/h in approximately 20% of study participants. The presence of a syndrome was the only factor predictive of worsening OSA after palatoplasty. These data suggest that palatoplasty does not worsen or cause OSA in most patients and that nonsyndromic children are at low risk for the development or worsening of OSA.

Rose et al; There was no increase in the incidence of manifest obstructive sleep apnea on repaired cleft palate patients, but there were more frequent hypopneas and snoring, a factor not reflecting severe desaturation events and probably not affecting daytime behavior of these patients.

Prado et al; The findings suggest that surgical closure of the palate has an obstructive effect on the upper airway during the first 24 hours after surgery, most likely due to surgical manipulation and secondary complications, such as tongue edema, bleeding, postextubation laryngitis, and others. This obstructive effect is mainly expressed as snoring, which is still observed in the long term, and other transient symptoms, such as difficulty breathing during sleep, yet without breathing pauses. Therefore, different from the study hypothesis, palatoplasty did not cause evident signs of OSA in the sample of children with cleft palate analyzed. However, the high prevalence of snoring observed in the long term indicate that children with a palatal cleft who undergo surgical repair are at risk for OSA. Future studies should analyze the occurrence of apnea by poly- somnography, which is the gold standard for the diagnosis of sleep breathing disorders.

In individuals with cleft lip and palate, the upper airway volume, in particular of the

oropharynx region, is significantly reduced in those with OSA, confirming hypothesis that the reduction of the pharyngeal space in this population may predispose to OSA.

Individuals with a Class Il malocclusion, i.e., with mandible retrusion, present with reduced pharyngeal dimensions when compared to Individuals with Class I or Class Ill malocclusions

Individuals with CLP, the opposite seems to occur, since, in most of these cases, there is a false Class Ill, due to a maxillary retrusion and not to a mandibular prognathism.

Oropharynx is the most affected region in CLP individuals. The authors speculate that a large percentage of these patients had oral breathing, which would explain an increase in the tongue size and the reduction in the airway at the oropharyngeal level.

Similar results were observed by Celikoglu et al., who, comparing the pharyngeal dimensions of children with unilateral cleft lip and palate and children without cleft, observed a significant decrease only for the region of the oropharynx but not for the nasopharynx.

5. CONCLUSION

The present findings suggest that surgical closure of the palate has an obstructive effect on the upper airway during the first 24 hours after surgery, most likely due to surgical manipulation and secondary complications, such as tongue oedema, bleeding, post extubation laryngitis, and others. This obstructive effect is mainly expressed as snoring, which is still observed in the long term, and other transient symptoms, such as difficulty breathing during sleep, yet without breathing pauses.

Therefore, palatoplasty did not cause evident signs of OSA in the sample of children with cleft palate analyzed. However, the high prevalence of snoring observed in the long term indicate that children with a palatal cleft who undergo surgical repair are at risk for OSA.

Our data showed morphological differences between subjects with and without cleft palate in an obstructive sleep apnea-specific cephalometric analysis. Morphological changes in the width of the pharyngeal airway, position of the hyoid, and the reduced size of the maxilla are also described in patients with SDB and snoring. It is speculative whether these morphological findings can be considered minor symptoms that support snoring in patients with cleft palate.

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