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REVIEW ARTICLE

Adenotonsillectomy in children with syndromic craniosynostosis: a systematic review and meta-analysis

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Abstract

Objective To conduct a systematic review and meta-analysis in children with syndromic craniosynostosis, to evaluate the effect of adenotonsillectomy for the treatment of obstructive sleep apnea (OSA).

Study design A systematic review and meta-analysis.

Search methods Data sources: a comprehensive search of PubMed, SCOPUS, Ovid Medline, and Web of science databases was performed through June 22nd, 2018. Manual searches and subject matter expert input were also obtained. This article includes studies assessing the effectiveness of adenotonsillectomy in syndromic craniosynostosis children, in which apnea–hypopnea index (AHI) or oxygen desaturation index (ODI) was reported.

Results A total of 3 retrospective studies (24 patients) met the inclusion criteria. Pooled random effect analysis did not identify a statistically significant difference between preoperative and postoperative AHI. But there was an overall reduction of AHI of 5.00 events per hour [95% confidence interval (CI) (– 17.79, 7.79); $P = 0.44$]. However, the fixed effect model demonstrated a statistically significant difference between preoperative and postoperative ODI with an overall reduction of 8.5 per hour [95% CI (– 15.01, – 1.99); $P = 0.01$].

Conclusion Adenotonsillectomy showed benefits for the treatment of OSA in syndromic craniosynostosis children, in terms of AHI and ODI. However, only ODI, but not AHI, reached statistical significance. Data were based on meta-analysis of retrospective reviews. Further studies that are conducted at multiple centers are needed to confirm the benefits of adenotonsillectomy for the treatment of OSA in syndromic craniosynostosis children.

Keywords Craniosynostosis · Apert · Crouzon · Pfeiffer · Sleep apnea · Adenotonsillectomy

Introduction

Syndromic craniosynostosis is a premature fusion of cranial sutures leading to deformities of skull and facial bones. These syndromes result from genetic mutation of fibroblast growth factor (FGFR) types 1, 2 and 3 which cause Crouzon's, Pfeiffer's, Apert's, Muenke's, and Jackson–Weiss syndromes [1]. The effects of craniosynostosis contribute to brain malformation, increased intracranial pressure, and narrowed oropharynx including airway space which can cause both central and obstructive breathing disorders [2].

Obstructive sleep apnea (OSA) is common in syndromic craniosynostosis patients with the prevalence in between 40 and 83% [3–6]. While adenotonsillectomy is the first-line treatment for OSA in most children with reported success rates of 53–82.9% [7–9], the role of this procedure in children with syndromic craniosynostosis has not been well established. Previous studies showed conflicting benefits of adenotonsillectomy in improving OSA in these patients [10–18].

Multiple studies demonstrated significant improvement of OSA in terms of apnea–hypopnea index (AHI) [6, 18] and oxygen desaturation index (ODI) [10, 11, 14, 15] after adenotonsillectomy in this group of children, especially the

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group in which enlarged adenoid and tonsils were noted [17, 18]. In contrast, Bannink et al. and Zandieh et al. reported that most of their patients did not have any OSA improvement after the operation [3, 13].

We, therefore, conducted a systematic review and meta-analysis to evaluate the effectiveness of adenotonsillectomy, measured by changes in AHI and ODI after the operation, to treat OSA in children with syndromic craniosynostosis.

Methods

Search strategy

A comprehensive literature search was carried out using four databases (PubMed, SCOPUS, Ovid Medline, and Web of science) to retrieve articles published up to 22 June 2018. Search items included "craniosynostosis", "Apert", "Crouzon", "Pfeiffer", "Muenke", "Jackson–Weiss" in conjunction with "sleep disordered breathing", "sleep apnea", "polysomnography", "AHI", "oxygen saturation" in conjunction with "adenotonsillectomy", "adenoidectomy", "tonsillectomy". We performed additional searches using medical subject headings and keywords: "Acrocephalosyndactylia", "craniofacial dysostosis", "sleep apnea syndrome", and "hypoxia". The titles and abstracts for each of the results were reviewed for relevance. The full-text versions of relevant articles were then evaluated completely. The references of the obtained articles were also reviewed, and any relevant studies in the reference lists were also obtained and included if they met the inclusion criteria. As an additional step, each time a relevant article was encountered during the review of title and abstract, the "related citations/articles" and "cited by" features of the four databases and Google Scholar were searched to identify any additional potentially relevant articles.

Study selection

The inclusion criteria were defined as craniosynostosis patients under 18 years of age who underwent adenotonsillectomy in which AHI or ODI was reported; the articles must be written in English. Any article that did not meet these criteria was excluded from the analysis.

Data abstractions and study quality assessment

The initial search was performed independently by two reviewers (PS and BC). Data included patient's age, characteristics, follow-up time, polysomnographic data of AHI and ODI. The corresponding authors of studies in which their data were insufficient [e.g., study means, standard deviations (SD), etc.] for the meta-analysis were contacted via email, in an attempt to obtain missing or additional data. The methodological assessment of article quality in this systematic review and meta-analysis followed the criteria stipulated by the National Institute for Health and Clinical Excellence (NICE) [19]. This checklist consists of eight items, and the overall score ranges from 0 to 8.

Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). AHI and ODI mean differences (preoperative and postoperative), standard deviations, and 95% confidence interval (95% CI) were calculated. For combined data, a two-tailed, paired t test was performed (P value < 0.05 was the cutoff for significance). The null hypothesis was that there was no difference between AHI and ODI before and after the adenotonsillectomy.

The REVMAN random effects model for pooling effects was applied if heterogeneity of treatment effects was present, and a fixed effects model was used if no heterogeneity was present. Forest plots were graphically inspected, and heterogeneity was assessed with the I^2 statistic (low: 25%, moderate: 50%, and high: 75%) [20]. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [21] were adhered to as much as possible.

Results

The web-based search yielded a total of 169 studies and abstracts after removal of duplicates. After preliminary review of titles and abstracts, a total of 18 studies were identified as being relevant, then full texts were downloaded for further evaluation. Of these 18 studies, a total of 14 studies were excluded as follows: 11 manuscripts did not have polysomnography (PSG) reports and 3 studies were not syndromic craniosynostosis. In summary, a total of 3 studies with a total of 24 patients were included in this study [6, 10, 13]. Figure 1 demonstrates the article selection flow diagram.

In the total of three studies, AHI was reported in two studies [6, 13] and ODI was reported in one study [10]. The authors contacted three corresponding authors via e-mail for the raw data but only one author replied [13]. Zandieh et al. provided data of preoperative and postoperative AHI of 11 cases who underwent adenotonsillectomy. Al-Saleh et al. reported 16 cases of medical and surgical interventions for OSA treatment in craniosynostosis [6]. Only six cases of adenotonsillectomy with complete preoperative and postoperative PSG were included in this study. Xie et al. [10] reported the result of various treatments in 25 patients of Apert's syndrome which included adenotonsillectomy, adenoidectomy, tonsillectomy, midfacial advancement,

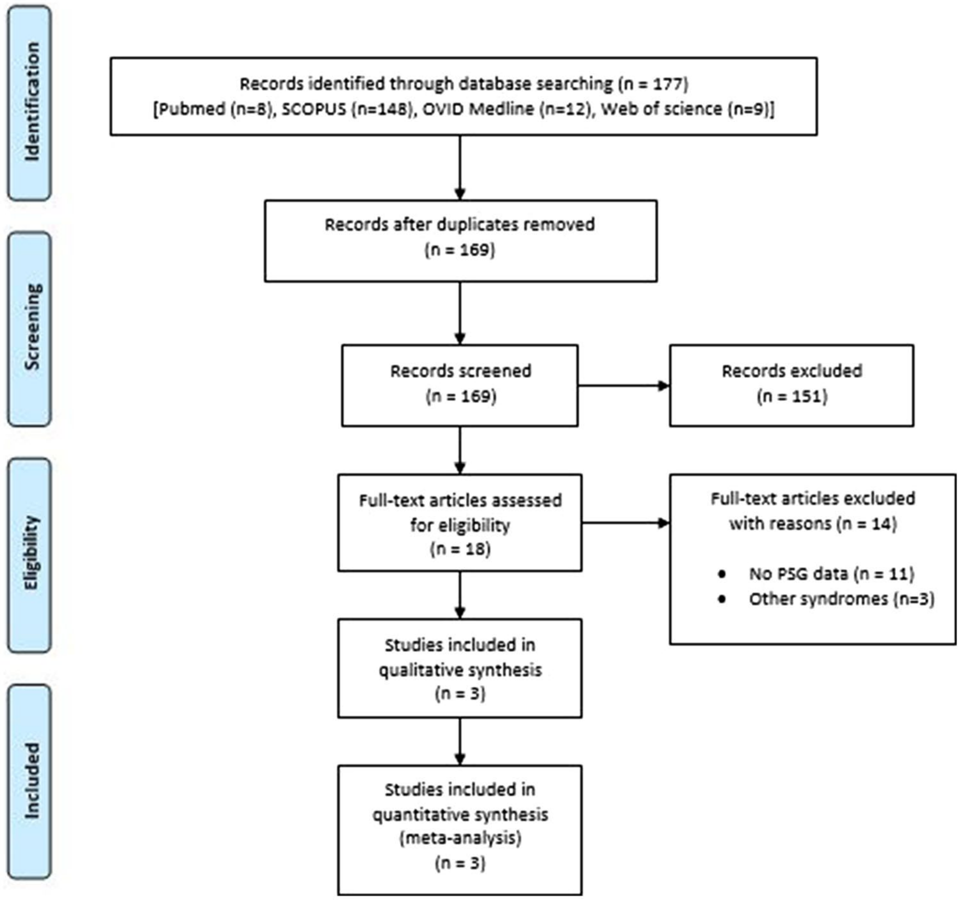

Fig. 1 PRISMA flow diagram for the article selection. *N* number of articles

and invasive ventilation or long-term oxygen. Only seven subjects who had preoperative and postoperative ODI were included. Demographic data are demonstrated in Table 1.

Methodological quality of the included studies

All the studies included in this review were retrospective case series and are subjected to the NICE quality assessment. The result demonstrated that the included studies satisfied a range between three to five of the eight items, scoring most satisfying in more than four items (Table 2).

Apnea–hypopnea index (AHI)

A total of two studies (16 patients) reported both average preoperative and postoperative AHI values with SD (Table 1) [6, 13]. Al-Saleh et al. provided average preoperative and postoperative AHI and SD in the article. But Zandieh et al. did not clearly provide the preoperative and postoperative AHI and SD in the article. However, the complete preoperative and postoperative AHI data of 11 patients were provided and included after contacting the corresponding author via e-mail [13].

Table 1 Characteristics of studies

References	Design	*n*	Age (year)	Patients characteristics	Preoperative AHI	Postoperative AHI	Preoperative ODI	Postoperative ODI
Al-Saleh [6]	Retrospective case series	6	4.4 ± 2.4	Apert (*n* = 3) Crouzon (*n* = 3)	18.8 ± 12.0	19.7 ± 28.8	–	–
Zandieh [13]	Retrospective case series	11	5.6 ± 14.2	–	25.2 ± 18.7	18.1 ± 16.9	–	–
Xie [10]	Retrospective case series	7	4.9 ± 2.3	Apert (*n* = 7)	–	–	10.9 ± 8.4	2.4 ± 2.6

Data represent mean ± SD

N number, *AHI* apnea–hypopnea index, *ODI* oxygen desaturation index

There was no statistically significant difference between preoperative and postoperative AHI [mean difference 5.0, 95% CI (– 17.79, 7.79); $P = 0.44$]. The test for heterogeneity was not significant ($P = 0.59$), and inconsistency was low heterogeneity ($I = 0\%$). This indicates that pooling the data was valid; thus, the fixed effect model was applied (Fig. 2).

With regard to the definition of AHI, both studies followed the criteria according to the 2007 American Academy of Sleep Medicine (AASM) scoring guidelines [22].

Oxygen desaturation index (ODI)

One study (seven patients) reported ODI [10]. Pooled mean preoperative and postoperative ODI values were 10.9 ± 8.4 events per hour and 2.4 ± 2.6 events per hour, respectively. The average ODI reduction was 8.5 per hour (95% CI – 15.01, – 1.99; $P = 0.01$). The heterogeneity was not applicable because only one study was included and analyzed (Fig. 3).

Regarding the definition of ODI, Xie et al. used an average number of oxygen desaturations of 4% or more below the baseline level per hour [23].

Discussion

Syndromic craniosynostosis is a condition in which the skull suture is prematurely closed [1]. This abnormality impacts not only the external appearance of the skull and facial bone but also the airway internally; thus, it can lead to multiple levels of pharyngeal airway obstruction. A child who has this syndrome may subsequently develop adenoid and tonsil hypertrophy, worsening his OSA severity [24]. While adenotonsillectomy, the first-line treatment, can be successful in children with OSA with a success rate between 53 and 83% [7–9], the beneficial result of this treatment may not be the same in children with the syndromic craniosynostosis.

We have reviewed three studies of adenotonsillectomy to improve OSA in children with craniosynostosis. Our study demonstrated no statistically significant difference in AHI reduction between preoperative and postoperative adenotonsillectomy. Despite the average difference in AHI reduction of five events per hour, data did not reach a statistical significance. With regard to AHI severity in children, a reduction of five events can make a dramatic change in OSA severity. Nevertheless, in comparison with children without craniosynostosis, children with this syndrome normally suffer from more severe degree of OSA,

Table 2 Quality assessment by NICE

References	Quality assessment of included studies							
	1	2	3	4	5	6	7	8
Al-Saleh [6]	No	Yes	Yes	Yes	No	No	Yes	Yes
Zandieh [13]	No	Yes	Yes	Yes	No	No	Yes	No
Xie [10]	No	Yes	No	Yes	No	No	Yes	No

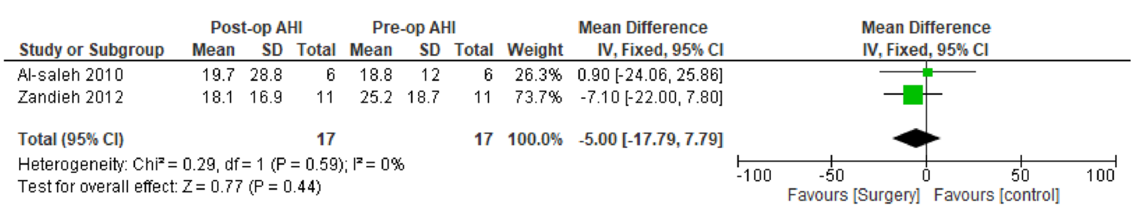

Fig. 2 Forest plot: fixed effects analysis for meta-analysis of mean difference of preoperative compared with postoperative AHI for adenotonsillectomy. There was no statistically significant difference in AHI between preoperative and postoperative periods [mean difference, 5.00 (95% CI – 17.79, 7.79; $P = 0.44$]. *SD* standard deviation, *IV* inverse variance

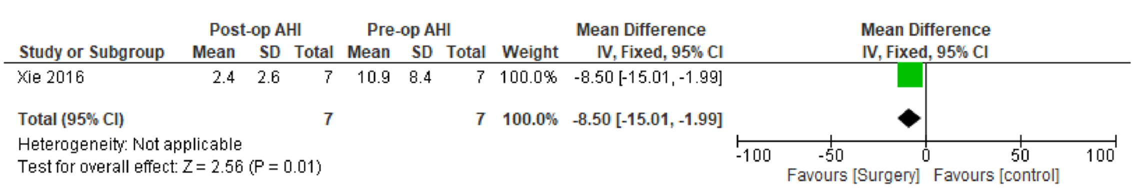

Fig. 3 Forest plot: fixed effects analysis for meta-analysis of mean difference of preoperative compared with postoperative ODI for adenotonsillectomy. There was statistically significant difference in ODI

due to narrower bony framework of the upper airway. This may explain why the included studies reported persistence of severe OSA postoperatively.

Consideration for continuous positive airway pressure (CPAP) as another primary or adjunctive treatment for OSA in children with craniosynostosis may be reasonable, in which a retrospective study reported a tendency of AHI reduction in children with various types of craniofacial malformation including syndromic craniosynostosis who were treated with both CPAP and adenotonsillectomy (from 6.2 to 3.5 events per hour and from 2.5 to 1.8 events per hour, respectively) [25]. Thus, long-term, comprehensive multidisciplinary approaches are still required for treating both craniosynostosis and OSA in these patients.

In contrast, there was a statistically significant ODI reduction of over eight events per hour. Though AHI is recognized as the primary parameter that reflects OSA, the test can be limited in some clinical setting because of expensiveness and availability. As such, ODI is currently considered as another parameter in the diagnosis of OSA [22, 26] as it can be promptly obtained from a wide range of sleep tests at lower cost and is more feasible for detecting OSA in children than in level I PSG [27]. A previous study reported strong correlation between AHI and ODI [28]. High reliability and high positive predictive value of ODI obtained from nocturnal pulse oximetry were noted for OSA diagnosis in a pediatric study [29]. Good sensitivity and specificity were also reported to detect undiagnosed OSA in surgical patient [30]. While AHI scoring criteria change over time, ODI criteria are more consistent and universal across various tests.

There was no report of major adverse events in these included studies. However, recurrent adenoid hypertrophy was noted in two studies, and revision of adenoidectomy was required [10, 13].

It is noteworthy that the included patients were mainly from hospitals in the western region of the world. The size and shape of the skulls, as well as the airways, in the patients with craniosynostosis may differ from those in other regions [31]. Generalization of this study should then be performed with some cautions.

Our systemic review and meta-analysis using a comprehensive search method focused on the effect of adenotonsillectomy in children with craniosynostosis. To the best of our knowledge, this is the first to evaluate the effect of adenotonsillectomy in children with syndromic craniosynostosis. The results of our meta-analysis demonstrate a significant postoperative ODI but not AHI reduction. However, due to limited primary studies that evaluated the effectiveness of the surgery in this group of patients, all the studies were case series. Future studies are needed and can be improved by including multiple centers, with prospective and consecutive recruitments.

Conclusion

Based on our systematic review and meta-analysis, adenotonsillectomy showed benefits for the treatment of OSA in syndromic craniosynostosis children in terms of significant improvement in ODI. Further studies including multiple centers, with prospective and consecutive recruitments, are needed to confirm the benefits of adenotonsillectomy for the treatment of OSA in syndromic craniosynostosis children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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