European Review for Medical and Pharmacological Sciences 2022; 26: 4583-4591

High-flow nasal cannula therapy for pediatric obstructive sleep apnea: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Heated and humidified high-flow nasal cannula (HFNC) therapy has been used to manage different respiratory conditions in pediatric patients. However, no review has summarized its efficacy for the management of pediatric obstructive sleep apnea (OSA).

MATERIALS AND METHODS: PubMed, Embase, CENTRAL, and Google Scholar were searched for all types of studies assessing the efficacy of HFNC for pediatric OSA. We compared pre-treatment and post-treatment obstructive apnea-hypopnea index (OAHI), obstructive hypopnea index (OHI), obstructive apnea index (OAI), SPO2 nadir and SPO2 mean values in a random-effect meta-analysis model.

RESULTS: Six studies reporting data of 67 pediatric patients treated with HFNC were included. Most of the data were from one-time titration. Meta-analysis revealed a statistically significant reduction in OAHI with HFNC therapy (MD: 15.58 95% CI: 8.30, 22.86 I^2=77% p=0.001). Similarly, pooled analysis revealed that both OHI (MD: 12.35 95% CI: 0.78, 23.92 I^2=98% p=0.04) and OAI (MD: 7.54 95% CI: 2.10, 12.98 I^2=79% p=0.007) were significantly reduced with HFNC treatment. Also, HFNC led to statistically significant improvement in SPO2 nadir values (MD: -8.17 95% CI: -10.40, -5.94 I^2=21% p<0.00001) but it did not change the mean SPO2 values before and after treatment (MD: -0.85 95% CI: -1.94, 0.25 I^2=52% p=0.13).

CONCLUSIONS: Evidence from a limited number of heterogeneous and uncontrolled titration studies indicates that HFNC improves OAHI and minimum oxygen saturation in pediatric patients with OSA. However, further research is required on the long-term efficacy and compliance of HFNC therapy with a focus on different pediatric age groups.

Key Words:
Obstructive sleep apnea, High-flow nasal cannula, Apnea-hypopnea index, Children, Infants.

Introduction

Sleep-disordered breathing in pediatric patients encompasses a wide range of disorders that occur during sleep and includes central apnea, hypoventilation, and obstructive hypoventilation. Obstructive sleep apnea (OSA) is the most severe form of obstructive hypoventilation wherein there are repeated events of partial or complete obstruction of the upper airway during sleep leading to disruption of normal ventilation and sleep pattern[1,2]. A recent meta-analysis pooling data[3] from 16 countries have estimated that around 1 billion individuals globally suffer from OSA with prevalence exceeding 50% in some countries. On the other hand, studies[4,5] focusing on pediatric populations have estimated the prevalence of OSA in children ranging from 0.2% to as high as 10.5%. The morbidity of OSA can be gauged by the fact that it increases the risk of several other systemic conditions like cardiovascular disorders, metabolic disorders (dyslipidemia and insulin resistance), and downgrades neurocognitive and behavioral functioning[6].

The cause of OSA in children can be multifactorial and can include hypertrophic tonsils and adenoids, mandibular dysplasia, obesity, etc. The treatment is usually tailored according to the cause of obstruction and includes tonsillectomy, adenoidectomy, weight reduction, oral appliance therapy, secondary airway surgery, and medical therapy[2]. Surgical procedures to relieve airway obstruction have delivered good results in pediatric OSA[7]. However, residual obstruction persists in some patients after surgery and nasal continuous positive airway pressure (nCPAP) is the most commonly recommended treatment option. Nevertheless, compliance with nCPAP has been a problem in children while others do not tolerate the device[8]. In such cases, there is a need for an alternative treatment option to manage this condition.

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In the past few years, there has been a spurt in the use of high-flow nasal cannula therapy (HFNC) for the management of respiratory conditions in pediatric patients[9,10]. Studies[9] indicate HFNC leads to similar mortality rates and intubation rates as compared to nCPAP in pediatric patients. HFNC involves delivering high flow heated and humidified air *via* the nose wherein the fraction of oxygen can be adjusted from 21% to 100%. This therapy has been reportedly used by some clinicians for the management of OSA[11,12]. However, individual studies[11,12] have been of small sample size and, to date, no review has comprehensively assessed the efficacy of HFNC therapy for the management of pediatric OSA. Thus, the current review aimed to pool data from individual studies to assess if HFNC leads to improvement in outcomes in pediatric patients with OSA.

Materials and Methods

Our systematic review and meta-analysis are reported as per the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[13]. The PROSPERO registration number of the study is CRD42021286207.

Literature Search

Two reviewers independently searched the electronic databases of PubMed, Embase, CENTRAL, and Google Scholar for relevant articles. The search strategy was formalized with the aid of a medical librarian and the search limits were set from the inception of the above-mentioned databases to 7th November 2021. Only English-language studies were included. The search terms used were: "sleep apnea", "obstructive sleep apnea", "nasal cannula", and "high-flow nasal cannula". Details of the search strategy common to all databases are presented in the **Supplementary Table I**. The articles found in the initial search were examined by their titles and abstracts. Studies found relevant to the review were identified and full text was sourced. These full texts were then examined in detail by the two reviewers separately for inclusion in the review. All disagreements were resolved in consensus with another reviewer. We also carried out manual scoping of the bibliography in the included studies for any additional articles.

Inclusion Criteria

The inclusion criteria were as follows: 1) all types of prospective or retrospective studies, conducted on pediatric patients (<18 years) with OSA; 2) studies were to report the use of HFNC for management of OSA; 3) studies were to report at least one of the following outcomes before and after HFNC treatment – obstructive apnea-hypopnea index (OAHI), obstructive hypopnea index (OHI), or obstructive apnea index (OAI); 4) the outcome data was to be acquired using polysomnography or respiratory polygraphy. There was no restriction of follow-up for inclusion in the review.

Exclusion criteria were: 1) studies assessing the efficacy of HFNC for adult patients; 2) studies not reporting relevant data; 3) studies published only as abstracts, editorials, and review articles.

Data Extraction

A data extraction sheet was used by two reviewers to extract relevant data from the studies. The following details were extracted: first author, year of publication, type of study, study location, type of patient population included, number of included patients, mean age, gender, weight, preterm births, genetic disorders, the flow rate for HFNC, baseline and final values of OAHI, OHI and OAI (as events/hour) along with SPO_2 nadir and SPO_2 mean values (as percentage). The primary outcome of the review was to assess change in OAHI after HFNC treatment by comparing pre- and post-treatment values. The secondary outcomes were changes in OHI, OAI, oxygen saturation (SPO_2) nadir, and mean SPO_2 values before and after HFNC treatment.

Risk of Bias Assessment

The quality of included studies was judged based on the quality assessment tool for before-and-after studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Studies were judged based on the following domains: (1) if the study question or objective was clearly stated; (2) if the eligibility criteria were prespecified and clearly described; (3) if the participants were representative of the population; (4) if all eligible participants who met the entry criteria were enrolled; (5) if a sample size calculation was performed; (6) if the intervention was clearly described and consistently delivered; (7) if the outcome measures were prespecified, clearly defined, valid, reliable, and assessed consistently; (8) if the follow-up rate was 80% or more; (9) if a statistical analysis was performed to assess changes in outcome measures before and after the intervention and if the *p*-values were provided for those changes, and (10) if multiple measurements were acquired before and after the intervention.

Table I. Details of included studies

Study	Location	Study population	Sample size	Mean age	Male/ Female (n)	Preterm birth (n)	Genetic disorders (n)	Weight (kgs)	Baseline OAHI events/ hour	Baseline mean SPO_2 (%)	Flow rate for HFNC	Follow-up
Kwok et al 2020[11]	China	Infants with OSA	10	NR	7/3	5	0	4.9 [4.2-5.7]	9.1 [5.1-19.3]~	88 [83-94]~	Given initially at 4 L/min and titrated up until a maximum flow rate of 8 L/min	Immediate
Ignatiuk et al 2020[12]	USA	Pediatric patients with moderate to severe OSA	22	12.8 (95% CI:7-18.6) months	14/8	7	13	6.5 [5.1-8]	29.9 [17.6-40.2]~	95.1 [94-96.2]~	6.9 [5.8-7.9] L/min	Immediate and long term (12 months)
Amaddeo et al 2019[18]	France	All patients severe OSA not compliant with home CPAP therapy	8	5± 3.9	2/3	NR	3	17.9± 10.6	25± 2	97± 1	5-20 L/min	1 month
Hawkins et al 2017[17]	USA	School aged children with OSA not compliant with CPAP therapy	10	NR	4/6	NR	3	NR	11.1 [8.7-18.8]~	91.3 [89.6-93.5]~	Given initially at 5-15 L/min and titrated up until a maximum flow rate of 20-50 L/min	Immediate
Joseph et al 2015[16]	Israel	All patients <18 years with severe OSA not compliant with CPAP therapy	5	2 months-15 years	3/2	1	2	NR	18.7± 15.2	NR	5-10 L/min	Immediate
McGinley et al 2009[15]	USA	Children between 5-15 years with OSA	12	10± 2 years	8/4	NR	NR	75± 41.5	11± 10.3	98± 1	Up to 20 L/min	Immediate

HFNC, high flow nasal canula; SPO_2, oxygen saturation; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; L, liters; n, number; NR, not reported; OAHI, obstructive apnea-hypopnea index; CI, confidence intervals~Median [interquartile range]

Every question was graded with a response of yes, no, or CD (cannot be determined). The following scoring categories were established: score of 8 to 10 of yes was graded as good, indicating a low risk of bias; a score of 5 to 7 of yes was graded as fair, indicating a moderate risk of bias; and a score of 1 to 4 of yes answers was graded poor, indicating either a lack of information or uncertainty over a high risk of bias.

Statistical Analysis

The software "Review Manager" [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark; 2014] was used for the meta-analysis. We extracted the mean and standard deviations (SD) of all continuous variables from the included studies. These were then combined to calculate the mean difference (MD) with 95% confidence intervals (CI). If studies reported continuous variables as median, range, and interquartile range, the same was converted into mean and standard deviation (SD) using the method of Wan et al[14]. All meta-analyses were conducted using the random-effects model. The I^2 statistic was used to examine heterogeneity. I^2 score of 25-50% meant low, values of 50-75% indicated medium, and >75% represented substantial heterogeneity. We also conducted a sensitivity analysis for the primary outcome wherein individual studies were excluded sequentially and the effect size was recalculated for the remaining studies. *p*-values less than 0.05 were considered statistically significant.

Results

Search Results

The number of search results at each stage is summarized in Figure 1. After the complete literature search, a total of 1073 articles were retrieved. These were then deduplicated and 378 articles we reviewed by their titles and abstracts. 370 of these were found to be non-relevant and were finally excluded. Finally, eight studies were examined by their full texts, two of which were excluded as they were on adults, and six studies on pediatric patients were included in our review[11,12,15-18].

Details of Included Studies

Details of all included studies are presented in Table I. The included studies were published between 2009 and 2020. Most of the studies were carried out in the USA while the remaining were conducted in Israel, China, and France. The number of patients in the included studies was small ranging from 5 to 22. A total of 67 patients were treated in the included studies. However, the age of included patients varied widely across the included studies. While one recent study included only infants[11], the remaining included patients with a wide age group. The flow rate of HFNC was also variable across the included studies. The study of Joseph et al[16] delivered oxygen *via* HFNC while all remaining studies used air. One study[18] reported a change in outcomes after 1 month of HFNC therapy while all others reported immediate outcomes. The study of Ignatiuk et al[12] also reported outcomes after 12 months of HFNC therapy. For the meta-analysis, only immediate outcomes (and 1-month outcome of Amaddeo et al[18]) were combined.

Meta-Analysis

All six studies reported data on OAHI[11,12,15-18]. Meta-analysis pooling data of all 67 patients revealed a statistically significant reduction in OAHI with HFNC therapy (MD: 15.58 95% CI: 8.30, 22.86 I^2=77% p=0.001) (Figure 2). There was no change in the significance of the results on the exclusion of any study.

Pooled analysis of data of 50 patients revealed that both OHI (MD: 12.35 95% CI: 0.78, 23.92 I^2=98% p=0.04) (Figure 3) and OAI (MD: 7.54 95% CI: 2.10, 12.98 I^2=79% p=0.007) (Figure 4) were significantly reduced with HFNC treatment.

SPO_2 nadir values were reported by all included studies[11,12,15-18]. Our meta-analysis combining data of 67 patients revealed that the treatment with HFNC sled to statistically significant improvement in SPO_2 nadir values (MD: -8.17 95% CI: -10.40, -5.94 I^2=21% p<0.00001) (Figure 5). Pooled analysis of data of 52 patients demonstrated that HFNC did not change the mean SPO_2 values before and after treatment (MD: -0.85 95% CI: -1.94, 0.25 I^2=52% p=0.13) (Figure 6).

Risk of Bias Analysis

The author's judgment on the risk of bias amongst the included studies is presented in **Supplementary Table II**. All studies were deemed to be of good quality.

Discussion

The role of nCPAP in the management of OSA is well established. The therapeutic mechanism of nCPAP involves normalization of gas exchange

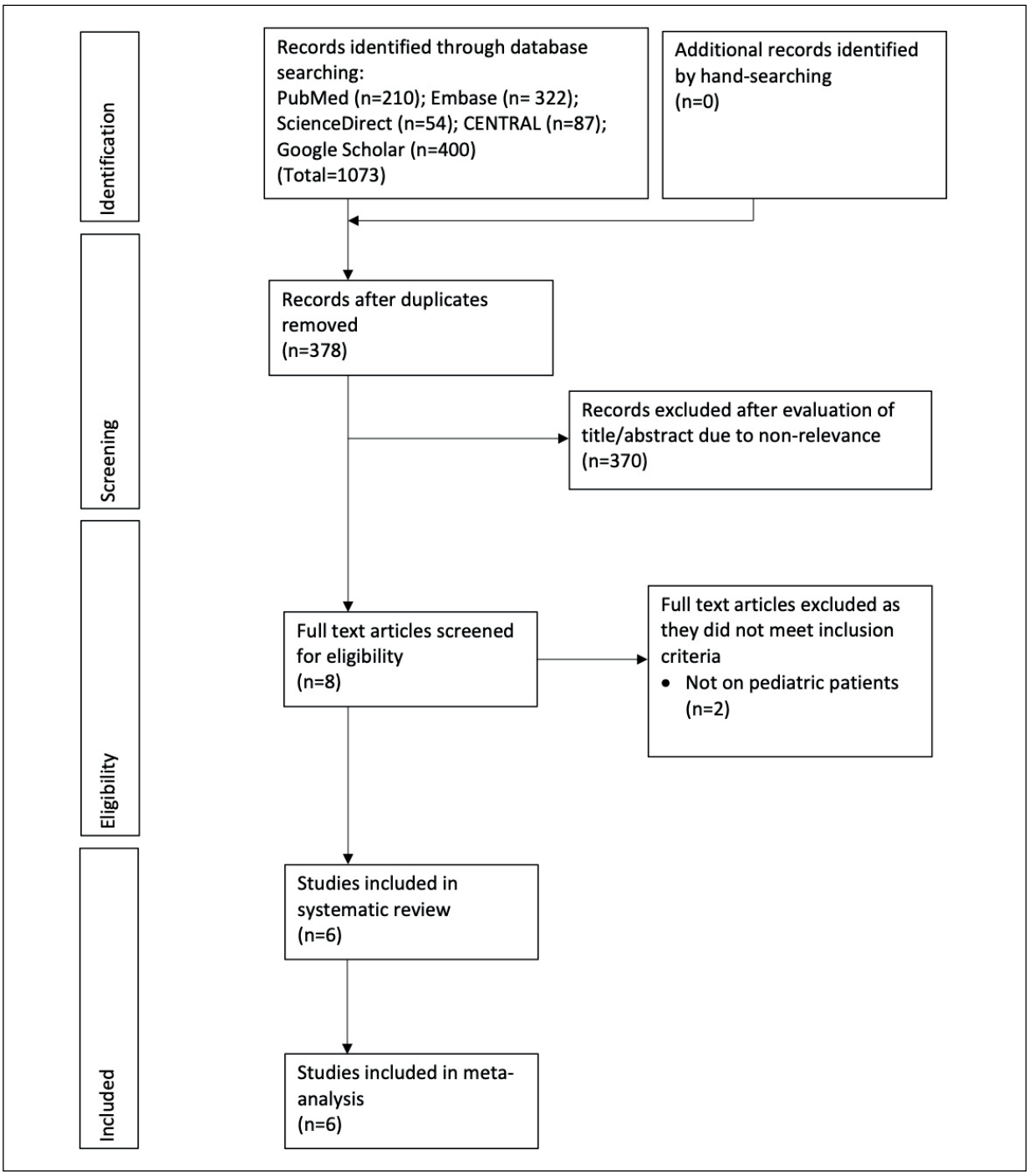

Figure 1. Study flow-chart.

during sleep, improvement of sleep efficiency which normalizes neurocognitive outcomes and reduces morbidity and mortality[8]. Nevertheless, the benefits of nCPAP are directly related to compliance with therapy, with a probable positive dose-effect relationship[19]. The use of nCPAP should ideally be equivalent to the entire physiological sleep time which may be greater than 12 hours, especially in syndromic patients. While no baseline duration of nCPAP use has been authenticated in pediatric patients, some studies[20,21] indicate the use of at least 4-6 hours every night for 70-80% of nights/months. However, it is not uncommon to find pediatric patients non-responsive

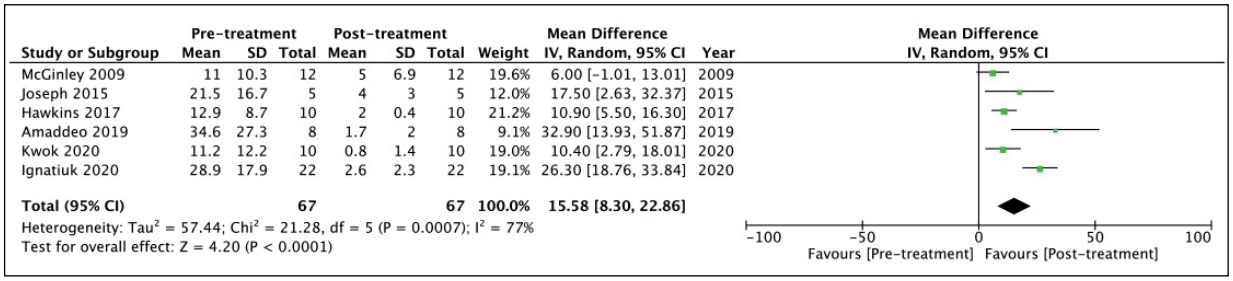

Figure 2. Meta-analysis of OAHI scores before and after HFNC therapy.

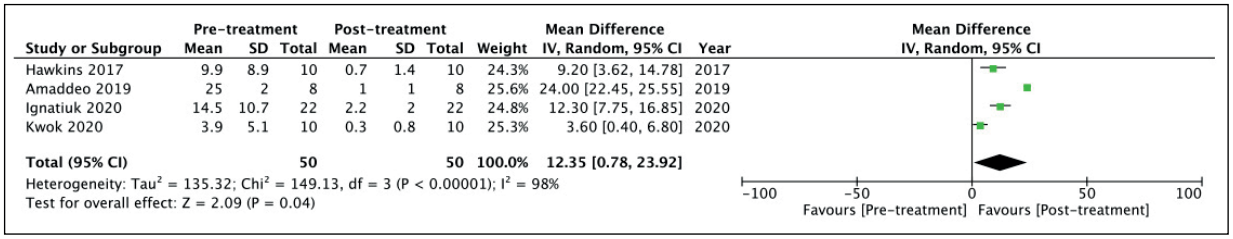

Figure 3. Meta-analysis of OHI scores before and after HFNC therapy.

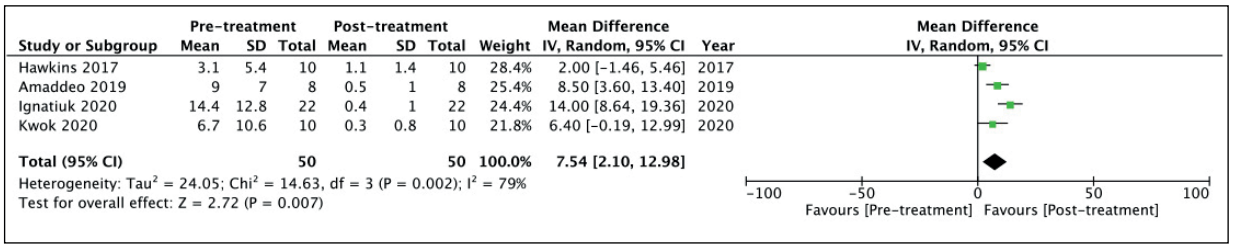

Figure 4. Meta-analysis of OAI scores before and after HFNC therapy.

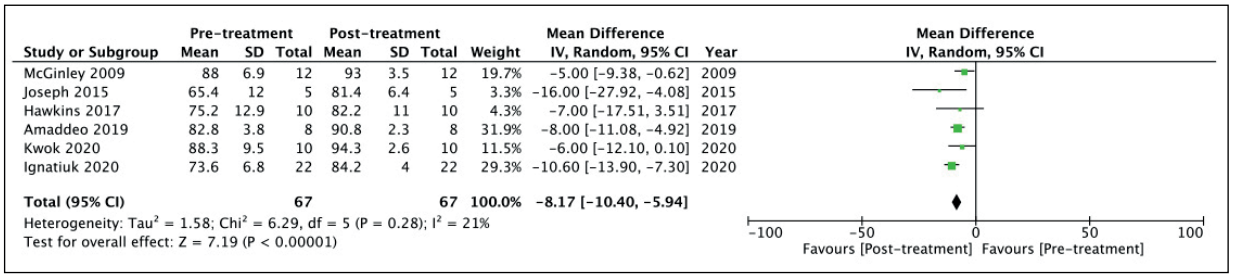

Figure 5. Meta-analysis of SPO_2 nadir values before and after HFNC therapy.

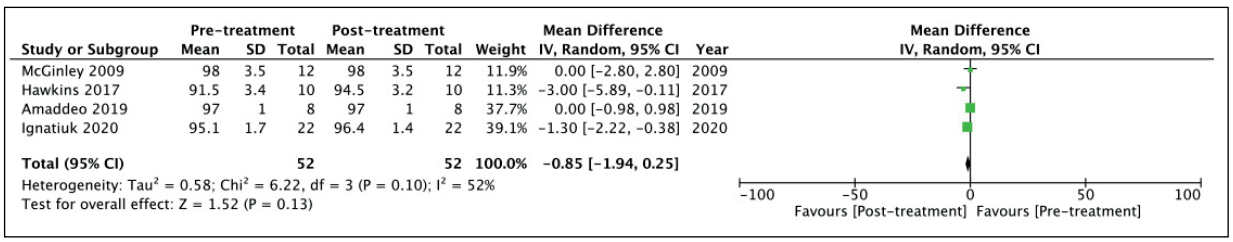

Figure 6. Meta-analysis of mean SPO_2 values before and after HFNC therapy.

or non-compliant to nCPAP and, in such cases, alternative therapies are needed. In patients with varying sites of obstruction, invasive procedures like turbinectomy, tongue base surgeries, uvulopalatopharyngoplasty, rapid maxillary expansion, mandibular distraction osteogenesis, or even tracheostomy may be additionally required[8]. Regardless these procedures may not be immediately possible due to several factors like the presence of morbid obesity, premature birth, or associated medical conditions; and in such cases, there is a need for a non-invasive therapy that could improve outcomes.

HFNC therapy is one of the most interesting modalities used for several respiratory conditions in children[9,10]. Its use for OSA in pediatric patients has generated interest as the cannulas used with it are more comfortable than the masks or nasal prongs used with nCPAP[18]. In our systematic review and meta-analysis, on pooling data from six uncontrolled studies with a total of 67 pediatric patients, we noted that HFNC was effective in significantly reducing OAHI, OHI, and OAI. Also, SPO_2 nadir values were significantly increased, indicating improved oxygen saturation during HFNC therapy. Important to note is that the results were consistent across studies despite the limited sample size of the individual cohorts. A few non-significant results were noted on the forest plots for the studies of McGinley et al[15] (for OAHI and SPO_2 nadir), Hawkins et al[17] (SPO_2 nadir), and Kwok et al[11] (SPO_2 nadir) probably due to the small sample size of these studies. However, the 95% CI of their results indicate a tendency for better outcomes with HFNC therapy.

There are multiple mechanisms by which HFNC can improve outcomes in OSA patients. Firstly, it decreases nasopharyngeal dead space which increases the alveolar fraction of oxygen and carbon dioxide. Secondly, the positive pressure generated with HFNC therapy reduces the negative pressure generated during inspiration which reduces respiratory resistance and work of breathing. Thirdly, heated air counteracts the effect of cold air which improves pulmonary compliance. Fourthly, the delivery of heated humidified air reduces the metabolic load of the nasopharynx for gas conditioning. Lastly, HFNC provides end-distending pressure to the lungs[22].

The results of our review are somewhat in contrast with the outcomes of HFNC seen in adult OSA patients. A recent study by Yan et al[23] has found that only 21% of 56 adult OSA patients treated with HFNC responded to therapy. A responder in their study was defined as a reduction of AHI >50% from baseline or fall of the score below 5 events/hour. Overall, the AHI of their patients reduced significantly from a baseline of 27.0 ± 14.7 to 21.5 ± 17.0 events/h ($p<0.001$) but the final AHI score was still high[23]. Contrastingly, the final OAHI score in all studies included in our review was ≤5 events/hour. It has been suggested that the baseline muscle tone influences the outcomes of HFNC treatment as there is no inherent pressure with the therapy as compared to nCPAP. This postulation has been put forward by Yan et al[23] to explain better the reduction of AHI in rapid eye movement (REM) sleep as compared to non-REM sleep and older *vs.* younger patients (since older patients have reduced muscle tone). This may also explain the contrasting results of our review with that of adults as pediatric patients tend to have lower muscle tone[24].

Limitations

A major limitation of our review and the included studies is that it presents uncontrolled data. Only pre-treatment and post-treatment values were compared which prohibits any conclusions regarding the superiority of HFNC *vs.* nCPAP. To the best of our knowledge, only one study[25] has compared outcomes of titration with HFNC *vs.* nCPAP, but in adult OSA patients. In a randomized crossover study, Yu et al[25] found that nCPAP was superior to HFNC in improving sleep quality and reducing respiratory events. Additionally, Luo et al[9] have also demonstrated that nCPAP is associated with a lower risk of treatment failure as compared to HFNC in infants with an acute lower respiratory infection, hypoxemia, and respiratory distress. Thus, we believe, at this point, that HFNC therapy cannot be considered as a superior or alternative therapy to nCPAP in pediatric patients and further comparative evidence is needed.

Several other limitations need to be considered while interpreting our results. Foremost, the number of patients included in the studies was very small. Secondly, the age range of the included patients was wide-ranging from infants to teenage children. Age as a variable is especially important as the etiology of OSA differs amongst different subgroups and treatment plans for OSA significantly depend on the age of the patients[26]. Our review, therefore, presents pooled data of a very heterogeneous patient population with different etiology

and different severity of OSA. However, the source of the heterogeneity was from the included studies itself as these studies included patients with a wide age group. To best assess the efficacy of HFNC therapy, a subgroup analysis based on different age groups, or an individual patient-level meta-analysis would have been more correct. However, this was limited due to a small number of studies with variability in the presentation of data. Thirdly, another important source of heterogeneity in our analysis was in the protocol of HFNC therapy with a difference in flow rates amongst the included studies. Also, our results present outcomes of only initial titration of HFNC and not long-term use. We were unable to comment on the long-term efficacy and tolerance rates of HFNC in pediatric patients.

Despite these limitations, ours is the first study to systematically evaluate the efficacy of HFNC therapy for pediatric OSA. We have presented a pooled analysis of 67 patients with OSA which is a considerable number since individual studies are of a small sample size. The meta-analysis provides preliminary data to pediatricians on the efficacy of HFNC therapy for OSA and therefore provides impetus to further research.

Conclusions

Evidence from a limited number of heterogeneous and uncontrolled titration studies indicates that HFNC improves OAHI and minimum oxygen saturation in pediatric patients with OSA. However, further research is required on the long-term efficacy and compliance of HFNC therapy with a focus on different pediatric age groups. There is also a need for comparative evidence vis-à-vis nCPAP.

Conflict of Interest

The authors declare there is no competing interest.

Acknowledgments

Not applicable.

Informed Consent

Not required.

Authors' Contribution

F. Du conceived and designed the study. Y.-H. Gu, Y.-C. He and W.-F. Deng collected the data and performed the analysis. F. Du and Z.-Z. Liu was involved in the writing of the manuscript and is responsible for the integrity of the study. All authors contributed to the article and approved the submitted version

Funding

Not applicable.

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