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Original article

Efficacy of leukotriene receptor antagonist in children with obstructive sleep apnea: A systematic review and meta-analysis

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Background: Obstructive sleep apnea (OSA) is a common disease in children. The most common cause is adenotonsillar hypertrophy. Adenotonsillectomy is the first line therapy. However, there are complications such as bleeding and respiratory compromise. Leukotriene receptor antagonist is an antiinflamatory medication which also use for treatment of OSA in children.
Objective: To conduct a systematic review and meta-analysis to evaluate the effect of leukotriene receptor antagonist (LTRA) on obstructive sleep apnea (OSA) in children.
Methods: Data source was a comprehensive search of MEDLINE, Scopus, Ovid, Web of Science, and the Cochrane Library both of which were reviewed in May 2018. Manual searches and subject matter expert inputs were also obtained. This review included studies assessing the efficacy of LTRA for the treatment of OSA in children, wherein apnea hypopnea indexes (AHI) were reported.
Results: A total of three studies (143 patients) met our inclusion criteria. Pooled random effects analysis demonstrated a statistically significant improvement of polysomnographic respiratory events, with average AHI reduction of 2.72 events per hour, [95% confidence interval (CI) (- 3.95, - 1.49); $P < 0.0001$] and overall increase in minimal arterial oxygen saturation of 3.27% [95%CI 1.78, 4.77); $P < 0.0001$] in favor of LTRA. Significant reduction in adenoidal-nasopharyngeal ratio (A/N ratio) in favor of LTRA of 0.21 [95% CI (- 0.25, - 0.17); $P < 0.00001$] was also demonstrated.
Conclusion: Leukotriene receptor antagonist provided benefits in children with OSA, by reducing AHI, increasing minimal arterial oxygen saturation and reducing adenoid size. Data were based on meta-analysis of control trials with 12 - 16 months of follow up.

Keywords: Leukotriene receptor antagonist, montelukast, sleep apnea, children.

Obstructive sleep apnea (OSA) is a common disease in children; the worldwide estimated prevalence of which is over 1 - 6%. [1 - 4] The treatment is mandatory as it is associated with various consequences, including cardiovascular abnormalities [5], neurocognitive and behavioral morbidity. [6] Adenotonsillectomy is the first line therapy in OSA children. [7] However, a high prevalence of residual OSA of up to 70% after adenotonsillectomy was reported. [8, 9] Moreover, the operation is painful and requires hospitalization and is associated with high risk of post-operative complications, including postoperative respiratory compromise and bleeding. [7, 10] Alternative non-surgical treatments included continuous positive airway pressure [11], rapid maxillary expansion [12], oral appliance [13], high-flow nasal cannula [14],

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positional therapy [15, 16], weight reduction [17] and anti-inflammatory medications, in which intranasal corticosteroids demonstrated a short-term beneficial effect on apnea hypopnea index (AHI), desaturation index, and respiratory arousal index in children with mild to moderate OSA. [18]

Leukotriene receptor antagonist (LTRA) is another anti-inflammatory medication, which reduces inflammation by inhibiting leukotriene synthesis at the level of leukotriene receptor. The clinical use is common for treating allergic rhinitis and asthma. [19, 20] As for pediatric OSA treatment, LTRA has also been recently reported as a beneficial treatment with a short-term use of 12 - 16 weeks, in terms of reducing adenoid size and obstructive respiratory events, increasing oxygenation and improving sleep architecture, in a various degrees of severity. [21 - 23] We therefore conducted a systematic review and meta-analysis to evaluate the effect of leukotriene receptor antagonist for the treatment of OSA in children. The primary outcome of this study is the improvement of obstructive apnea hypopnea index (OAHI) between leukotriene receptor antagonist and control and the secondary outcomes included minimal oxygen saturation and adenoid size.

Materials and methods

Computerized and manual searches were performed to identify all relevant data. A search of five databases (MEDLINE, Scopus, Ovid, Web of Science, and the Cochrane Library) was performed from inception through December 2017, with an update through May 2018. Only studies in English were included. Keywords, MeSH terms, and phrases searched included combinations of the following "leukotriene receptor antagonist OR montelukast," AND "sleep apnea". An example of a search on MEDLINE is (("leukotriene antagonists"[Pharmacological Action] OR "leukotriene antagonists"[MeSH Terms] OR ("leukotriene"[All Fields] AND "antagonists" [All Fields]) OR "leukotriene antagonists"[All Fields] OR ("leukotriene"[All Fields] AND "receptor" [All Fields] AND "antagonist"[All Fields]) OR "leukotriene receptor antagonist"[All Fields]) OR ("montelukast"[Supplementary Concept] OR "montelukast"[All Fields])) AND ("sleep apnoea"[All Fields] OR "sleep apnea syndromes"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "syndromes"[All Fields]) OR "sleep apnea syndromes"[All Fields] OR ("sleep"[All Fields] AND "apnea"[All Fields]) OR "sleep apnea" [All Fields])

The titles and abstracts for each of the results were reviewed for relevance. Full text versions of relevant articles were obtained for complete evaluation. References from the selected articles were also reviewed and included in the review. As an additional step, each time a relevant article was encountered during the review of titles and abstracts, the "related citations/articles" and "cited by" features of the five databases and Google Scholar were searched to identify any additional potentially relevant articles.

Study selection

Inclusion criteria consisted of randomized controlled trials (RCTs) comparing LTRA against placebo in children between one and 16 years old. Report of quantitative outcomes data of AHI or respiratory disturbance index (RDI) comparing LTRA and control was required. Only English language study designs were included. Exclusion criteria consisted of studies without respiratory outcome, combined treatments and studies on adults.

Data abstractions and study quality assessment

Two authors (PS and NC) performed literature searches, screened titles and abstracts, and retrieved articles for further review. Data included patient's age, sex, body mass index (BMI) and quantitative polysomnographic data of AHI, minimal oxygen saturation and adenoidal-nasopharyngeal (A/N) ratio. The Cochrane Collaboration's tool was used for assessing risk of bias. [24] It appraised the study's adequacy in relation to six domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

We assigned a judgment of either "Yes" (low risk of bias), "No" (high risk of bias) or "Unclear" (unclear or unknown risk of bias).

Statistical analysis

Statistical analysis was performed, using Cochrane Collaboration's Review Manager (REVMAN) Software version 5.3. OAHI, minimal oxygen saturation and A/N ratio mean differences (leukotriene receptor antagonist and placebo or no treatment), standard deviation (SD), and 95% confidence interval (95% CI) were calculated. The null hypothesis was that there is no difference between

leukotriene receptor antagonists and control. The REVMAN random effects model for pooling effects was applied if heterogeneity of treatment effects was presented 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%). [25] Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [26] were adhered to as much as possible.

Results

The search identified a total of 461 articles after removal of duplicates. After the preliminary review of titles and abstracts, a total of 7 studies were identified as relevant, and full texts were downloaded for further evaluation (Figure 1).

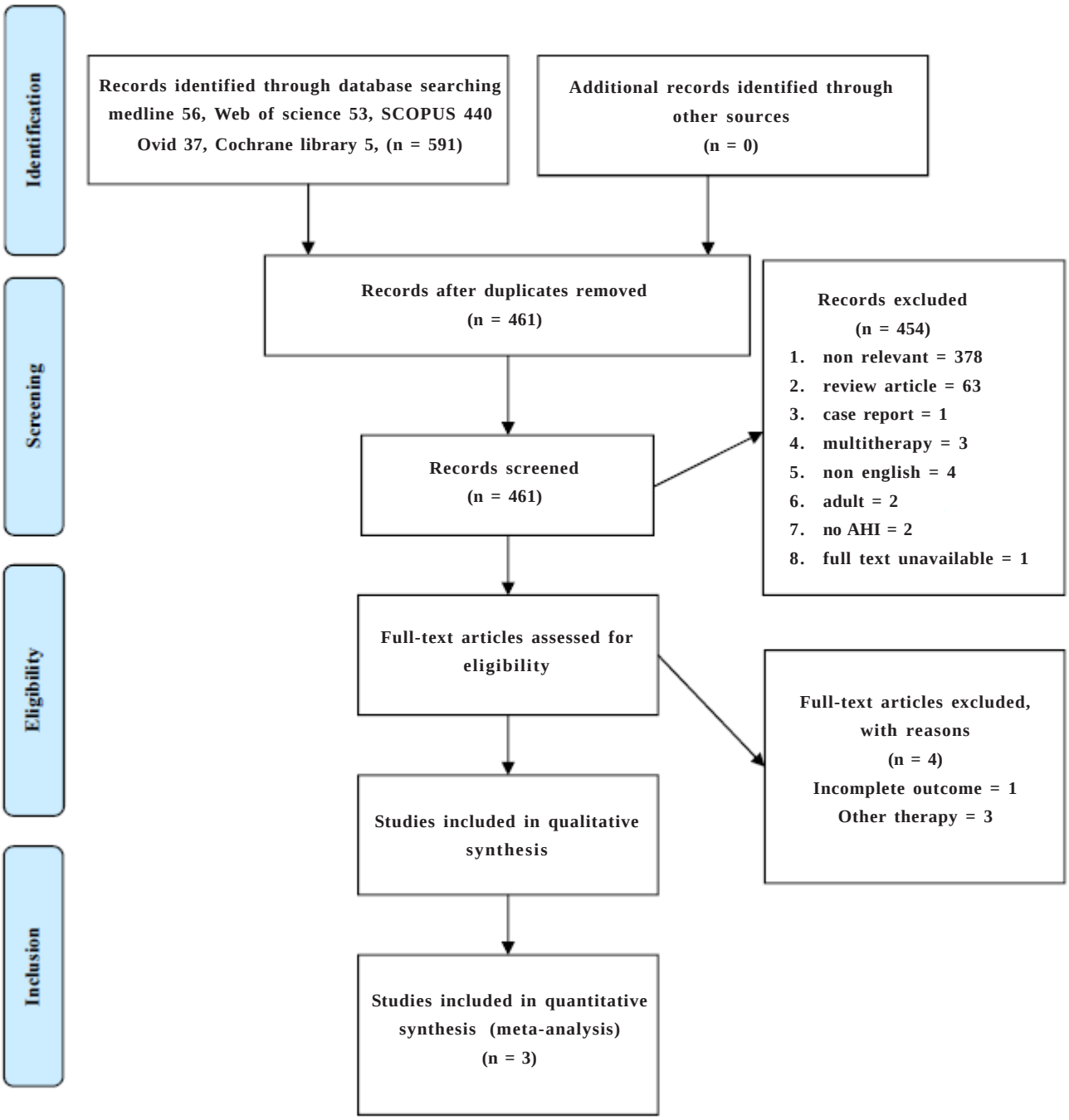

Figure 1. PRISMA flow diagram demonstrates literature search and study selection. *N* number of article.

A total of three articles were included in this study [21-23], with a total of 143 patients identified within these articles. The mean patient age was 5.28 ± 2.17 years old. The mean obstructive apnea hypopnea index (OAHI) was 6.71 ± 2.90 events per hour. The study of Goldbart AD, *et al*. reported children's weight as average body mass index (BMI) [21], which was 19.70 ± 0.90 kg/m^2 whereas the study of Goldbart AD, *et al*. and Kheirandish-Gozal L, *et al*. used average Z score which was 0.80 ± 1.20 and 1.40 ± 0.46, respectively [22, 23] (Table 1).

Methodological quality of the included studies

The included studies consisted of 2 randomized control trials and 1 open label trial which are all level 1 evidence. The Cochrane Collaboration's tool was used for assessing the risk of bias (Figure 2).

Table 1. Summary data of included studies.

References	N	Male/Female	Mean age (years)	OAHI (events/ hour)	Study duration (weeks)	Follow up (weeks)	Study
Goldbart AD, *et al*. (2005)	40	18/22	5.51 ± 1.92	4.88 ± 0.21	16	16	open label
Goldbart AD, *et al*. (2012)	46	23/23	4.75 ± 2.15	5.85 ± 3.21	12	12	RCT, double blind
Gozal D, *et al*. (2016)	57	28/29	5.55 ± 2.45	8.69 ± 4.56	16	16	RCT , double blind

Definition of abbreviations: N = number of participants, OAHI = obstructive apnea–hypopnea index. Some data are expressed as means ± SD.

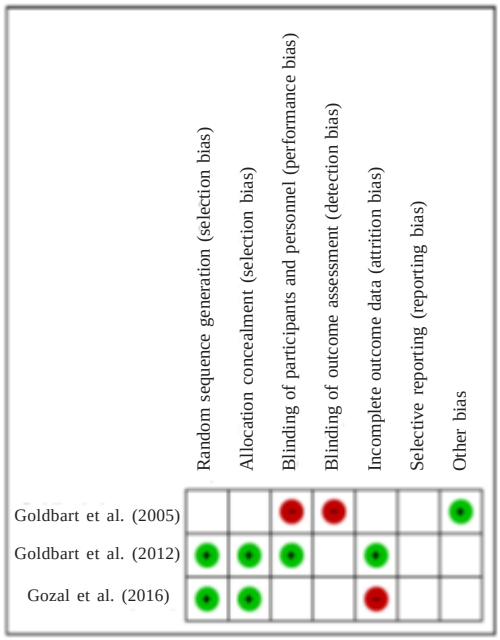

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

We deemed one trial as high risk of bias (Goldbart AD, *et al.*) and two other trials as unclear risk of bias (Kierandish-Gozal L, *et al.*).

Obstructive apnea hypopnea index (OAHI)

All of the included studies defined obstructive apnea as the absence of airflow with continued chest wall and abdominal movement for a duration of at least two breaths. In the study of Goldbart AD, *et al.*, hypopnea was defined as a decrease in oronasal flow greater than 50% on either the thermistor or nasal pressure transducer signal with a corresponding decrease in arterial oxygen saturation greater than 4% or arousal [21] whereas the study of Goldbart AD, *et al.* and Kierandish-Gozal L, *et al*. defined hypopnea as a 50% decrease in nasal flow with a corresponding 3% decrease in arterial oxygen saturation, and/or arousal or awakening. [22, 23] The OAHI was defined as the number of apneas and hypopneas per hour of total sleep time in all studies.

Pool analysis of the data demonstrated a statistically significant reduction of 2.72 events per hour in OAHI between LTRA and control [95% confidence interval (CI) (- 3.95, - 1.49); $P < 0.0001$]. The test for heterogeneity was not significant ($P = 0.07$). However, moderate heterogeneity was demonstrated ($I^2 = 62\%$); thus, the random effect model was utilized for heterogeneity among these studies (Figure 3).

Minimal oxygen saturation

Pool analysis of the data demonstrated a statistically significant increase of 3.27 % in minimal oxygen desaturation between leukotriene receptor antagonists and control [95% CI 1.78, 4.77); $P < 0.0001$]. The test for heterogeneity was not significant ($P = 0.22$) and inconsistency was low heterogeneity ($I^2 = 33\%$); this indicates the use of the fixed effects model (Figure 4).

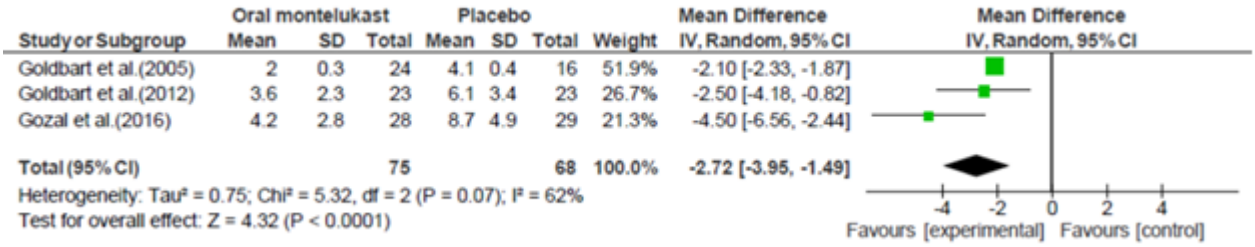

Figure 3. Forest plot: random effects analysis for meta-analysis of mean difference of Obstructive apnea/hypopnea index (OAHI) events per hour between leukotriene receptor antagonists and placebo or no treatment. There was statistically significant difference in OAHI (mean differences 2.72, 95% confidence interval (CI) (−3.95, – 1.49); $P < 0.0001$]. IV independent variable, SD standard deviation.

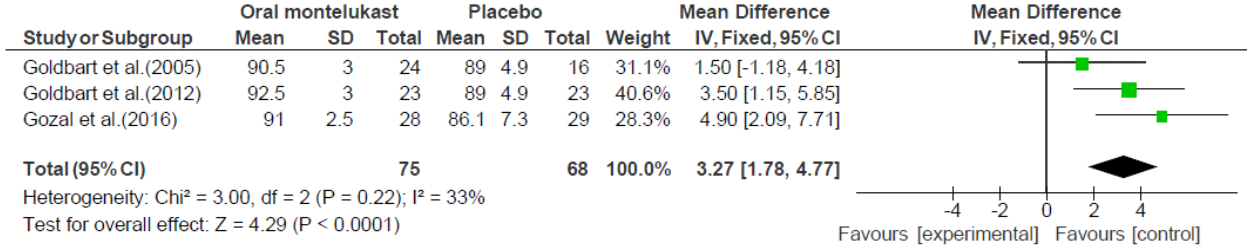

Figure 4. Forest plot: fix effects analysis for meta-analysis of mean difference of minimal oxygen desaturation between leukotriene receptor antagonists and control. There was statisticaly significant difference in minimal oxygen desaturation [(mean differences 3.27, 95% confidence interval (CI) (1.78, 4.77); $P < 0.0001$]. IV independent variable, SD standard deviation.

Adenoid size

Two studies (86 patients) reported adenoid size. [21, 22] Both reported adenoid size as adenoidal-nasopharyngeal (A/N) ratio using the method of Fujioka M, *et al*.[27] which divided the value of "A" (distance from the point of maximal convexity along the inferior margin of adenoid to the anterior margin of basio-occiput) by the value of "N" (distance from posterior nasal spine to spheno-occipital synchrondrosis.

Pool analysis of the data demonstrated significant reduction of adenoid size in that 0.21 reduction of A/N ratio was noted between leukotriene receptor antagonists and control [95% CI (- 0.25, - 0.17); $P < 0.00001$]. The test for heterogeneity was significant ($P = 0.01$). However, high heterogeneity was demonstrated ($I^2 = 85\%$); thus, the random effects model was utilized for heterogeneity among these studies (Figure 5).

Adverse drug events

Only minor adverse events were reported in the study of Kheirandish-Gozal L, *et al*., in which headache was reported in one patient with LTRA, and in one patient with placebo. Nausea was reported in one patient with LTRA, and in two other subjects with placebo. [23] The other two included studies reported no adverse drug events.

Discussion

OSA in children was linked to inflammation. In comparison with control subjects, increases in various inflammatory mediators including leukotriene in exhaled breath condensate and in tonsil tissue were noted among children with OSA, and were disease severity-dependent. [28, 29] Studies also reported more expression of leukotriene receptor in the tonsil tissue of children with obstructive sleep apnea in comparison with controls who has recurrent infection. [30, 31] With the use of LTRA, reduction of cell proliferation and inflammatory cytokines in OSA children were reported [28, 32], and this may reduce the size of hypertrophic tonsils and adenoid.

Our study demonstrated that LTRA can improve OSA in children with a statistically significant reduction of OAHI of 2.72 events per hour. Decreasing by the number of 2 events per hour can make a big change in pediatric OSA by reducing severity from moderate degree to mild degree, or mild degree to cure. Pool analysis of the data showed 3.27% increase in minimal oxygen saturation which was also statistically significant.

Significant reduction of adenoid size was also noted with the use of leukotriene receptor antagonist with a statistically significant reduction of A/N ratio by 0.21. The improvement of the nasopharyngeal airway supported the theoretical hypothesis of how leukotriene antagonist receptor improved OSA. The widen-nasopharyngeal airway may improve OSA according to Poiseuille's law, in which the air flow would be improved if the radius increased.

Our systematic review and meta-analysis clearly focused on the effect of leukotriene receptor antagonist for treatment in OSA children, with comprehensive search methods and clearly define inclusion and exclusion criteria. We also tried to collect unpublished data as much as we could. To the best of our knowledge, our study is the first ever that evaluates the effect of leukotriene receptor antagonists in OSA children. Although only small magnitude reduction of OAHI was demonstrated, this number can make a big change to the clinical outcome, especially in mild to moderate degree of OSA. The included studies considered LTRA usage with the period of 12 to 16 weeks as safe, as only minor adverse drug reactions were reported only in Kheirandish-Gozal study [23], in which there was no difference in number between LTRA and placebo.

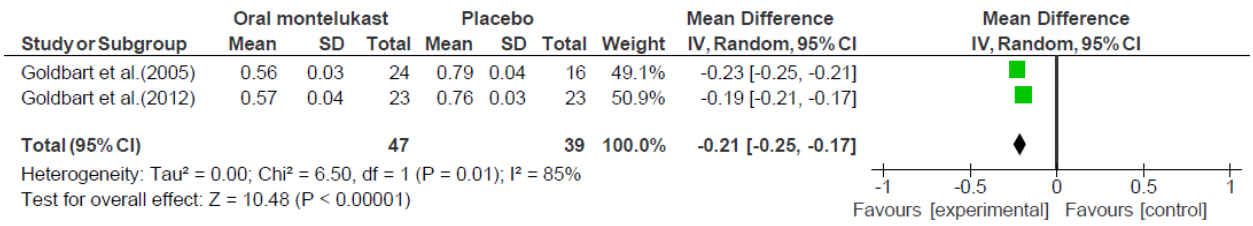

Figure 5. Forest plot: random effects analysis for meta-analysis of mean difference of A/N ratio between leukotriene receptor antagonists and control. There was statistically significant difference in A/N ratio [mean differences 0.21, 95% confidence interval (CI) (- 0.25, - 0.17); $P < 0.00001$]. IV independent variable, SD standard deviation.

Other systematic review and meta-analysis study which combined Montelukast and nasal corticosteroids for treatment pediatric OSA also showed improvement of AHI and lowest oxygen saturation in mild pediatric OSA. [33]

However, our study has limitations. One of the included studies was an open label trial. [21] This may cause performance bias and affect the outcome of our study. Another study had numbers of dropped out which may cause attrition bias. [23] However, both of them met our inclusion criteria and had qualitative outcome so we decided to include in our study. Although we used our best effort for the searching, there might still be some publication bias due to unpublished data.

In this study, we can conclude that LTRA can improve OSA in children by reducing AHI, increasing minimal oxygen saturation and reducing adenoid size. However, due to small numbers of studies and limitations of the studies as mentioned above, future studies with numerous populations and methodologically randomization are still needed.

Conclusion

Leukotriene receptor antagonist provides benefits in OSA children in terms of significant improvement of OAHI, minimal oxygen saturation and A/N ratio. Data were based on meta-analysis of control trial with 12 - 16 months of follow-up. However, due to small number of studies and no randomization, further studies with larger populations with methodologically randomization are needed to confirm their effectiveness on OSA children.

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Declaration of interest: none

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Conflict of interest

The authors, hereby, declare no conflict of interest.

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