

Montelukast for Children With Obstructive Sleep Apnea: A Double-blind, Placebo-Controlled Study

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KEY WORDS

obstructive sleep apnea, tonsillectomy and adenoidectomy, sleep disordered breathing, leukotrienes

ABBREVIATIONS

AHI—apnea/hypopnea index

OAI—obstructive apnea index

OSA—obstructive sleep apnea syndrome

T&A—adenotonsillectomy

Dr Goldbart had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis. Drs Tal and Goldbart were responsible for study concept and design and acquisition of data; Drs Tal and Greenberg-Dotan were responsible for analysis and interpretation of data; Drs Tal, Goldbart, and Greenberg-Dolan were responsible for drafting of the manuscript; Drs Tal and Goldbart were responsible for critical revision of the manuscript for important intellectual content; and Dr Greenberg-Dolan was responsible for statistical analysis.

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WHAT'S KNOWN ON THIS SUBJECT: Children with obstructive sleep apnea (OSA) are usually treated by surgical removal of their upper airway lymphadenoid tissue. Recently, medications were offered to patients with nonsevere OSA. Montelukast, for this indication, had never been studied in a randomized controlled manner.



WHAT THIS STUDY ADDS: Montelukast effectively reduced polysomnographic findings, symptoms, and the size of the adenoidal tissue in children with nonsevere OSA. The findings support the potential of a leukotriene modifier as a novel, safe, noninvasive alternative for children with mild to moderate OSA.

abstract

OBJECTIVES: Children with nonsevere obstructive sleep apnea (OSA) benefit from alternative therapeutic interventions such as leukotriene modifiers. We hypothesized that montelukast might improve OSA in children. We tested this hypothesis in a double-blind, randomized, placebo-controlled fashion.

METHODS: Of 50 possible candidates, we recruited 46 children with polysomnographically diagnosed OSA. In this prospective, double-blind, randomized trial, children received daily oral montelukast at 4 or 5 mg (<6 or >6 years of age, respectively) or placebo for 12 weeks. Polysomnographic assessments, parent questionnaires, and radiographs to assess adenoid size were performed before and after therapy.

RESULTS: Compared with the 23 children that received placebo, the 23 children that received montelukast showed significant improvements in polysomnographic measures of respiratory disturbance (obstructive apnea index), children's symptoms, and adenoid size. The obstructive apnea index decreased by >50% in 65.2% of treated children. No attrition or side effects occurred.

CONCLUSIONS: A 12-week treatment with daily, oral montelukast effectively reduced the severity of OSA and the magnitude of the underlying adenoidal hypertrophy in children with nonsevere OSA. *Pediatrics* 2012;130:e575–e580

Obstructive sleep apnea (OSA) is a highly prevalent disorder in children (2%–3%).¹ Although a combination of structural and neuromuscular abnormalities contributes to the occurrence of OSA in children,² the severity of OSA is primarily related to the size of the adenoids and tonsils.^{3,4} Therefore, an adenotonsillectomy (T&A) is currently the most common treatment of children with OSA. When OSA is not treated, it can result in serious morbidity, which primarily affects the neurobehavioral and cardiovascular systems.^{5–9} In addition, it can require frequent health care utilization from the first year of life.¹⁰

Similar to adults, children with OSA develop systemic inflammation represented by increases in C-reactive protein. Interestingly, this was correlated with cognitive and cardiovascular morbidity^{11,12} that decreased after T&A.^{13,14}

Leukotrienes are key inflammatory mediators in the respiratory system. These lipid mediators are involved in the pathogenesis of childhood diseases, like asthma. They are systemically¹⁵ and locally¹⁶ involved in the propagation of inflammation in children with OSA.

Human cysteinyl leukotriene receptor-1 expression was elevated in the tonsillar tissues of children with OSA.¹ Cysteinyl leukotriene receptor-1, which interacts with leukotrienes and mediates the inflammatory pathway, was overexpressed in adenotonsillar cells¹⁷ and tissues derived from children with OSA.^{18,19} Thus, antiinflammatory agents with a safe therapeutic profile may provide an intervention alternative to T&A. Montelukast is an oral, bioavailable, cysteinyl-leukotriene receptor antagonist that is effective, safe, well tolerated, and US Food and Drug Administration approved for preventive therapy of the inflammatory component in asthma and allergic rhinitis in children 1 year old and older. Furthermore, it did not induce tolerance in long-term studies.

An open study with montelukast improved sleep-disordered breathing symptoms, polysomnographic findings, and the nasopharyngeal airway caliber.²⁰ A similar clinical response was observed when the combination of a leukotriene modifier and nasal steroids was given to children after a T&A.²¹

The purpose of this double-blind, placebo-controlled study was to test the hypothesis that montelukast therapy might be associated with improved nocturnal symptoms, anatomic characteristics, and polysomnographic results in children with OSA.

METHODS

The study was approved by the Soroka University Medical Center Human Research Committee and was listed at the National Institutes of Health site (NCT 00299910). Informed consent was obtained from the legal caregiver of each child. Children were recruited among all pediatric patients referred for evaluation of snoring. We calculated that at least 20 patients/group will be required to establish an improvement of at least 20% in the outcome parameters measured (such as obstructive apnea index [OAI], adenoid nasopharyngeal ratio), assuming $\alpha = .05$ and $\beta = .9$. Diagnostic tests included a clinical evaluation, lateral neck radiograph, and an overnight sleep study at the Soroka University Medical Sleep-Wake Center. Inclusion criteria were as follows. Eligible children were >2 years and <10 years, had habitual snoring, and fulfilled the criteria for nonsevere OSA (obstructive apnea/hypopnea index [AHI] <10) on the initial overnight polysomnographic assessment.²² We excluded children with obesity, defined as a BMI z score of >1.645 (95%); craniofacial, neuromuscular, syndromic, or defined genetic abnormalities; current or previous use of montelukast; acute upper respiratory tract infection; use of any corticosteroids or antibiotics

within 4 weeks preceding the initial sleep study; and any children that had had T&A in the past.

Study Design

The study was conducted as a double-blind, randomized, placebo-controlled design.

Children were recruited by one of the authors (A.D.G.). A clinical research coordinator randomly assigned each child to 1 of 2 treatment groups ($n = 23$ in each group). We chose block randomization (blocks of 4, by using a table of random digits) to create the allocation sequence. Each child received 12 weeks of treatment with montelukast (Singulair, Merck) or placebo tablets. Montelukast was given at 4 and 5 mg per day to children <6 and >6 years of age, respectively. The placebo tablets were prepared by the hospital pharmacy (Soroka University Medical Center; Beer Sheva, Israel). The numbers on the containers (medication and placebo) were drawn by the chief pharmacist (according to the numbers in the randomization table), who gave the list to the investigators only at the end of the study. During the study, the investigators were blinded to group assignment. Montelukast and placebo tablets were provided in identical, similarly colored, opaque capsules. Parents were instructed to give the treatment at bedtime. Upon completion of the 12-week course, patients underwent a second polysomnograph test. Parents were contacted monthly by the investigators to determine compliance and potential side effects.

Lateral Neck Radiographs

For assessment of airway patency, lateral neck radiographs were performed with standard techniques in the radiology department of the hospital. The neck was extended, and the patient was instructed to breathe through the nose. The adenoidal/nasopharyngeal ratio

was measured according to the method of Fujioka and colleagues²³ by 2 investigators (A.D.G. and A.T.), who were blinded to the polysomnographic findings. Lateral neck radiographs were performed before and after the 12-week course.

Overnight Polysomnography

All participating children were studied with polysomnography. No sleep deprivation or sedation was implemented. Children were studied in a dedicated quiet, darkened room with an ambient temperature of 24°C in the company of one of their parents.

The polysomnographic study was performed with a computerized, commercially available, sleep-monitoring system (SensorMedics Inc, Yorba Linda, CA). Data were streamed to an optical disk for later analysis. Polysomnography was performed as previously described.¹² All of the studies were initially scored by a certified technician. The scores were then blindly reviewed by 2 physicians experienced in pediatric polysomnography. Analysis of the polysomnograms was performed with standard techniques.²⁴ In brief, sleep staging was performed with the standard criteria published by the American Academy of Sleep Medicine in 2007.²⁵ Obstructive apnea was defined as airflow cessation with continued chest wall and abdominal movement over at least 2 breaths.²⁵ Hypopneas were defined as a $\geq 50\%$ decrease in nasal flow with a corresponding $\geq 3\%$ decrease in SpO_2 , and/or arousal or awakening.²⁵ OAI was defined as number of obstructive apneic events per hour of sleep. We determined the mean and nadir SpO_2 values. Arousals were defined as recommended by the revised American Academy of Sleep Medicine guidelines.²⁵

Data Analysis

Results are presented as means \pm SD, unless stated otherwise. The primary

outcomes were the OAI and obstructive AHI, as well as the apnea index and respiratory arousal index; the secondary outcome was the adenoid size estimate. All numeric data were subjected to statistical analyses with either *t* tests or 2-way analysis of variance procedures for repeated measures, as described by Neuman-Keuls. Post hoc tests were performed as appropriate. A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

A total of 46 children were recruited out of 50 consecutive, potentially eligible candidates. A total of 75 children were screened; 25 were found ineligible for the study. The reasons for ineligibility were an AHI of >10 per hour of total sleep time ($n = 20$), and a previous T&A ($n = 5$). In addition, among the 50 eligible children, 4 children or their families lacked interest in the study. These 4 children did not differ in any aspect from those who did participate in the study. Of the final 46 participants, all completed the protocol. There was no

withdrawal, and no side effects were reported by the participants. Table 1 shows the demographic and polysomnographic characteristics of the 46 children who completed the study.

The 23 children treated with oral montelukast for a 12-week period showed significant improvements in several polysomnographic parameters like OAI. Improvements were also noted in the AHI and the SpO_2 nadir (although not significant; Fig 1). In fact, we recorded a $>50\%$ decrease in the AHI in 65.2% of treated children. Sleep macroarchitecture was not affected by therapy, with the exception of a decrease in stage 1 sleep (Table 1). In addition, a significant reduction in adenoid size occurred; the adenoidal nasopharyngeal ratio decreased from 0.81 ± 0.04 before treatment to 0.57 ± 0.04 after 12 weeks of montelukast therapy ($P < .001$; Fig 2). These findings contrasted with the 23 children in the placebo-treated control group. The controls exhibited no changes for most of the measurements, with the exception of a mild worsening of the total arousal

TABLE 1 Demographic and Polysomnographic Characteristics in 46 Children With Sleep-Disordered Breathing Who Were Treated Either With Montelukast or Placebo

	Montelukast ($n = 23$)		<i>P</i>	Placebo ($n = 23$)		<i>P</i>
	Pre	Post		Pre	Post	
Age, y	4.8 \pm 2.0		NS	4.7 \pm 2.3		NS
Gender	10F/13M			9F/14M		
BMI (z score)	0.77 \pm 1.11	0.80 \pm 1.20	NS	0.71 \pm 1.30	0.73 \pm 1.23	NS
A/N ratio	0.81 \pm 0.04	0.57 \pm 0.04	<.001	0.77 \pm 0.05	0.76 \pm 0.03	NS
Arousal index (total) (/h TST)	12.9 \pm 1.5	11.4 \pm 1.3	NS	12.7 \pm 2.0	13.6 \pm 2.0	<.02
OAI (/h TST)	3.9 \pm 1.6	1.7 \pm 1.0	<.01	3.5 \pm 1.6	3.7 \pm 1.0	NS
Desaturation index (/h TST)	3.5 \pm 1.22	2.2 \pm 2.3	.09	3.7 \pm 3.2	3.1 \pm 3.4	NS
Obstructive AHI (/h TST)	6.0 \pm 3.22	3.6 \pm 2.3	.07	5.7 \pm 3.2	6.1 \pm 3.4	NS
TST, h	6.33 \pm 0.38	6.46 \pm 0.26	NS	6.28 \pm 0.34	6.37 \pm 0.33	NS
Mean sleep latency, min	13.9 \pm 1.6	17.8 \pm 2.7	NS	14.6 \pm 1.9	15.3 \pm 1.8	NS
Sleep efficiency, %	85.3 \pm 6.5	87.0 \pm 4.9	NS	87.0 \pm 5.9	89.6 \pm 5.6	NS
Minimal SpO_2	90.3 \pm 3.1	92.5 \pm 3.0	.09	90.4 \pm 2.9	89.0 \pm 4.9	NS
Mean saturation	95.4 \pm 1.7	96.1 \pm 1.9	NS	96.2 \pm 2.1	95.7 \pm 2.7	NS
Awakenings	7.5 \pm 5.4	7.1 \pm 4.1	NS	7.2 \pm 4.4	8.0 \pm 4.9	NS
Wake (%TST)	4.1 \pm 1.0	3.6 \pm 1.0	NS	4.2 \pm 0.9	4.1 \pm 1.2	NS
Stage 1 (%TST)	9.1 \pm 1.1	6.0 \pm 1.0	<.05	10.5 \pm 1.4	11.7 \pm 1.4	NS
Stage 2 (%TST)	46.1 \pm 2.0	48.3 \pm 1.8	NS	42.3 \pm 2.8	45.3 \pm 2.5	NS
Stage 3+4 (%TST)	24.0 \pm 1.7	24.8 \pm 1.2	NS	24.1 \pm 2.1	22.1 \pm 2.7	NS
Stage REM (%TST)	16.0 \pm 1.0	18.5 \pm 1.0	NS	19.0 \pm 1.3	18.5 \pm 1.4	NS

Measurements were taken at study entry (pre) and after 12 weeks of treatment (post). *P* values compare the measurements taken pre- and posttreatment in each group. A/N ratio, adenoidal/nasopharyngeal ratio; TST, total sleep time; REM, rapid eye movement; NS, not significant.

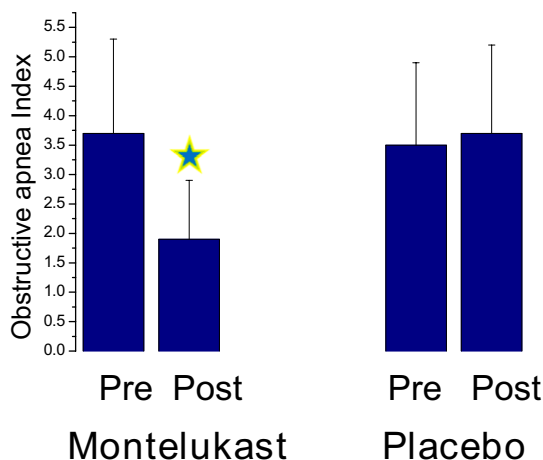


FIGURE 1

Montelukast treatment resulted in a significant improvement in the OAI. The pretreatment average of 3.7 ± 1.6 before (pre) dropped to 1.9 ± 1.0 after (post) treatment; $P < .05$. In contrast, 12 weeks of placebo treatment did not significantly change the OAI; means: 3.5 ± 1.6 (pre) vs 3.7 ± 1.0 (post) treatment; $P = .75$. Star indicates a significant difference between pre and post values.

index ($P < .05$; Table 1). Significant differences emerged in the sleep questionnaire. Only the montelukast arm showed improvements in all parameters (Table 2). Of note, there were no age-related differences in the response to treatment (with a cutoff of 4 years

old). No adverse events were reported during the study period.

DISCUSSION

This study showed that oral montelukast, administered over a period of 12 weeks in children with OSA, effectively

alleviated the severity of nocturnal respiratory disturbance, reduced the size of adenoid tissues, and significantly improved sleep symptoms. Furthermore, the treatment was not associated with any side effects and was well tolerated. These findings reproduced, in a double-blind manner, the results of an open study performed a few years ago in American children for a period of 16 weeks.²⁰

Before discussing the potential implications of our findings, some aspects of this study deserve comment. As part of our study design, we enrolled only patients who had mild symptoms and whose polysomnographic findings were in the mild to moderate range of respiratory disturbance. Thus, a priori, we could expect only a very limited range of improvement in either the respiratory abnormalities or the anatomic changes. Nevertheless, significant improvements resulted from the intervention with oral montelukast, and there was a clear lack of improvement with placebo. Finally, although the sample size was sufficiently large to support our findings, we would emphasize that this is a preliminary study that requires corroboration from larger-scale studies.

The use of antiinflammatory therapy in pediatric OSA is not an original approach, particularly considering that the surgical removal of hypertrophic adenoids and tonsils for OSA is associated with increased risk for potential postoperative complications; moreover, surgery is also associated with increased health-related costs. Indeed, Brouillette et al examined patients with moderate-to-severe OSA before undergoing T&A; they found significant improvements in respiratory disturbances after a 6-week course with intranasal fluticasone, without any changes in the size of the adenoids.²⁶ Subsequent studies of patients with milder OSA have suggested similarly beneficial

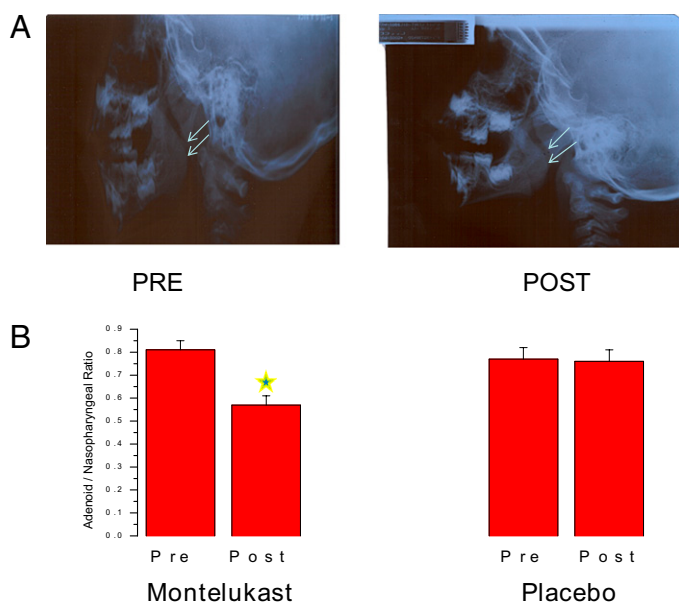


FIGURE 2

Adenoid size (adenoidal/nasopharyngeal ratio) significantly decreased with montelukast. The ratio decreased from 0.81 ± 0.04 before (pre) to 0.57 ± 0.04 after (post) treatment; $P < .001$. In contrast, children who received placebo displayed no significant changes. Star indicates a significant difference between pre and post values.

TABLE 2 Results of Questionnaire Administered to Children with Sleep-disordered Breathing at Diagnosis (Pre) and After 12 Weeks of Therapy (Post)

Question (scale 0–4)	Montelukast (n = 23)		P	Placebo (n = 23)		P
	Pre	Post		Pre	Post	
Hard to awaken	1.65 ± 0.45	0.84 ± 0.37	<.001	1.54 ± 0.49	1.25 ± 0.78	NS
Witnessed apnea	0.79 ± 0.46	0.00 ± 0.00	<.001	0.51 ± 0.41	0.57 ± 1.11	NS
Breathing difficulties	3.06 ± 1.21	1.80 ± 0.37	<.001	3.40 ± 0.00	2.04 ± 0.23	NS
Snoring	3.51 ± 0.60	1.57 ± 0.48	<.001	3.27 ± 0.51	2.68 ± 0.69	NS
Sweating	2.69 ± 0.5	0.7 ± 0.4	<.001	2.58 ± 0.51	2.62 ± 1.30	NS
Mouth breathing	3.09 ± 0.86	1.64 ± 0.37	<.001	3.01 ± 0.78	2.91 ± 1.40	NS
Awakenings	2.26 ± 0.51	1.13 ± 0.43	<.001	2.68 ± 0.49	2.42 ± 0.80	NS
Restless sleep	3.18 ± 0.50	1.66 ± 0.43	<.001	3.28 ± 0.50	2.47 ± 0.68	NS

Answers were scored are on a scale of 0 = never to 4 = most of the time. P values compare the measurements taken pre- and posttreatment in each group. NS, not significant.

effects, including a double-blind study with budesonide.^{27,28}

Although differences in the severity of OSA, selection criteria, and the overall methods make it difficult to accurately compare those studies, the overall outcomes were markedly similar, and they supported a role for the use of an antiinflammatory treatment, like nasal corticosteroids, as a nonsurgical alternative for pediatric OSA. Recent evidence indicated that cognitive and academic functions were impaired in children with all severities of sleep-disordered breathing.²⁹ Therefore, the concept of antiinflammatory therapy may indeed be applicable for children with all spectra of OSA.

Leukotrienes and their receptors are abundant in the tonsils, adenoids,^{19,20}

and exhaled condensates of OSA patients.¹⁶ This supports the hypothesis that antiinflammatory therapy against these specific mediators may positively affect children with OSA. Indeed, the previous open study that tested 16 weeks of therapy reported striking differences between treated and nontreated children. The current study, performed in a double-blind fashion, showed the same compelling results. Therefore, this antiinflammatory approach has a clear effect in children with a nonsevere form of OSA. This approach can be offered to parents as an option before, or instead of, surgery. However, it is important to acknowledge the need to follow up and switch to surgery when a child does not respond to antiinflammatory therapy.

We need to stress that the main radiographic outcome was the size of the adenoids and not the tonsils. Although leukotriene receptors are overexpressed in tonsils of children with OSA, the major effect of montelukast is seen in the adenoids²⁰ and was therefore carefully studied in this research protocol.

The patients in the current study were not obese. Thus, it is also important to note that this approach is mainly advocated for children with enlarged adenoids, not children with obesity or with enlarged tonsils as the only symptom.

CONCLUSIONS

There is increasing evidence that even mild OSA may be associated with significant cognitive, behavioral, and vascular morbidity. This sequel may have a major impact on quality of life and health care costs. The results of this study supported the introduction of a leukotriene modifier as a novel, safe, therapeutic alternative for the treatment of children with a nonsevere form of OSA. However, before this approach can be accepted as a medical standard of care, large-scale studies are warranted to reinforce our findings.

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