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Original Article

# Intranasal corticosteroids for mild childhood obstructive sleep apnea – a randomized, placebo-controlled study

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ABSTRACT

*Background:* The use of non-surgical treatment for childhood obstructive sleep apnea (OSA) is gaining popularity, especially in children with mild disease.
*Objective:* To test the hypothesis that intranasal corticosteroids reduce disease severity in children with mild OSA.
*Study design:* A randomized, double-blinded, placebo-controlled trial of intranasal mometasone furoate (MF) versus placebo in children aged 6 to 18 years with mild OSA. The primary outcome was the change from baseline obstructive apnea hypopnea index (OAHI), as documented by overnight polysomnography, after four months of treatment.
*Results:* Sixty-two children were recruited but 12 dropped out. This left 24 and 26 children for final analysis in the MF and placebo group, respectively. The OAHI and oxygen desaturation index (ODI) improved significantly in the MF group only. The OAHI decreased from $2.7 \pm 0.2$ to $1.7 \pm 0.3$ in the MF group, but increased from $2.5 \pm 0.2$ to $2.9 \pm 0.6$ in the placebo group ($p = 0.039$). The mean changes in ODI in the MF group and placebo group were $-0.6 \pm 0.5$ and $+0.7 \pm 0.4$, respectively ($p = 0.037$).
*Conclusion:* Four months of treatment with intranasal mometasone furoate effectively reduces the severity of mild OSA in children.



## 1. Introduction

Childhood obstructive sleep apnea (OSA) is characterized by prolonged partial and/or intermittent complete upper airway obstruction during sleep, which disrupts normal ventilation and sleep architecture [1]. The prevalence of childhood OSA in healthy children has been reported to be up to 5% [2,3]. If the condition is not treated, it can lead to a variety of important complications, namely: neurobehavioral deficits, systemic hypertension, and ventricular and endothelial dysfunction [4–6]. Neurocognitive deficits have also been reported, even in children with mild disease (obstructive apnea hypopnea index [OAHI] 1–5) [7].

Adenotonsillar hypertrophy is the most common cause of childhood OSA, and adenotonsillectomy remains the first-line treatment of choice; it can significantly improve the apnea hypopnea index [1,8]. A recent randomized trial showed that when compared with watchful waiting, adenotonsillectomy in school-age children with OSA resulted in greater reductions in symptoms and greater improvements in behavior, quality of life, and polysomnographic findings [9]. However, adenotonsillectomy may not be universally suitable for all children with OSA and relative contraindications include: very small tonsils and adenoid; bleeding disorders refractory to treatment; and submucus cleft palate or other medical conditions making patients medically unfit for surgery [1]. The procedure is not without risks, and complications such as hemorrhage and post-surgical respiratory compromise have been reported to occur in up to 28% of OSA patients [10,11]. The acceptance of surgery as treatment for sleep apnea in Hong Kong is generally low, and parents are always seeking non-surgical alternatives. Furthermore, there is no consensus on the cut-off of OSA severity for adenotonsillectomy, and it is usually reserved for children with moderate-to-severe disease, namely those with an OAHI >5/hr. At the time of writing, the management of children with the milder form of OSA has not been unified; however, the use of non-surgical treatment options is gaining popularity.

Nasal and oropharyngeal inflammation is present in children with OSA and may play an important role in the pathogenesis of

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breathing disturbances during sleep [12]. Local and systemic inflammatory markers and pro-inflammatory cytokines are increased in children with OSA and promote lymphoid tissue proliferation [13]. Therefore, anti-inflammatory agents, especially topical nasal spray corticosteroids, are suggested to have a potential role in reversing adenotonsillar enlargement [14–16]. Furthermore, these medications have proven effectiveness against allergic rhinitis, which is a common co-morbidity in children with OSA [2]. A recent Cochrane review suggested the necessity for further randomized, controlled trials in order to evaluate the use of topical nasal corticosteroids in children with OSA [3].

The present study was a randomized, double-blinded, placebo-controlled trial to test the hypothesis that topical intranasal corticosteroids reduce disease severity in children with mild OSA. The primary endpoint of interest was the change from baseline OAHI, as documented by overnight polysomnography (PSG), after four months of treatment. The secondary endpoints included the change from baseline in: (1) tonsil and adenoid size; and (2) nasal symptoms. It was hypothesized that treatment with intranasal corticosteroids would lead to a significant reduction in OAHI.

## 2. Methods

### 2.1. Subjects and study design

Children aged 6–18 years, who attended the sleep disorder clinic and reported to have symptoms of sleep disordered breathing (SDB), were recruited from May 2006 to March 2008 for overnight PSG. Suitable subjects were invited to participate in the study if they had habitual snoring (≥3 nights per week) and their PSG revealed mild OSA (OAHI of ≥1–5). Exclusion criteria were the presence of any of the following: genetic syndromes, congenital or acquired neurological diseases, neuromuscular diseases, craniofacial abnormality, previous upper airway surgery, known fixed nasal obstruction such as previous nasal fracture or deviated nasal septum.

Restricted block randomization was implemented. The children were allocated to receive mometasone furoate (MF) or placebo, using double-blinded randomization with a sealed opaque envelope method. The allocation was based on a computer-generated randomization list with varying block sizes. The procedures of randomization and allocation were performed by one of the investigators (AM Li), who was not involved in the data collection. Corticosteroids (MF) and placebo were provided in numbered identical containers. The appearances of the active drug and placebo were indistinguishable. Each corticosteroid spray delivered 50 mcg of active drug. The study drug was given as two sprays per nostril in the evening for the subsequent four months. The dose was chosen as it has been shown to be safe and effective for children with allergic rhinitis [17]. The participants were not allowed other medications that could influence nasal inflammation or patency, such as leukotriene receptor antagonist, antihistamines, and decongestants. Before the start of treatment, each child had completed a symptom questionnaire and had undergone an upper airway evaluation by an otorhinolaryngologist. All participants underwent PSG, upper airway examination, and questionnaire assessment again at the end of a 4-month treatment period. Each participant was also given a diary to complete on a daily basis in order to ensure therapy compliance and to document any side effects from the medication.

This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and Centre for Clinical Trials, The Chinese University of Hong Kong (reference number: CUHK_CCT00119). Informed consent and assent were obtained from the legal caregiver of each child and the child, respectively.

### 2.2. Overnight polysomnography evaluation

The overnight PSG was performed in a dedicated sleep laboratory with Siesta ProFusion II PSG machine (Compumedics, Australia) [18]. The following parameters were recorded: electroencephalogram (EEG) from four channels (C3/A2, C4/A1, O1/A2, O2/A1), bilateral electro-oculogram, electromyogram (EMG) of mentalis activity, and bilateral anterior tibialis. Piezo respiratory effort belts measured respiratory movements of the rib cage and abdomen. Electrocardiogram and heart rate were continuously recorded from two anterior chest leads. Arterial oxyhemoglobin saturation (SaO2) was measured by an oximeter (Ohmeda Biox 3900 Pulse Oximeter; Ohmeda, Louisville, CO) with a finger probe. Respiratory airflow pressure signal was measured via a nasal catheter placed at the anterior nostril nares and connected to a pressure transducer. A snoring microphone placed near the throat measured snoring. Body position was monitored via a body position sensor.

OSA was defined as absence of airflow with persistent respiratory effort lasting at least two baseline breaths, irrespective of $SaO_2$ changes. Mixed apnea was defined as the absence of airflow for a duration of at least two breath cycles without inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event. Obstructive hypopnea was defined as a reduction of 50% or more in the amplitude of the airflow signal with persistent respiratory effort. It was only quantified if it was at least two baseline breaths and was associated with oxygen desaturation of at least 3% and/or arousals. OAHI was defined as the total number of obstructive apneas, mixed apneas and obstructive hypopneas per hour of total sleep time. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation at least 3% per hour of sleep. Arousal was defined as an abrupt shift in EEG frequency during sleep, which may include theta, alpha and/or frequencies greater than 16 Hz, but not spindles, with 3–15 s in duration. During REM sleep, arousals were scored only when accompanied by concurrent increases in submental EMG amplitude. Arousal index (ArI) was defined as the total number of arousal per hour of total sleep time.

The PSG data were scored and interpreted by an experienced sleep technologist who was blinded to the subjects' group allocation.

### 2.3. Upper airway examination

The size of tonsils and adenoid was examined endoscopically by means of a flexible fiberscope (Olympus 3 mm; Olympus, Japan). An otorhinolaryngologist, who was blinded to the group allocation and PSG result of the participants, performed the examination. Tonsil and adenoid size were reported as percentages of the oropharyngeal and nasopharyngeal airway and graded according to the following system (Table 1) [19].

### 2.4. Nasal symptom score and frequency of snoring

Nasal symptoms during the past month were assessed before and after the intervention with a visual analog scale ranging from 0 to 10 for each of the following four components: nasal blockage, nasal discharge, nasal pruritus, and eye pruritus. A composite score was

**Table 1**
Grading of adenoid and tonsil size.

| Grade | Percentage of airway occupied by soft tissue |
|---|---|
| 1 | 0–25% |
| 2 | 26–50% |
| 3 | 51–75% |
| 4 | 76–100% |