Intranasal Budesonide and Quality of Life in Pediatric Sleep-Disordered Breathing: A Randomized Controlled Trial

Gunnhildur Gudnadottir, MD¹, Eva Ellegård, MD, PhD², and Johan Hellgren, MD, PhD¹

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. To study the efficacy of budesonide nasal spray on the health-related quality of life and symptoms among children with sleep-disordered breathing.

Study Design. Randomized, parallel, double-blind, placebo-controlled trial.

Setting. Tertiary referral center.

Subjects and Methods. Sixty children (ages, 4-10 years) who were referred because of snoring and/or apneas for >3 months were included between January 2015 and June 2016 and randomized in a double-blind design to treatment with 64 µg/mL of budesonide nasal spray (n = 30) or placebo nasal spray (n = 30) twice daily for 6 weeks. The primary outcome measurement was the change in the mean OSA-18 total score from baseline. Other variables examined were individual OSA-18 domains, a visual analog scale for quality of life, symptoms (snoring, apneas, and nasal obstruction), and adenoid and tonsil size. The trial was investigator initiated and not sponsored by the pharmaceutical industry.

Results. Fifty-five children completed the trial. An intention-to-treat analysis revealed a significantly greater improvement in the mean OSA-18 total score after treatment with budesonide than placebo (19.5 vs 7.5, \(P = .0014\)). Intranasal budesonide also improved 2 OSA-18 domains (sleep disturbance, caregivers’ concerns), the visual analog scale score for quality of life, as well as snoring, apneas, and nasal obstruction. No serious adverse events were reported that could be linked to the treatment.

Conclusion. Among children with sleep-disordered breathing, 6 weeks’ treatment with intranasal budesonide significantly improved quality of life and symptoms as compared with placebo nasal spray.

Keywords

sleep-disordered breathing, children, OSA-18, quality of life, intranasal steroids, adenoid

Received June 25, 2017; accepted October 26, 2017.

Sleep-disordered breathing (SDB) is a common condition, affecting 4% to 11% of children.¹ The symptoms range from simple snoring to severe obstructive sleep apnea (OSA), often with a substantial negative effect on health-related quality of life (HRQoL).² SDB is typically caused by hypertrophy of the tonsils and/or adenoids, and adenotonsillectomy is usually an effective treatment, reducing symptoms and apnea-hypopnea index (AHI) and improving HRQoL,³ although it carries a risk of complications.⁴ Recently published guidelines from the European Respiratory Society task force on the diagnosis and management of obstructive SDB in childhood recommend nasal steroids as the first line of treatment for children with SDB.⁵,⁶ This is based on research showing that nasal steroid treatment reduces the size of the adenoids,⁷ alleviates symptoms (snoring, apneas, and nasal obstruction),⁸ and improves polysomnography (PSG) results.⁹ To our knowledge, there is no previous randomized, placebo-controlled study of the effect of intranasal steroid treatment on the HRQoL of children with SDB.

The OSA-18 is a validated instrument for monitoring the HRQoL of children with SDB.¹⁰ It has been widely used in research on the effect of tonsil surgery on children’s HRQoL¹¹ and is therefore suitable for monitoring the clinical efficacy of intranasal steroid treatment. There is no clear correlation between the severity of OSA (based on PSG) and HRQoL (based on OSA-18),¹² and snoring can have a substantial negative effect on HRQoL, even when the AHI is low. Studies have also shown that primary snoring can have a greater impact on cognitive and behavioral functions.

¹Department of Otorhinolaryngology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
²Department of Otorhinolaryngology, Halland’s Hospital, Kungsbacka, Sweden

Corresponding Author:
Gunnhildur Gudnadottir, MD, Department of Otorhinolaryngology, Sahlgrenska University Hospital, Gröna stråket 9, SE-413 46 Gothenburg, Sweden.
Email: gunnhildur.gudnadottir@vgregion.se
than more severe OSA.\textsuperscript{13-15} Therefore, examining the effect of nasal steroids on children’s HRQoL is equally as important as the effect on their PSG results. The purpose of the trial was to investigate the effect of budesonide nasal spray on HRQoL in a sample of children with SDB. The study was investigator initiated and was conducted without any support from the pharmaceutical industry.

**Methods and Materials**

**Study Design**

This is a prospective, randomized, double-blind, placebo-controlled clinical trial with 2 parallel groups of pediatric patients referred to a tertiary ear, nose, and throat department with symptoms of SDB. The study was conducted at Sahlgrenska University Hospital, Gothenburg, Sweden, from January 2015 to June 2106. The guardians of each child and the child, when appropriate, gave their informed consent to participate in the study. No changes were made to the study protocol after the commencement of the study. The trial was designed and reported in accordance with the CONSORT statement (http://www.consort-statement.org). It was approved by the Regional Ethical Board, Gothenburg (Dnr 719-13), and the Swedish Medical Products Agency (Dnr 5.1-2014-84538) and registered at the European Clinical Trials Database (EudraCT 2013-004620-10).

**Patient Selection.** Referrals of children with a history of snoring and/or apneas were screened throughout the 18-month duration of the trial by the research nurse and the investigating physician (G.G.). Potential participants received a letter with a description of the study and were contacted by telephone a few days later for further information.

The inclusion criteria were as follows: children aged 4 to 10 years with a history of snoring and/or apneas for the last $\geq$3 months and with a valid address in Sweden between January 2015 and December 2016. The age range was set to include children who were old enough to collaborate in all elements of the trial, and children $>10$ years of age were excluded as pubertal changes could affect study outcomes.

The exclusion criteria were as follows: guardian not able to read and write Swedish; an acute respiratory infection at inclusion; the use of nasal or systemic corticosteroids or antibiotics within 4 weeks prior to enrollment; a history of tonsil or adenoid surgery; craniofacial, neuromuscular, or genetic disorders; severe SDB symptoms requiring urgent surgery; or unwillingness to participate in a randomized study.

**Randomization.** At the first visit, the included children were randomly allocated to treatment with budesonide nasal spray (64 $\mu$g/mL; Rhinocort Aqua) or placebo nasal spray. The placebo spray consisted of a solution identical to the budesonide spray, except for the active substance. The nasal spray was administered as 1 dose in each nostril twice daily, with an allocation ratio of 1:1. The study drugs were manufactured by APL (Apotek Produktion & Laboratorier AB, Gothenburg, Sweden) and were delivered in identical coded glass bottles in identical sealed containers, each containing 3 bottles of the same drug. The investigating physician was blinded to the appearance of the glass bottles. The total sample size was 60 patients. Numbers 1 to 60 were randomly assigned to budesonide or placebo in blocks of 4 by APL, via a computerized random number generator, without any stratification. The containers were delivered consecutively to the patients according to their order of appearance at the first visit. The guardians broke the seal of the container at home at the start of treatment. Blinding was strictly maintained until completion of the study protocol.

**Patient Assessment and Interventions.** Baseline demographic data were collected for all the children in terms of age, sex, height, weight, tonsillar size, and adenoid size at the first visit. All the children were examined by an otorhinolaryngologist (G.G. or J.H.). The adenoids were inspected with a flexible pediatric fiberscope (ENF-XF; Olympus, Shinjuku, Japan). The size of the adenoids was measured as the percentage obstruction of the nasal choana on the examined side (0%-100%). The tonsil size was graded on a grade scale of 0 to 4 according to Brodsky.\textsuperscript{16} All the guardians filled in the OSA-18 questionnaire and a general health questionnaire. Before initiation of treatment, all included children were scheduled for a Phadiatop allergy test (fluorescent enzyme immunoassay; ImmunoCAP, Quest Diagnostics, Secaucus, New Jersey) and an at-home overnight polygraphy sleep study with a Nox T3 portable home sleep monitor (Nox Medical, Reykjavik, Iceland), which recorded nasal airflow (via a cannula), thoracic and abdominal respiratory effort (with respiratory inductance plethysmography), oximetry (with a wireless pulse oximeter fitted to the finger), body position, actigraphy, and audio recording. Sleep indices were scored by a licensed sleep physician according to the 2015 pediatric guidelines of the American Academy of Sleep Medicine.\textsuperscript{17} A minimum of 3 hours of valid sleep data with functioning nasal airflow, respiratory inductance plethysmography, and oximetry was used as a cutoff limit for an acceptable recording. Sleep recordings not fulfilling these criteria were discarded. The sleep physician was blinded to the treatment group allocation and the order of registration.

During the 6-week treatment period, the guardians filled in a diary once weekly, reporting the number of nights with snoring, apneas, or nasal blockage and adverse events. The number of days that the child used the study drug was also reported for each week.

At the follow-up visit, 1 to 2 weeks after treatment completion, the medical examination, OSA-18 questionnaire, and polygraphy were repeated. The children were then assessed in terms of their need for further treatment according to standard clinical practice. In some cases, planned surgical treatment may have been delayed somewhat due to study participation, with the guardians’ consent.

**Quality-of-Life Questionnaires.** Quality of life was assessed with the Swedish version of the OSA-18, a validated 18-item
questionnaire with proven test-retest reliability, construct validity, and internal consistency. It contains questions across 5 domains (sleep disturbance, physical symptoms, emotional distress, daytime function, caregivers’ concerns). Each item is scored in relation to its frequency from “never” to “all the time” on a scale of 1 to 7 with a maximum score of 126. A total score <60 suggests a small impact on HRQoL; 60 to 80, a moderate impact; and >80, a large impact. The OSA-18 also includes a direct global rating of the child’s general HRQoL based on a 10-point visual analog scale (VAS; 0 = poorest, 10 = best).

**Outcome Measurements.** The primary outcome of this study was an improvement in the OSA-18 total score. Secondary outcomes included the subdomains of the OSA-18, the global HRQoL (according to the VAS), and changes in adenoid and tonsil size. The frequency of SDB symptoms reported in the diaries was also analyzed between the 2 treatment groups.

**Statistical Analysis.** The power calculation, based on a previous study, showed that 30 patients were required in each treatment group to detect a change of at least 7 points in the total OSA-18 score with 80% power and an α level of 5%. Patients were analyzed according to their randomization groups in an intention-to-treat analysis. Fisher’s permutation test, a nonparametric test, was used to compare primary and secondary outcomes between the 2 treatment groups. Cohen’s d and a 95% CI were calculated for the difference in OSA-18 total score after treatment.

A 2-sided \( P \) value <.05 was considered statistically significant. A multivariate linear regression analysis was conducted with the baseline OSA-18 total score and treatment group as independent variables and the differences from baseline as dependent variables. This was done to adjust for the difference in the baseline OSA-18 score between the treatment groups. The diary findings were analyzed as follows: for each patient, a linear regression coefficient was calculated to describe the trend over time—that is, the slope of the regression line from week 1 to week 6 for each patient and each variable in the diary, with the individual values from each time point. The time point in weeks (1-6 weeks) is the independent variable, and the variable in the diary at each time point is the dependent variable. The slope of the regression line for each individual contributes to the analysis of trend over time.

To test whether the trend over time (regression coefficient) differed from zero, Fisher’s test for paired comparison was used. Children were classified as overweight or obese with the age- and sex-specific cutoffs set by Cole et al.

SPSS 22 (IBM, Chicago, Illinois) and Microsoft Visual Basics were used to perform statistical analyses.

**Results**

Throughout the duration of the trial, from January 2015 to June 2016, 134 patients were screened, and 60 were included and randomized to treatment groups (Figure 1). No children were excluded due to severe SDB. An analysis of the 5 patients lost to follow-up revealed no difference from the other participants with regard to age, sex, or the mean baseline OSA-18 total score. The mean baseline OSA-18 total score was higher in the budesonide group than...
in the placebo group (65.2 vs 54.8, \( P = .013 \); Table 1). The improvement in the OSA-18 total score was significantly greater in the budesonide group than in the placebo group (–19.5 vs –7.5, \( P = .0014 \); Table 2). Cohen’s \( d \) for the difference in the OSA-18 total score after treatment is 0.93 (95% CI, 0.39–1.47).

Figure 2 shows the change in the OSA-18 total score between baseline and after 6 weeks of treatment for each individual. There was a significantly larger improvement in the budesonide group regarding 2 OSA-18 subdomains, sleep disturbance and caregivers’ concerns, as well as in the VAS for overall quality of life (Table 2). Adenoid size decreased in the budesonide group by a mean of 9.8 (95% CI, –16.3 to –3.4; \( P = .004 \)), but there was no decrease in the placebo group (–4.1; 95% CI, –10.7 to 2.6; \( P = .23 \)). Tonsil size according to Brodsky remained unchanged after treatment in both groups: –0.1 in the treatment group (95% CI, –0.31 to 0.11) and 0.1 (95% CI, –0.10 to 0.34) in the placebo group.

The multivariate linear regression analysis did not significantly change the effect of the baseline OSA-18 total score on the outcome for primary and secondary variables. When adjusting for the baseline OSA-18 total score, the improvement in the OSA-18 total score was still greater in the budesonide group (\( P = .010 \)). Baseline tonsil size, adenoid size, or body mass index did not have a statistically significant effect on the size of the improvement in the OSA-18 total score.

There was no significant difference in allergic sensitization between the groups, and according to the regression analysis, allergic sensitization had no effect on the change in the OSA-18 total score between baseline and 6 weeks of treatment. Regression coefficients over time showed –0.22 for snoring (\( P < .001 \)), –0.20 for apneas (\( P = .008 \)), and –0.19 for blocked nose (\( P < .001 \)) in the budesonide group, with the following corresponding figures for the placebo group: –0.04, –0.01, and 0.00, all with \( P > .30 \) (Figure 3). The difference between the groups was significant for all 3 symptoms (\( P < .02 \)).

No serious adverse effects could be linked to either treatment. Four patients, 3 in the budesonide group and 1 in the placebo group, experienced mild epistaxis. One child in the placebo group was admitted to hospital overnight due to headaches and dizziness. A mean daily use of nasal spray per week was reported by 77% in both groups.

Only 43% of the polygraphies fulfilled the minimum cutoff of 3 hours of valid data. The most common reason was missing nasal flow (40%). Table 1 presents the baseline AHI, obstructive desaturation index, and minimum oxygen saturation from the 28 children with successful pretreatment polygraphies. Only 9 children in the budesonide group and 7 children in the placebo group had successful registrations before and after treatment. According to these registrations, the AHI in the budesonide group was 3.3 before treatment and 1.5 after treatment, and the corresponding AHIs in the placebo group were 3.3 and 2.4.

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**Table 1. Baseline Characteristics of 60 Patients Randomized to Treatment with Budesonide or Placebo Nasal Spray.**

<table>
<thead>
<tr>
<th>Budesonide (n = 30)</th>
<th>Placebo (n = 30)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>5.2 (4.7-5.8)</td>
<td>5.2 (4.7-5.7)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (47)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (53)</td>
<td>11 (37)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>15.6 (15.0-16.2)</td>
<td>15.6 (14.9-16.3)</td>
</tr>
<tr>
<td><strong>Positive Phaditop allergy test</strong></td>
<td>6 (22.0)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td><strong>Tonsil grade according to Brodsky</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (6.7)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>2</td>
<td>14 (46.7)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>3</td>
<td>12 (40.0)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>4</td>
<td>2 (6.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td><strong>Adenoid size: choanal obstruction, %</strong></td>
<td>75 (69-81)</td>
<td>73 (66-81)</td>
</tr>
<tr>
<td><strong>OSA-18 score</strong></td>
<td>65.2 (58.8-71.7)</td>
<td>54.8 (50.1-59.5)</td>
</tr>
<tr>
<td><strong>Quality of life, VAS</strong></td>
<td>6.4 (5.6-7.2)</td>
<td>7.1 (6.4-7.7)</td>
</tr>
<tr>
<td><strong>AHI</strong></td>
<td>3.3 (0.9-5.7)(^c)</td>
<td>3.3 (1.0-5.5)(^c)</td>
</tr>
<tr>
<td><strong>ODI</strong></td>
<td>1.6 (0.3-2.8)(^c)</td>
<td>1.2 (0.8-1.6)(^c)</td>
</tr>
<tr>
<td><strong>Min SpO(_2)</strong></td>
<td>87.7 (83.1-92.2)(^c)</td>
<td>89.8 (86.7-92.9)(^c)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; min SpO\(_2\), minimum oxygen saturation; ODI, oxygen desaturation index; VAS, visual analog scale.

\(^a\)Values are presented as n (%) and mean (95% CI) unless noted otherwise. Nasal sprays were administered twice daily for 6 weeks (budesonide, 64 \( \mu \)g/mL).

\(^b\)\( P < .05 \).

\(^c\)\( n = 14 \).
Discussion

To our knowledge, this is the first randomized, placebo-controlled, double-blind study primarily evaluating the effect of nasal steroids on disease-specific HRQoL among children with SDB. After 6 weeks of treatment, there was a significant improvement in disease-specific HRQoL, as well as an improvement in specific symptoms, in the budesonide treatment group. The results confirm that nasal steroid treatment can be effective for children with SDB.

The effect of nasal steroid treatment on SDB symptoms and adenoidal hypertrophy has been studied, showing an improvement in symptoms, a reduction in adenoid size, and a decrease in AHI among children with mild to moderate OSA syndrome. To our knowledge, the effect of nasal steroids on the OSA-18 results has been assessed in only 1 open-label study, showing a 7-point improvement in the OSA-18 total score after 4 weeks of treatment with mometasone furoate, which was considered clinically significant.

Numerous studies have used the OSA-18 questionnaire to evaluate the efficacy of surgical methods in treating pediatric SDB. The improvement in the mean total OSA-18 score in the present study was 19.5 after 6 weeks of budesonide treatment, as opposed to 7.5 in the placebo group, which is statistically significant and clinically relevant. Studies of the effect of adenotonsillar surgery on HRQoL have shown mean improvements of 30 to 36 points in the OSA-18 total score, where the mean baseline scores were 61 to 72. In the CHAT trial, where children were randomized to adenotonsillectomy or watchful waiting, the children had a mean baseline OSA-18 total score of 53.6, which is similar to that in the present study. After 7 months, the improvement was 21.4 in the intervention group and 4.5 in the watchful-waiting group. A direct comparison between the present trial and previous surgical trials is not possible, since the patients in the present study were not all candidates for surgery, making the study populations noncomparable.

Mean tonsil size, adenoid size, body mass index, or OSA-18 total score at baseline did not predict the outcome of the treatment, but a reduction in adenoid size was seen after treatment. Possible explanations include the direct
reduction of adenoid size by the lympholytic action of steroids on adenoidal tissue, the anti-inflammatory effects of steroids, or a reduction in the significance of the adenoids as a reservoir for infection. The tonsil size remained unchanged, which was to be expected, as the effects of nasal steroids are mainly local in the nose and epipharynx.

Symptoms due to an obstructive adenoid can be similar to those of allergic rhinitis, and differentiation between them can be challenging in children. Nasal steroids have a well-documented effect on allergic rhinitis in children, but the response to treatment was not affected by allergic sensitization, which is in agreement with the results of previous studies. Double-blind studies have shown a reduction of 14% to 20% in adenoid size, whereas the reduction has been larger in nonblind trials. The adenoid size reduction of 10% in the present study is somewhat smaller. The treatment and follow-up periods in the present trial were similar to those in previous studies of the effect of nasal steroids on OSA syndrome and adenoid size, but it is, of course, possible that a longer treatment period or follow-up might have changed the results in either direction. More research is needed on the optimal treatment length.

One important strength of this study is that it was conducted without sponsorship from the pharmaceutical industry. This reduces the risk of financial conflicts of interest, which can be a potential problem in industrially sponsored research.

This trial has some weaknesses that need to be addressed. Few patients were lost to follow-up, but they all belonged to the placebo group. The sample size was based on a power analysis, but a larger sample would have added strength to the results. The randomization resulted in similar treatment groups, except for a higher baseline OSA-18 total score in the budesonide group. The group with the higher baseline value had more room for improvement, but the difference between the groups remained statistically significant, even after correction with a multivariate linear regression analysis. The prevalence of overweight children is low in Sweden, which is reflected in the study population. Overweight children are less likely to respond to tonsil surgery and medical treatment. The OSA-18 is based on the

Figure 3. Frequency of (a) snoring, (b) apneas, and (c) nasal obstruction reported by guardians in a diary after each treatment week on a 5-grade scale (0 = never, 5 = every night). Values are presented as mean and 95% CI.
caregivers’ subjective report of the children’s symptoms, which may not always be accurate, as the caregivers may miss SDB symptoms, especially if the child sleeps in a separate room. Confirmation of the effect on AHI would have added strength to the results. At-home respiratory polygraphies were performed in the study, according to routine practice at the study hospital, where PSG is rarely used in children. Unfortunately, the quality of the polygraphy recordings was too poor to draw any reliable conclusions. Unsupervised polygraphies are known to have a high failure rate as compared with PSG,33 and they are probably not useful in a research setting, given our experience from this trial. Budesonide has, however, been shown to have a significant effect on AHI per PSG in a randomized controlled trial.9 In clinical practice, PSG results are rarely available: in accordance with the guidelines of the American Academy of Otolaryngology—Head and Neck Surgery Foundation, PSG is performed only on selected patients with SDB, and treatment decisions are based primarily on clinical examination and history.34 It is therefore interesting to examine the effect on SDB even without access to PSG results.

Conclusion
This randomized, double-blind, placebo-controlled study showed that 6 weeks of treatment with intranasal budesonide had a significantly better effect on HRQoL and symptoms among children with SDB than a placebo nasal spray.

Acknowledgments
We gratefully acknowledge the contributions to this study by research nurse Louise Hafsten and statistician Helena Johansson.

Author Contributions
Gunnhildur Gudnadottir, conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript and approved the final manuscript as submitted; Eva Elleågard, conceptualized and designed the study, data analyses and manuscript preparation and approved the final manuscript as submitted; Johan Hellgren, principal investigator, conceptualized and designed the study, data collection, data analyses and manuscript preparation and approved the final manuscript as submitted.

Disclosures
Competing interests: None.
Sponsorships: None.
Funding source: The study was supported by research grants from Sahlgrenska University Hospital (ALF), the Göteborg Medical Society, ACTA Otolaryngologica, and the Local Research and Development Board for Gothenburg and Södra Bohuslän.

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