

The safety and efficacy of short-term budesonide delivered via mucosal atomization device for chronic rhinosinusitis without nasal polyposis

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Background: Budesonide is a potent corticosteroid commonly prescribed for management of inflammation in chronic rhinosinusitis (CRS). The standard for prescribing budesonide is via impregnated nasal saline irrigation (INSI), although recently the mucosal atomization device (MAD) has emerged as a theoretically superior method of distributing medication into the sinuses. The MAD atomizes medication into small droplets and this is thought to enhance absorption and improve bioavailability. However, no studies have shown whether enhanced absorption and improved bioavailability of budesonide via MAD causes adrenal suppression. The objective of this study is to determine whether budesonide via MAD affects the hypothalamic-pituitary-adrenal (HPA) axis.

Methods: Twenty CRS patients were recruited from a tertiary rhinology clinic and randomized to take budesonide (1 mg) via MAD or via INSI twice a day for 60 days. The adrenocorticotropic hormone (ACTH) stimulation test and 22-item Sinonasal Outcomes Test (SNOT-22) questionnaire were administered on days 1, 30, and 60 of the study. Plasma budesonide and cortisol levels were simultaneously quantified using a high-performance liquid chromatography-tandem mass spectrometry technique.

Results: There was no indication of adrenal suppression in either group (n = 20) based on ACTH stimulation test results nor was there significant plasma budesonide levels detected in either group. Quality of life, as indicated by SNOT-22, did not differ between groups at 60 days ($p = 0.404$; 95% confidence interval [CI], -37.2 to 15.9), but SNOT-22 scores for patients using MAD did show statistically significant improvement at 60 days compared to baseline ($p = 0.02$).

Conclusion: The MAD is likely a safe and effective method of delivering budesonide to the sinuses in the short term.

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Key Words:

chronic rhinosinusitis; budesonide; irrigations; mucosal atomization device; safety; quality of life

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Chronic rhinosinusitis (CRS) with nasal polyps (CR-SwNP) and without nasal polyps (CRSsNP) is a common condition affecting millions of North Americans. Common therapy for the inflamed nasal mucosal lining includes topical or systemic corticosteroids. Concern with systemic steroids is well documented and includes side effects such as morphological changes, hyperglycemia, infection, delayed wound healing, loss of bone density, dermal thinning, development of cataracts, and peptic ulceration.¹ Consequently, otolaryngologists prefer to use an agent that is potent enough to decrease the inflammation of the nasal mucosa while avoiding systemic side effects. In recent years, otolaryngologists have turned to topical budesonide as a potential solution to this problem.

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Budesonide, a corticosteroid, acts by binding to glucocorticoid receptors that in turn activate transcription of genes that modulate inflammation.² These gene products are expressed in varying amounts by almost all cells and tissues. Within the nasal airways they have been localized to the surface mucosa, submucosal glands, endothelial cells, and the inflammatory cells of nasal mucosa and nasal polyps.³ These gene products stimulate cytokines, endopeptidases, and other anti-inflammatory agents that exert the clinical effects observed. Like most important molecular pathways, this one is highly regulated and involves a negative feedback mechanism that decreases the number of glucocorticoid receptors available for binding following long periods of exposure to a stimulating hormone ligand.² In light of this pathway, there is cause for concern that long-term use of corticosteroids may result in suppression of the hypothalamic-pituitary-adrenal (HPA) axis that governs cortisol production. The severity of adrenal suppression will depend on several variables, including the pharmacokinetics of the particular drug and the mode of delivery.

The current practice at our institution is to administer budesonide via the mucosal atomization device (MAD; Wolfe-Tory Medical, Salt Lake City, UT). The MAD atomizes medication into tiny particles from 30 to 100 μm in size, thus increasing the surface area for absorption of medication. No studies have investigated the potential risk of increased drug absorption into the systemic circulation when budesonide is applied via the MAD. Our current study aimed to determine if budesonide administered using the MAD would result in sufficient absorption of drug through the sinonasal mucosa to cause suppression of the HPA axis.

Patients and methods

A prospective randomized controlled trial was conducted at the St. Paul's Sinus Centre, Vancouver, Canada. This trial was conducted with approval from the University of British Columbia Clinical Research Ethics Board (H10-03434) and registered as an institutionally funded clinical trial (www.clinicaltrials.gov; ID: NCT01405339). Inclusion criteria were patients diagnosed with CRSsNP, based on the Canadian clinical practice guidelines for sinusitis,⁴ and who had received bilateral functional endoscopic sinus surgery (FESS) in the past. Patients were consented for enrolment between September 1, 2011 and October 15, 2012. Patients were excluded if they were below 19 years of age, currently using systemic or topical inhaled steroids, or had used systemic steroids or topical inhaled steroids within the 30 days of their recruitment visit. Patients were also excluded if they had a history of pituitary disease, were morbidly obese, used oral contraception, or had concurrent or recent use of medications that accelerate the clearance or interfere with the production of cortisol. Patients who had a known hypersensitivity to cortisol, corticotropin, or cosyntropin were also excluded.



FIGURE 1. Devices used to deliver topical budesonide to the nose and paranasal sinuses. NeilMed rinse bottle (left) and mucosal atomization device (right).

Recruitment

Patients were randomized in an equal ratio to the control and experimental arm based on a closed-envelope system at the time of recruitment. At the end of their day 1 morning visit, patients were instructed to begin twice-daily administration of budesonide. Patients in the impregnated nasal saline irrigation (INSI) arm were instructed to administer 1 mg of budesonide (Pulmicort, AstraZeneca, London, United Kingdom) twice daily in 120 mL of saline solution using a NeilMed squeeze bottle (NeilMed Pharmaceuticals, Santa Rosa, California) (Fig. 1). Instructions were to irrigate half the solution (60 mL) through each nostril. Patients in the MAD arm were instructed to administer 1 mg of budesonide twice daily via the MAD syringe (Fig. 1). Patients atomized 0.5 mg (aqueous) into each nostril while assuming the lying head back position (Mygind position).

All atomizer devices and irrigation squeeze bottles used in this trial were provided to patients at no cost.

Adrenocorticotrophic hormone stimulation test

The adrenocorticotrophic hormone (ACTH) stimulation test was performed on all patients at day 1, day 30, and day 60 of the trial. Prior to the start of treatment on day 1, a baseline blood sample was drawn to test for the presence of preexisting adrenal dysfunction (as evidenced by deficient morning plasma cortisol presence). Following this, 250 μg of cosyntropin in 1 mL of normal saline was administered intramuscularly to patients. After 60 minutes, an additional blood sample was drawn. This protocol was repeated at each study visit. All blood samples were processed for plasma and stored at -120°C until ready for high-performance liquid chromatography–tandem mass spectroscopy (HPLC-MS/MS) analysis.

HPLC-MS/MS quantification

In this study we employed a novel approach to quantitative plasma analysis that improved the accuracy of data collection. LC-MS/MS of plasma is the best approach to quantitative analysis of cortisol and budesonide present systemically

in blood.⁵ Many clinical methods involving fluorimetry, competitive protein binding, or radioimmunoassay measure various cross-reacting steroids and are not specific for cortisol.^{6,7} In disease states or in tests of endocrine function, other steroids are secreted that could interfere with cortisol levels detected by the aforementioned assays. LC is ideal for this purpose because cortisol can be isolated and quantified in the presence of many other steroids.

For the purpose of this study, an ultra HPLC-MS/MS assay was developed and validated for the simultaneous quantification of cortisol and budesonide in human plasma.⁸ This was advantageous because a single blood sample could yield a snapshot of both budesonide and cortisol presence in the systemic circulation. The assay validation was performed according to U.S. Food and Drug Administration (FDA) Regulatory Guidelines. The range of the method was 1.0 to 500 ng/mL with a lower limit of quantitation (LLOQ) of 1.0 ng/mL for both compounds, requiring at least 100 μ L of plasma sample.

22-Item Sinonasal Outcomes Test

The validated 22-item Sinonasal Outcomes Test (SNOT-22) was administered to patients on day 1 to obtain a baseline measure of symptom severity.⁹ A follow-up SNOT-22 was administered at day 30 and day 60 to track the development of symptoms during the trial treatment period.

Statistical analysis

A *p* value greater than a type I error of 5% was used to determine statistical significance. Analysis of stimulated cortisol levels, plasma budesonide, and SNOT-22 at days 1, 30, and 60 in each group were analyzed using nonparametric analysis of variance (ANOVA) for repeated measures. An unpaired *t* test was used to compare the change in post-ACTH plasma cortisol and plasma budesonide from day 1 to day 60 between the MAD and INSI groups. Post-ACTH stimulation plasma cortisol levels detected above the threshold of 160 ng/mL indicated normal HPA function.¹⁰

Results

Twenty patients were enrolled and divided in an equal ratio between the experimental (MAD) and control (INSI) arm. There were 4 males in the MAD and 6 males in the INSI group. There was no significant difference in baseline cortisol levels between the 2 groups ($p = 0.82$). In the INSI group, there was no significant difference between stimulated cortisol levels prior to start of treatment and 60 days after treatment ($p = 0.07$) (Fig. 2). For the MAD group, there was significant difference between the stimulated cortisol at day 1 and day 60 ($p = 0.004$) (Fig. 3). However, none of the patients in either of the groups had a value <160 ng/mL indicating adrenal suppression.¹⁰ Moreover, when the difference in stimulated cortisol was compared between day 1 and day 60 for both groups, there was no significant difference between the groups ($p = 0.09$) (Fig. 4).

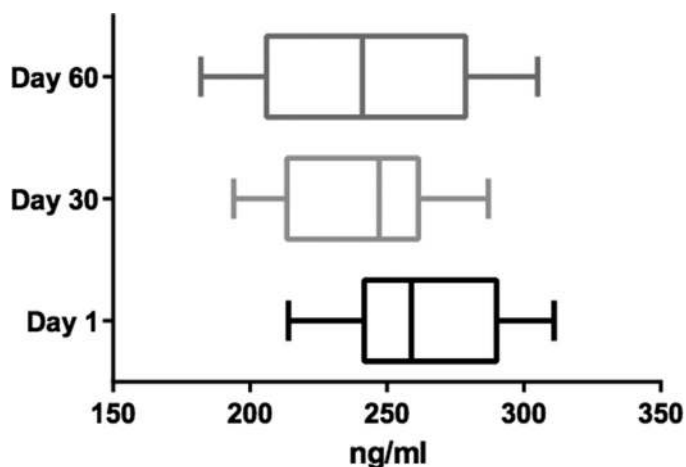


FIGURE 2. Post-ACTH stimulation test plasma cortisol levels in INSI treatment arm from baseline to 60 days. ACTH = adrenocorticotropic hormone; INSI = impregnated nasal saline irrigation.

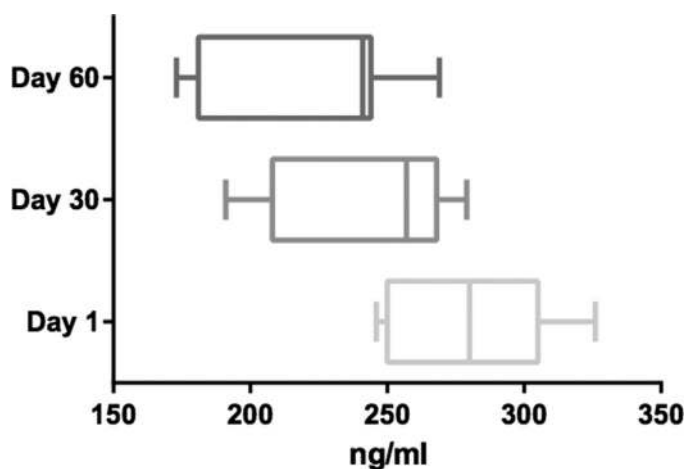


FIGURE 3. Post-ACTH stimulation test plasma cortisol levels in MAD treatment arm from baseline to 60 days. ACTH = adrenocorticotropic hormone; MAD = mucosal atomization device.

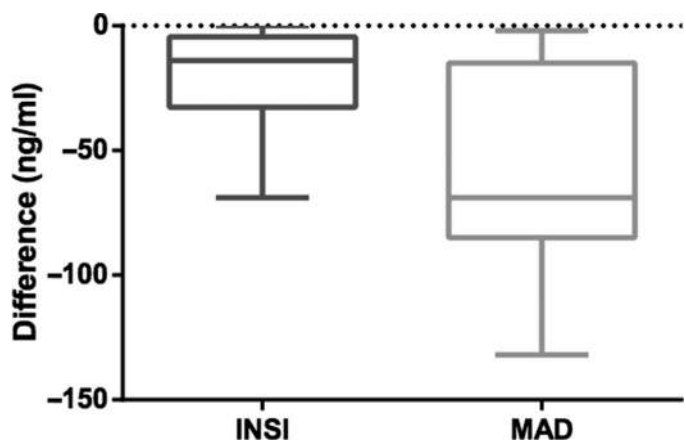


FIGURE 4. Mean change in post-ACTH stimulation test plasma cortisol levels between day 60 and day 1 (baseline) in each treatment arm. ACTH = adrenocorticotropic hormone.

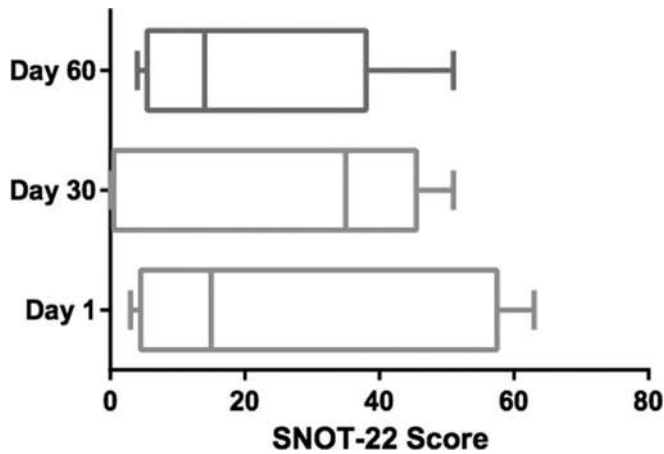


FIGURE 5. Subjective quality of life (SNOT-22) scores recorded over 60-day trial period in INSI treatment arm. Decreasing score denotes improvement. INSI = impregnated nasal saline irrigation; SNOT-22 = 22-item Sinonasal Outcomes Test.

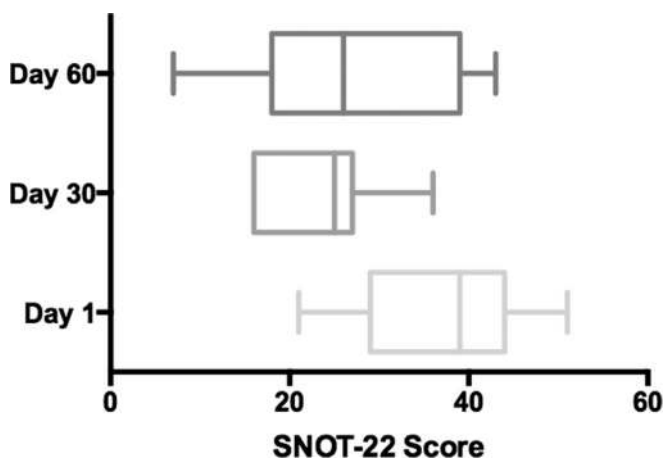


FIGURE 6. Subjective quality of life (SNOT-22) scores recorded over 60-day trial period in MAD treatment arm. Decreasing score denotes improvement. MAD = mucosal atomization device; SNOT-22 = 22-item Sinonasal Outcomes Test.

In order to determine the extent of budesonide absorption into the systemic circulation, plasma concentration of budesonide was quantified alongside cortisol in samples collected at 30 and 60 days. There was no detectable plasma budesonide in either group, despite employing an LC-MS/MS assay capable of detecting concentrations as low as 1 ng/mL.

At baseline, SNOT-22 scores were not significantly different between treatment groups ($p = 0.58$). Although SNOT-22 scores in the INSI group reflected a clinically significant improvement, they did not exhibit a statistically significant improvement over the course of the trial ($p = 0.69$) (Fig. 5). In the MAD treatment group, there was a statistically significant improvement in SNOT-22 scores after 60 days of treatment ($p = 0.02$) (Fig. 6).

There were no reports of serious adverse events from patients in either treatment arm. One patient in the MAD group experienced 2 nosebleeds that resolved sponta-

neously without medical attention. Three patients in the INSI group expressed their discomfort with the frequency and high volume of irrigation.

Discussion

Intranasal steroids are commonly used to treat a number of conditions including allergic rhinitis, and CRSwNP or CRSsNP. Clinical investigations of the effect of intranasal corticosteroids on the HPA axis can be difficult to compare as the study participants differ on variables such as inclusion of allergic rhinitis, CRS, healthy volunteers, preoperative and postoperative patients, adults and children. These studies also use different steroids at a range of doses and with various delivery methods (spray/drops/rinses). The outcome measures used also vary between studies.

Subjects in this randomized controlled trial received a short term (60 days) of topical corticosteroid therapy consisting of 1 mg budesonide twice daily via MAD or INSI, depending on the treatment arm to which they were randomized. Only minor changes in post-ACTH plasma cortisol were detected in subjects in the INSI treatment arm over the course of the trial (Fig. 2). Although a statistically significant decrease in post-ACTH plasma cortisol was detected from day 1 (baseline) to day 60 in the MAD treatment arm (Fig. 3), this change was not sufficient to satisfy clinical criteria for a diagnosis of adrenal suppression. Nonetheless, Figure 3 depicts a disconcerting trend toward the threshold for adrenal suppression that warrants further investigation over a longer period of exposure.

Many intranasal steroid preparations have been studied including prednisolone acetate nasal spray,¹¹ fluticasone propionate spray and nasules,^{12–17} triamcinolone acetonide spray,^{14,16,18} mometasone furoate spray,^{19–21} fluticasone furoate spray,^{22–24} beclomethasone dipropionate spray,^{25–28} betamethasone nasules,^{29,30} budesonide spray and respules,^{25,31–35} and budesonide respules added to saline irrigations.^{36,37} Few studies have shown any measurable impact on the HPA axis. A randomized double-blind study by Fowler et al.,²⁹ in patients with nasal polyposis, showed suppression of the HPA axis following an 8-week course of betamethasone drops but a similar length course with fluticasone nasules had no effect. A further study by the same team also showed that 6 weeks of treatment with the recommended dose of intranasal betamethasone drops suppressed the HPA axis.³⁰ However, beclomethasone dipropionate nasal spray is not associated with any suppressive effect on the HPA axis in both adults and children^{26–28} and does not produce systemic side effects, even with prolonged use of up to 6 years.²⁵

The addition of budesonide respules to sinonasal irrigations is becoming more common in the management of CRSwNP and CRSsNP. This combination has not shown any suppression of the HPA axis either preoperatively or postoperatively.^{36,37} Budesonide alone delivered in aerosol form also has no measurable effect on the HPA axis,^{25,31–34} in adults with perennial rhinitis^{25,34} and children.^{33,35} In

a study of adult volunteers administering either 200 or 400 μg twice a day for 4 days, a decrease in urinary cortisol was observed in both groups.³⁸ However, other studies in adults with nonallergic rhinitis, a 12-month treatment period was not associated with significant changes in plasma cortisol levels²⁵ or adrenal suppression.³⁴ Also, 100 or 200 μg once daily for 4 weeks in children with seasonal allergic rhinitis did not affect urinary cortisol,³⁵ and a further study on 2 to 5-year-olds with allergic rhinitis showed a dose of 64 μg once daily was well tolerated and had no measurable suppressive effect on the HPA axis.³³

In CRS, budesonide is often administered in the form of an irrigation (0.5 mg budesonide in 240 mL of normal saline). Because the concentration of steroid in this formulation is much higher than that of standard nasal steroid sprays, there are concerns about systemic absorption with subsequent suppression of the HPA axis. Sachanandani et al.³² demonstrated that budesonide nasal irrigation (0.25 mg of budesonide diluted in 5 mL of normal saline in each nasal cavity) for 30 days improved clinical symptoms in post-FESS, CRS patients without HPA suppression. Similarly, in patients with nasal polyposis placed on budesonide irrigations for 8 weeks, Balla et al.³⁶ demonstrated no significant adrenal suppression.


Several factors may contribute to the systemic distribution and absorption of budesonide. Patients suffering from CRSwNP were excluded from this study because it was thought that a polypoid middle meatal space would limit the mucosal surface area for contact and absorption, thus obscuring the true dose-suppression relationship of budesonide we set out to study. Further, CRSsNP patients, having undergone complete bilateral FESS in the past, were the focus population because their paranasal topography would be most consistent and apt for absorption studies. To maximize delivery of topical medication to the sinus cavities, the optimal delivery device and head position should be adopted. Unfortunately, there is no consensus in the literature on the best head position or delivery device for application of intranasal topical medication.^{39,40} The MAD is a novel delivery device that has been shown to effectively deliver medication to the frontal, ethmoid, and maxillary sinus in post-FESS patients.⁴⁰ A recent human cadaver study from our center demonstrated that a fluorescein solution applied via the MAD in the Mygind or lying-head-back (LHB) position resulted in greater distribution of fluorescein to all evaluated areas compared to that in the Mof-fat or head-down-and-forward (HDF) position.⁴¹ In light of these findings, our institution advises CRS patients to apply aqueous budesonide respules via the MAD while assuming the Mygind position. This study is clinically significant because it provides support to the hypothesis that there is potentially no adrenal suppression after 60 days

of administering budesonide via the MAD and patients experience a significant improvement in the SNOT-22 scores over 60 days compared to those using INSI.

The administration of budesonide as a nasal lavage or via the MAD syringe continues to be “off-label” use. Therefore, the risk associated with administering budesonide via either of these 2 methods requires full patient disclosure. This is the first study to show that budesonide administered via the MAD is potentially safe in the short-term (60 days). This study also corroborates previously published papers on the safety of INSI. Like all studies investigating the safety of budesonide irrigation, this study is underpowered. Safety studies are costly and require a large sample size in order to establish substantive evidence of tertiary adrenal suppression. The use of MAD in our study shows a trend toward adrenal suppression based on Figure 3; therefore, longer-term studies with adequate sample size are necessary. We suspect that because the MAD delivers a more concentrated dose of aqueous budesonide than INSI, and produces mist particles of optimal size for deposition across a broad surface area of nasal mucosa, this may result in greater drug absorption into the systemic circulation. Thus, the MAD may be more likely to produce the conditions leading to adrenal suppression than would the INSI mode of delivery. The data obtained from this pilot study should serve as a stepping-stone toward a larger scale study. It would be prudent that a follow-up study be appropriately powered to provide patients with strong evidence that the use of impregnated nasal lavage or MAD is safe.

Clinically, those administering budesonide via the MAD over 60 days experienced a statistically significant symptomatic improvement compared to those using INSI. The MAD provides a fine mist that is also tolerable. The INSI can be difficult for some patients due to the high volume of saline involved in order to deliver the same daily dose of steroid. Three patients in this study using the INSI complained of discomfort associated with twice-daily irrigation. Although there were no adverse outcomes associated with INSI, compliancy is important in the treatment of CRS; therefore, physicians should consider the use of the MAD given the ease and comfort of administration it affords patients.

Conclusion

The MAD is a novel delivery device and this is the first study to show that it is potentially safe as a delivery device for budesonide as evidenced by a lack of adrenal suppression over a short term (60 days). CRS patients administering budesonide via MAD may also experience significant symptomatic improvement compared to those using a budesonide-impregnated nasal lavage. 

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