APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Effect of budesonide nasal irrigation on Hypothalamic-Pituitary-Adrenal Axis in patients with chronic rhinosinusitis post endoscopic sinus surgery: A prospective study

Jesada Kanjanaumporn,[1,2] Sorranut Thaweboon,[1] Songklot Aeumjaturapat,[1,2] Kornkiat Snidvongs,[1,2] Supinda Chusakul,[1,2] Kachorn Seresirikachorn,[1,2] Lalita Prathanee[1,2]

Abstract

Background: Corticosteroids added to high volume saline nasal irrigation have been introduced as a more effective method of delivering corticosteroids to the sinuses than nasal sprays. However, information regarding the effect of this intervention on the hypothalamic-pituitary-adrenal (HPA) axis is still limited.

Objective: To evaluate the safety of long-term corticosteroid (6 months) nasal irrigation in patients with chronic rhinosinusitis (CRS) post endoscopic sinus surgery.

Methods: Seventeen patients with CRS were included. After undergoing endoscopic sinus surgery, the patients were prescribed budesonide nasal irrigations (250 ml via squeeze bottle) twice daily (1 mg/day) for six months. The serum morning cortisol levels of these patients were then evaluated at 3 and 6 months post-operatively.

Results: Median serum morning cortisol levels were 10.5 mcg% at pre-operative baseline; 10.3 mcg% at 3 months; and 11.2 mcg% at 6 months on post-operative follow-up. There were no significant changes in the serum morning cortisol levels (*P* value = 0.71 and 0.63 respectively). Three of 17 patients (17.65%) had mildly abnormal serum morning cortisol levels (4, 4.3 and 4.9 mcg%) at 3 months. However, these levels were within a normal range at 6 months.

Conclusion: Serum morning cortisol levels were not significantly changed after usage of budesonide nasal irrigation for 6 months.

Key words: budesonide nasal irrigation, corticosteroid, serum morning cortisol, chronic rhinosinusitis, endoscopic sinus surgery

Citation:
Kanjanaumporn, J., Thaweboon, S., Aeumjaturapat, S., Snidvongs, K., Chusakul, S., Seresirikachorn, K., Prathanee, L. (0000). Effect of budesonide nasal irrigation on Hypothalamic-Pituitary-Adrenal Axis in patients with chronic rhinosinusitis post endoscopic sinus surgery: A prospective study. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-121124-1968

Affiliations:
[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Endoscopic Nasal and Sinus Surgery Excellence Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Corresponding author:
Jesada Kanjanaumporn
Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University
1873 Rama4 road, Pathumwan, Bangkok, Thailand
E-mail: 24jate@gmail.com

Introduction

Rationale

Chronic rhinosinusitis (CRS) is a disorder associated with mucosal inflammation of the nasal passages and sinus cavities that persist for at least twelve weeks.[1] The clinical diagnosis is made according to the EPOS guidelines where two or more symptoms should be present, "one of which must be either nasal blockage/obstruction/congestion or nasal discharge (anterior or posterior nasal drip), ± facial pain, and ± smell abnormality".[2]

With their anti-inflammatory properties, corticosteroids are one of the most effective methods in treating CRS. Previously, corticosteroids were delivered to the sinuses in the form of an intranasal spray, oral tablet or steroid drop. In recent years, corticosteroids added to high-volume normal saline for nasal irrigation were introduced as a new, more effective method to deliver corticosteroids into the sinuses, especially in patients post-endoscopic sinus surgery (ESS).[3] Usage of this delivery method also resulted in a lower Sino-nasal Outcome Test-20 (SNOT-20) score, which correlates with decreased sinonasal symptoms,[4] compared to those who received conventional methods of corticosteroid delivery.[5] However, information regarding the effect of corticosteroid nasal irrigation on the hypothalamic-pituitary-adrenal (HPA) axis is still limited. Current usage of high-volume corticosteroid nasal irrigation is still off-label, and its safety profile has not been clearly defined. At present, the United States Food and Drug Administration (USFDA) has only approved low-volume, metered doses of corticosteroid sprays.

Bhalla et al.[6] performed a retrospective review of 18 patients with CRS with nasal polyps post-ESS with post-operative 1 mg per day budesonide nasal irrigation for eight weeks. All pre- and post-treatment serum morning cortisol levels were within normal limits, and no statistical difference was observed ($P = 0.417$).

Similarly, Welch et al.[7] also concluded that budesonide nasal irrigation (0.5 mg/2 ml in 250 ml of saline solution) twice daily for six weeks did not decrease serum morning cortisol and urinary cortisol levels in the patients with recurrent polyposis after ESS.

Furthermore, a cross-sectional study on the safety of long-term high-volume sinonasal irrigations with budesonide (2 mg daily for at least 12 months) in patients with CRS demonstrated no evidence of HPA axis suppression after more than two years of therapy. Of the 35 patients who participated in this study, 19 had low serum cortisol levels which were considered normal after adrenocorticotropic hormone: cosyntropin (ACTH) stimulation testing.[8]

On the other hand, Soudry et al.[9] conducted a retrospective case series of 48 patients who had undergone ESS with post-operative budesonide nasal irrigation (0.5 mg budesonide in 240 ml saline once or twice daily) for at least six months. An ACTH stimulation test performed to assess their adrenal function found 11 patients with abnormally low stimulated cortisol levels (< 18 μg/dL). However, no patients reported symptoms of adrenal suppression. In addition, the laboratory values returned to near-normal levels in three out of four patients who stopped using budesonide for at least one month. Thus, they concluded that long-term use of budesonide nasal irrigations were generally safe, but subclinical HPA axis suppression may occur in some patients.

Recently published prospective studies focus only on the side effects of high-volume corticosteroid nasal irrigation in a short-term period (4-8 weeks).[10] Safety of long-term use still has limited supporting evidence and is controversial (with only two published retrospective or cross-sectional studies).[8,9] Therefore, this study aims to evaluate the safety of long-term corticosteroid (6 months of budesonide) nasal irrigation in post-ESS patients with CRS.

Objectives

To evaluate the long-term safety of a 6-month course of budesonide nasal irrigation in post-ESS CRS patients using sequential measurements of serum morning cortisol levels.

Materials and Methods

This study is a prospective study conducted at the Endoscopic Nasal and Sinus Excellence Center, King Chulalongkorn Memorial Hospital, with a certificate of ethical approval from the Institutional Review Board; Faculty of Medicine Chulalongkorn University (IRB No. 380/60). Written informed consent was obtained from all participants before their enrollment in the study.

Inclusion criteria were patients between 18-70 years old with CRS with or without nasal polyps who had planned endoscopic sinus surgery (full-house FESS) with immediately post-operative budesonide nasal irrigation 1 mg/day. Exclusion criteria were 1. patients with related underlying disease (pituitary disease, adrenal gland disease, or morbid obesity) 2. Patients who received systemic glucocorticoids (intravenous, intramuscular, or oral forms) except during the operative period 3. Pregnancy 4. Patients who underwent estrogen therapy or received estrogen oral contraceptive pills, 5. abnormal serum morning cortisol levels before using budesonide nasal irrigation.

Patients were instructed to continue budesonide nasal irrigations twice daily for a total of 6 months post-operatively.

Outcome assessment

Serum morning cortisol levels were drawn between 8.00 AM to 10.00 AM pre-operatively. Those with abnormal pre-operative serum morning cortisol levels were excluded. After ESS, the patients were prescribed budesonide nasal irrigation twice daily (0.5 mg budesonide (Pulmicort respule) was added to 250 ml of normal saline solution and used as irrigation via a squeeze bottle) (without intranasal corticosteroid used). The total dosage of budesonide was 1 mg/day. At three months and six months follow-up, serum morning cortisol levels were re-evaluated. If serum morning cortisol levels were abnormal at 6 months, an ACTH stimulation test would be considered to confirm the diagnosis of HPA axis suppression.

Data collection

Demographic information (age, gender, body weight, and height), diagnosis (CRS with or without nasal polyps), gynecologic history (last menstrual period, pregnancy), underlying comorbid conditions, current medications, operative data (operation and operative date), dosage of budesonide nasal irrigation, and serum morning cortisol levels were collected.

Statistical analysis

STATA version 15.0 was used for statistical analysis. Since the data was not distributed in a normal distribution, a non-parametric Friedman test was performed for morning cortisol level analysis. *P*-value < 0.05 indicates statistical significance.

Results

From October 1st 2017 to January 31st 2020, 22 patients with CRS with or without nasal polyps post-ESS were enrolled in the study. They were treated with post-operative 1 mg/day budesonide nasal irrigation. Two patients were excluded after a 3-month follow-up due to concurrent usage of oral contraceptive pills, and another three patients were excluded due to loss of follow-up. (**Figure 1**)

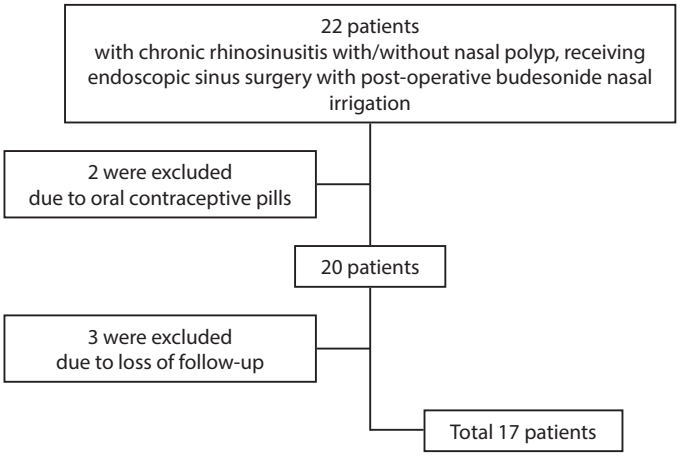

Figure 1. Summary of patients flow chart.

At 3 and 6 months post-surgery, all patients reported improvements in nasal congestion, rhinorrhea, and sense of smell. Endoscopic examination showed reduced mucosal edema and polyp size in CRSwNP patients.

Demographic data

A total of 17 patients were included in the study: 11 males (61.1%) and six females (38.9%). The median age was 47 years old (IQR = 19 (39.5, 58.5)) with an age range of 20 years old to 68 years old. Of 17 patients, 14 patients had CRS with nasal polyps, and 3 patients had CRS without nasal polyps. (**Table 1**) Five out of 17 patients (29.4%) had comorbid asthma. No other significant comorbidities were reported among the study participants. Nine patients received a short course of oral corticosteroids (OCS; prednisolone) during the operative period (10-30 mg oral prednisolone 5 days after surgery).

Table 1. demographic data.

Baseline characteristic		
Age (median) (years)		47 (IQR = 19 (39.5, 58.5))
Sex (n, %)	Male	11 (64.7%)
	Female	6 (35.3%)
CRS type (n, %)	With nasal polyp	14 (82.4%)
	Without nasal polyp	3 (17.6%)

Serum morning cortisol levels

The median serum morning cortisol level was 10.5 (IQR = 7.25 (7.25, 14.5)) mcg% at pre-operative baseline; 10.3 (IQR = 6.45 (6.15, 12.6)) mcg% at 3 months post-operative follow-up; and 11.2 (IQR = 7.85 (7.85, 15.7)) mcg% at 6 months post-operative follow-up. There was no significant difference between the baseline morning serum cortisol levels and levels at three months and six months (*P* = 0.71 and 0.63, respectively). (**Figure 2**)

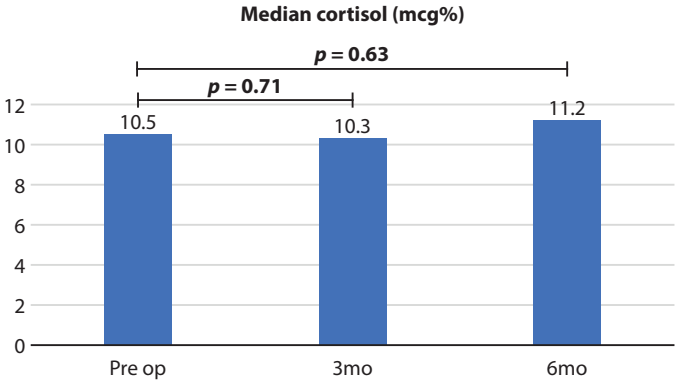

Figure 2. Morning cortisol levels at baseline, three months and six months post-operation

Out of 17 patients, eight patients did not receive oral corticosteroids (OCS; prednisolone) during the operative period. The median pre-operative baseline serum morning cortisol level in this subgroup was 10.45 mcg% (IQR = 7.1 (7.375, 14.475)); 9.35 mcg% (IQR = 5.975 (5.125, 11.1)) at 3 months post-operative follow-up; and 7.85 mcg% (IQR = 7.2 (7.05, 14.25)) at 6 months post-operative follow-up. Subgroup analysis (patients who did not receive oral corticosteroids during the operative period) demonstrated no significant changes in serum morning cortisol levels at three months and six months follow-up compared to baseline (*P* = 0.63 and 0.52, respectively). (**Figure 3**)

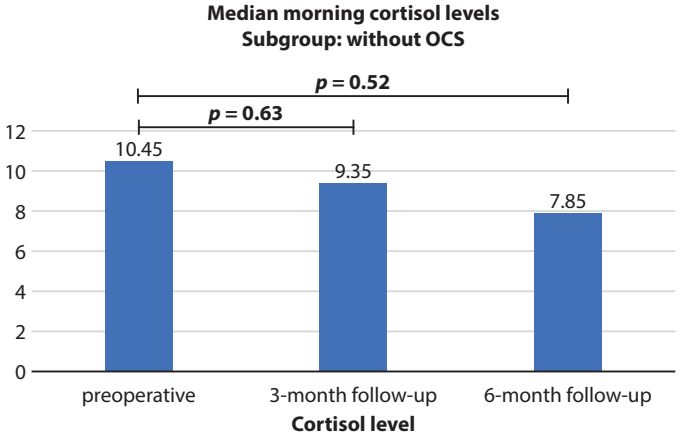

Figure 3. Morning cortisol levels at baseline, three months, and six months post-operation in the subgroup analysis (without oral corticosteroids (OCS))

However, 3 of 17 patients (17.65%) had mildly abnormal serum morning cortisol levels (4, 4.3 and 4.9 mcg%) at 3 months (2 of 3 patients did not receive OCS during the operative period). While these values were below the reference range (5-25 mcg/dL), they were only marginally lower and not clinically significant. Their levels returned to within the normal range at 6 months (16.3, 7 and 7.9 mcg%, respectively) even with continued usage of budesonide nasal irrigation. None of the patients had symptoms of adrenal suppression. We did not send the ACTH stimulation test for these 3 patients because their cortisol levels normalized at 6 months.

Discussion

The results of this study suggest that 1 mg of budesonide high-volume nasal irrigation administration for 6 months does not affect HPA axis function in patients with CRS. HPA axis assessment was made via serum morning cortisol levels, both pre and post sinus surgery. The median morning serum cortisol level pre-treatment was 10.5 mcg% (range 5.1-20.7 mcg%). Therefore, all patients pre-treatment had cortisol levels within the normal range of 5-25 mcg%. Repeat morning serum cortisol levels at six months post-treatment yielded a median serum cortisol level of 11.2 mcg% (range from 5.3 to 17.5 mcg%). There was no significant difference after six months of irrigation therapy. There were no complications reported from budesonide irrigation for the entire duration of the study. The results from this study suggest that long-term use of nasal budesonide irrigation may be a safe treatment option in patients with CRS after sinus surgery.

However, 3 patients had abnormal serum morning cortisol levels at their 3-month follow-up which normalized at their 6-month follow-up (continued usage of budesonide nasal irrigation). The marginally low cortisol levels observed in three patients at 3 months, which subsequently normalized without intervention, likely represent physiological variations rather than clinically significant abnormalities. Nevertheless, subclinical HPA axis suppression should be suspected and clinicians should consider sending laboratory check-ups three months after initiating irrigation therapy. Although patients with transient reductions in cortisol levels during budesonide irrigation remained asymptomatic, the clinical implications of these findings warrant further investigation. The potential risk of subclinical adrenal suppression, particularly during stress periods, is a notable concern, especially in the two patients observed without prior oral corticosteroid use. These findings suggest that clinicians should exercise caution when prescribing budesonide irrigation to patients with a potential risk for adrenal insufficiency, particularly during times of physiological stress.

The importance of topical intranasal corticosteroid irrigation in management of CRS is well known and has existed in every clinical practice guideline for several years.[2,11,12] Corticosteroid sprays, nebulizers and drops are accepted as very safe with minimal bioavailability, which does not affect the HPA axis.[13,14,15] Devices affect the beneficial effects of nasal corticosteroids over placebo in the improvement in symptoms score.[2] High-volume corticosteroid nasal irrigation has been shown to be an effective method of drug delivery into the nasal and paranasal sinuses after sinus surgery to control mucosal inflammation by improving total VAS, nasal blockage, nasal drainage, and endoscopy scores without serious side effects.[5] Unfortunately, usage of this delivery method remains off-label due to a dearth of information on the safety profile.

Prolonged usage of topical corticosteroids is associated with risks of systemic absorption, which can lead to many side effects like glaucoma, osteoporosis, hip avascular necrosis, and HPA axis suppression.[16] Increased dosage and duration of use may increase risk. Budesonide is a potent topical steroid that has a reported systemic bioavailability of about 35%.[17] It binds to the glucocorticoid receptor and inhibits inflammation. Budesonide respule 0.5-1 mg mixed with 240-250 ml nasal saline delivered into the sinuses via squeeze bottle for nasal irrigation is a high-dose and high-volume irrigation. Usage of high-dose corticosteroids should prompt concern for potential increased systemic exposure and complications.

Not many studies to-date have evaluated the safety of high-volume nasal budesonide irrigation. Bhalla RK. et al.[6] performed a retrospective study that evaluated 18 refractory CRS (with nasal polyp) patients who received high-dose high-volume budesonide irrigation. Morning serum cortisol levels pre-irrigation and eight weeks after irrigation were used to assess HPA axis function. They show no evidence of HPA axis suppression. Welch KC et al.[7] performed a prospective study with ten CRS patients who underwent ESS and received 0.5 mg budesonide with 240 ml normal saline nasal irrigation. They evaluated serum cortisol and 24-hour urine cortisol levels pre- and post-treatment. They demonstrated no significant changes in both measurements. In 2013, Seiberling K.[18] studied the effect of budesonide irrigation on intraocular pressure, showing no significant impact. The results from these studies suggest high-volume nasal budesonide irrigations are safe for short-term use (4-8 weeks).

However, safety of long-term use is still controversial due to a lack of high quality data (only two retrospective or cross-sectional studies). A retrospective study from Smith KA. et al.[8] found that long-term high-volume sinonasal irrigations with budesonide (2 mg daily for at least 12 months) result in no evidence of HPA axis suppression. In addition, 19 of 35 patients in this study had low serum cortisol levels which were considered normal after ACTH stimulation testing. In the other cross-sectional case series, Soudry et al.[9] reported that 23% (11 of 48) of post-surgical CRS patients had subclinical HPA axis suppression. Moreover, the concomitant use of other topical nasal steroids was associated with an increased risk of suppression.

The potential for delayed effects on the hypothalamic-pituitary-adrenal (HPA) axis after discontinuing budesonide nasal irrigation remains uncertain. Although transient cortisol reductions normalized over time in our study, the possibility of delayed adrenal suppression cannot be excluded. Long-term studies are needed to clarify this risk, particularly in patients undergoing prolonged therapy or with additional risk factors.

Our research is the first prospective study to examine the long-term effects of high-dose high-volume budesonide nasal irrigation. The results from this study suggest that six months of daily high-volume nasal budesonide irrigations may not be associated with HPA axis suppression. However, several patient factors affecting serum morning cortisol levels could not be controlled for in the study, such as stress, sleep deprivation, caffeine consumption, and chronic alcoholism. A limitation of this study is that we did not directly measure the degree of eosinophilic infiltration, which could potentially influence treatment response and outcomes. The lack of ACTH stimulation testing for patients with low cortisol levels at 3 months is a limitation of this study. While cortisol levels normalized by 6 months, ACTH stimulation testing could have provided more comprehensive information about HPA axis function during the period of low cortisol. Further studies are still needed to confirm the effects of budesonide since the sample size in our study is relatively small. Despite these limitations, we suggest that results from this study justify prolonged use of corticosteroid sinonasal irrigation as a viable option in the clinicians' armamentarium.

Conclusion

Serum morning cortisol levels in patients were not significantly changed after using budesonide nasal irrigation for 6 months. However, physicians still need to be aware of possible subclinical HPA axis suppression.

Conflict of interest

No potential conflict of interest was reported by the author.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Authorship contribution

- Assoc Prof Jesada Kanjanaumporn - Conception or design of the work, Data collection, Data analysis and interpretation, Drafting the article, Critical revision of the article, Final approval of the version to be published
- Sorranut Thaweboon - Conception or design of the work, Data collection, Data analysis and interpretation, Drafting the article
- Assoc Prof Songklot Aeumjaturapat - Final approval of the version to be published
- Assoc Prof Kornkiat Snidvongs - Final approval of the version to be published
- Assoc Prof Supinda Chusakul - Final approval of the version to be published
- Kachorn Seresirikachorn - Final approval of the version to be published
- Lalita Prathanee - Data analysis and interpretation, Drafting the article, Critical revision of the article

References

1. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2003 Sep;129(3 Suppl): S1-32.
2. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1–464.
3. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngol --Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2008 Jul;139(1):137–42.
4. Jang DW, Lachanas VA, Segel J, Kountakis SE. Budesonide nasal irrigations in the post-operative management of chronic rhinosinusitis. Int Forum Allergy Rhinol. 2013 Sep;3(9):708–11.
5. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int Forum Allergy Rhinol. 2018 Apr;8(4):461-470.
6. Bhalla RK, Payton K, Wright ED. Safety of budesonide in saline sinonasal irrigations in the management of chronic rhinosinusitis with polyposis: lack of significant adrenal suppression. J Otolaryngol - Head Neck Surg J Oto-Rhino-Laryngol Chir Cervico-Faciale. 2008 Dec;37(6):821–5.
7. Welch KC, Thaler ER, Doghramji LL, Palmer JN, Chiu AG. The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. Am J Rhinol Allergy. 2010 Feb;24(1):26–8.
8. Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016 Mar;6(3):228–32.
9. Soudry E, Wang J, Vaezeafshar R, Katznelson L, Hwang P. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. Int Forum Allergy Rhinol. 2016 Feb 16;6.
10. Rudmik L. High Volume Sinonasal Budesonide Irrigations for Chronic Rhinosinusitis: An Update on the Safety and Effectiveness. Pharmacoepidemiol Drug Saf. 2014 Apr 1;3:1–5.
11. Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong A, et al. International Consensus Statement on Rhinology and Allergy: Rhinosinusitis. Int Forum Allergy Rhinol. 2020 Nov 24;
12. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2015 Apr;152(2 Suppl): S1–39.
13. Vlckova I, Navrátil P, Kana R, Pavlicek P, Chrbolka P, Djupesland PG. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. Rhinology. 2009 Dec;47(4):419–26.

14. Wang C, Lou H, Wang X, Wang Y, Fan E, Li Y, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2015 Apr; 135(4):922-929.e6.
15. Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2000 Oct;30(10): 1460–8.
16. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. Otolaryngol Clin North Am. 2010 Aug;43(4):753–68.
17. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy. 2008 Oct;63(10):1292–300.
18. Seiberling KA, Chang DF, Nyirady J, Park F, Church CA. Effect of intranasal budesonide irrigations on intraocular pressure. Int Forum Allergy Rhinol. 2013;3(9):704–7.