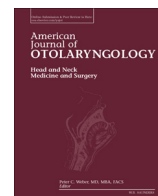




Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

Effect of nebulized budesonide on decreasing the recurrence of allergic fungal rhinosinusitis☆

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ARTICLE INFO

Article history:

Received 8 December 2016

Available online xxx

Keywords:

Nebulized budesonide

Allergic fungal rhinosinusitis

ABSTRACT

Objective: The aim of this study was to evaluate the clinical efficacy and the effects on decreasing the recurrence of AFRS (allergic fungal rhinosinusitis) of a budesonide inhalation suspension delivered via transnasal nebulization to patients following endoscopic sinus surgery.

Subjects and methods: Thirty-five patients were recruited into this study. Final diagnoses were reached using Bent and Kuhn's criteria. The eligible patients were randomly divided into two groups: the budesonide transnasal nebulization group (group A) and the topical nasal steroids group (group B). Nasal symptoms, Lund-Mackay scores, and Kupferberg grades were evaluated before surgery, after surgery and during the follow-up to assess the effects of these two approaches.

Results: A total of 30 patients with AFRS who were eligible were included in the study. Four of the 15 patients in group B (26.67%) developed recurrent disease, whereas no patients in group A developed recurrent disease. This difference was statistically significant ($p = 0.032$).

Conclusion: Nebulized budesonide is an effective and safe treatment for patients with AFRS following endoscopic sinus surgery, as evidenced by the reduced recurrence rate observed in the budesonide transnasal nebulization group relative to the topical nasal steroids group.

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1. Introduction

Since allergic fungal rhinosinusitis (AFRS) was initially described in the early 1980s by Millar et al. [1] and Katzenstein et al. [2], otolaryngologists, immunologists, pulmonologists, and patients have struggled to manage this disease. The incidence of AFRS is estimated to be 5 to 10% in all chronic rhinosinusitis (CRS) patients who undergo sinus surgery [3]. The variable incidence may be dependent on geographical variation and problems diagnosing the disease [4]. In 1994, Bent III and Kuhn [5] proposed five diagnostic criteria for AFRS: type I hypersensitivity, nasal polyposis, characteristic findings on computerized tomography (CT) scans, the presence of fungi on direct microscopy or culture, and allergic mucin containing fungal elements without tissue invasion. The diagnosis criteria show that the pathogenesis represents an allergic hypersensitive response to extramucosal fungi within the sinus cavity.

Although the management of AFRS has advanced tremendously with a better understanding of the underlying pathogenesis, an optimal treatment strategy is still far from clear. Once a diagnosis of AFRS has been established, a combination of surgery with a comprehensive

postoperative medical regimen to manage the disease is almost always required.

AFRS is characterized by recidivism after surgery, with potentials for recidivism ranging from 10% [6] to nearly 100% [7]. The published rates of AFRS recurrence may be misleading and are highly dependent on the length of follow-up, but the high recidivism rate cannot be overlooked.

Based on available evidence in the literature [8], corticosteroids are typically regarded as the mainstay of medical treatment for this condition. Topical intranasal steroid sprays have proven to be an effective treatment for AFRS and have a minimal risk profile [8]. However, in some conditions, topical sprays cannot reach the posterior nasal spaces and paranasal sinuses, which may underlie the high recurrence rate. Furthermore, despite providing more potent and rapid benefits to control the inflammation associated with AFRS [9] systemic corticosteroids have significant side effects, such as hypothalamic-pituitary-adrenal axis dysfunction. Thus, a need has arisen for an alternative topical therapy in patients with AFRS.

Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca, London, United Kingdom) is another form of corticosteroid therapy that has been demonstrated to be efficacious and safe in patients with asthma [10], chronic obstructive pulmonary disease [11], and CRS with NPs [12]. Furthermore, budesonide inhalation suspension has been shown to enhance ventilation efficiency and drug deposition in the paranasal sinus

☆ The authors have no funding, financial relationships, or conflicts of interest to disclose.

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[13]. However, little information exists regarding the use of budesonide transnasal nebulization for the treatment of AFRS.

Thus, the aim of this study was first to evaluate the clinical efficacy and the effect of decreasing the recurrence of budesonide inhalation suspension delivered via transnasal nebulization in patients with AFRS and then to compare this effect with budesonide nasal pump sprays.

2. Patients and methods

Thirty-five patients were recruited into this historical, random and prospective study from the Department of Otolaryngology at the Eye, Ear, Nose, and Throat Hospital of Fudan University in Shanghai, China from November 2011 to February 2015. Informed consent was provided by all patients.

All cases of AFRS were evaluated with a detailed clinical history and a head and neck examination including anterior rhinoscopy. Nasal symptoms (including nasal obstruction, nasal discharge, loss of smell, and headache/facial pain) were assessed before surgery and postoperatively at the 4th, 12th, and 24th weeks of follow-up using visual analog scales with scores of 0–10 [12]. The total nasal symptom score (TNSS) was calculated as the sum of the scores of the 4 individual symptoms simultaneously. CT of the axial and coronal planes of the nose and PNS was performed in all patients before surgery and at the 12th and 24th weeks of follow-up in the postoperative period using Lund-Mackay scores [14]. Nasal endoscopy (NE) findings were graded based on Kupferberg grades [15] at the 4th, 12th, and 24th weeks of follow-up in the postoperative period. An Aspergillus skin hypersensitivity test was performed in all patients. The final diagnosis was made using Bent and Kuhn's criteria [5].

Both groups underwent functional endoscopic sinus surgery after diagnosis and preliminary investigation. In all cases, the surgical procedure included adequate decongestion of the nasal cavities and opening of all the sinuses, namely the maxillary, anterior and posterior ethmoids and the frontal and sphenoid sinuses, via removal of polyps and the fungal mucin from all these sinuses while preserving the normal mucosa. Operative findings were recorded, and surgical specimens were sent for fungal smears and histopathological examination. Histological evidence for the presence of allergic mucin, eosinophils, fungal hyphae and tissue invasion was recorded. Any patient with evidence of tissue invasion was excluded from the analysis.

Eligible patients were randomly divided into two groups: the budesonide transnasal nebulization group (group A) and the topical nasal steroids group (group B). No patients received any preoperative oral steroids. The study was recorded using a single-blind approach; the doctor and recorder were different persons, and recorder did not know which group the patients were in. The patients were assigned in a ratio of 1:1 to receive 1 mg of budesonide transnasal nebulization (Pulmicort Respules; AstraZeneca, London, United Kingdom) with a Pari Sinus Nebulizer and Pari Master Compressor (PARI GmbH, Starnberg, Germany) or budesonide nasal pump sprays (Rhinocort; AstraZeneca, London, United Kingdom) twice daily for 2 weeks, once a day for the next 2 weeks, once every two days for the next 4 weeks, twice per week for the next 8 weeks, and then once a week to maintain treatment. Postoperatively, both groups were advised to perform regular alkaline nasal irrigation twice per day.

Follow-up was performed after surgery. Every patient came to the outpatient center for nasal endoscopy for cleaning of the nasal cavity at the 1-week follow-up visit. At each follow-up visit, a TNSS score, NE score (Kupferberg grade) and CT scan score (Lund-Mackay score) were calculated. The differences in the values for each parameter between those at the beginning of the study and those at each follow-up visit were calculated and compared between the two groups. Both groups were compared regarding the above parameters to assess the effect of the two therapies. Patients in both groups have been under continuous follow-up until the present date. The study was approved by the

Institutional Review Board of the Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, China.

Statistical analysis was performed using IBM SPSS statistics v20.0. The results are expressed as the means $\pm$ SD in the text and tables. The patients' age, gender, Kupferberg grades, Lund-Mackay scores, and TNSS before surgery were obtained at baseline. Pearson's correlation was used to analyze two-variable correlations. $P < 0.05$ was considered statistically significant.

3. Results

A total of 30 patients with AFRS who were eligible were included in the study from November 2011 to February 2015. Group A (budesonide transnasal nebulization group) included 15 patients, and group B (topical nasal steroids group) included 15 patients. No patients dropped out, and no serious side effects were reported during the study. The median follow-up time was 18.72 ± 3.99 months (range 9.8–36.6 months) in group A and 18.45 ± 8.45 months (range 12.4–38.4 months) in group B. The mean $\pm$ SD age of patients was 43.27 ± 12.57 (18–63) years in group A and 42.4 ± 15.7 (20–68) years in group B. Group A consisted of 9 males and 6 females, while B group consisted of 8 males and 7 females. No significant difference was found between the two groups in terms of age and gender ($p > 0.05$).

The skin test was significant in all patients in the two groups. Nasal polyposis was the most common sign. Unilateral nasal polyposis was observed in 7/15 (63.3%) patients in group A, while 6/15 (40%) patients in group B had unilateral nasal polyposis at the time of presentation. Diagnostic NE was performed, and the findings were classified based on Kupferberg grade. The Kupferberg grades were 2.67 ± 0.49 in group A and 2.60 ± 0.50 ($p = 0.67$) in group B. CT was used to determine Lund-Mackay scores; group A had an average score of 15.4 ± 5.37 , whereas group B had an average score of 16.0 ± 5.67 ($p = 0.765$) (Table 1). Consequently, the clinical parameters were not significantly different between groups before the study.

Nasal symptoms (including nasal obstruction, nasal discharge, loss of smell, and headache/facial pain) were assessed before surgery and at the 4th, 12th, and 24th weeks of follow-up in the postoperative period using visual analog scales in the two groups. The TNSS was calculated as the sum of the scores of 4 individual symptoms simultaneously. The mean TNSS values were 23.33 ± 9.18 in group A and 24.27 ± 9.23 in group B. The groups were statistically similar with respect to TNSS values ($p = 0.626$) (Table 1). The mean differences in TNSS values at the 4th, 12th, and 24th weeks of follow-up relative to baseline were 7.73 ± 3.79 , 6.40 ± 1.80 , and 5.67 ± 1.05 , respectively, in group A and 9.07 ± 4.68 , 6.67 ± 2.35 , and 6.00 ± 1.92 , respectively, in group B; between-group differences were not significant ($p > 0.05$).

The mean differences in Kupferberg grades at the 4th, 12th and 24th weeks of follow-up relative to baseline were 0.13 ± 0.35 , 0.00 ± 0.00 , and 0.00 ± 0.00 , respectively, in group A and 0.40 ± 0.63 , 0.13 ± 0.35 , and 0.07 ± 0.26 , respectively, in group B; between-group differences were significant at the 4th week ($p = 0.041$) but were not significant at the other time points ($p > 0.05$) (Fig. 1). CT of the axial and coronal planes of the nose and PNS was performed and evaluated in all patients before surgery and at the 12th and 24th weeks of follow-up in the postoperative period using Lund-Mackay scores. The mean differences between the preoperative scans and the postoperative scans at

Table 1
Clinical parameters for the two groups.

Before surgery	Group A	Group B	p
Age (years)	43.27 ± 12.57	42.4 ± 15.7	0.874
Gender (male/female)	9/6	8/7	0.713
Kupferberg grades	2.67 ± 0.49	2.60 ± 0.50	0.67
Lund-Mackay scores	15.4 ± 5.37	16.0 ± 5.67	0.765
TNSS	23.33 ± 9.18	24.27 ± 9.23	0.769

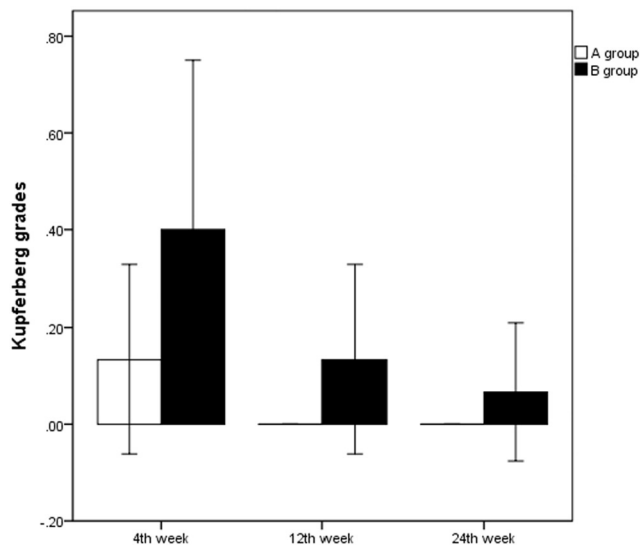


Fig. 1. Mean differences in nasal endoscopic grades (Kupferberg grades) at the 4th, 12th and 24th weeks of follow-up relative to baseline.

the 12th and 24th weeks were 0.20 ± 0.41 and 0.13 ± 0.35 , respectively, in group A and 0.60 ± 0.74 and 0.80 ± 0.94 , respectively, in group B, and these differences were statistically significant at the 24th week ($p = 0.036$) (Fig. 2). Recurrence was defined as a Lund-Mackay score >10 and a Kupferberg NE grade ≥ 2 [14]. The recurrence times were 7.3, 14.2, 11.1, and 10.2 months, yielding a mean time of 11.18 ± 1.27 months in group B; 4 of 15 (26.67%) patients in group B developed recurrent disease. No patient in group A developed recurrence. This difference between the two groups was statistically significant ($p = 0.032$), which may indicate that budesonide transnasal nebulization can reduce the recurrence rate in AFRS patients.

4. Discussion

AFRS treatment usually involves surgery in combination with medical therapies to maintain the disease in a dormant state. However, the optimal medical regimen remains controversial. Hence, the purpose of this study was to provide a better method to reduce the recurrence of AFRS.

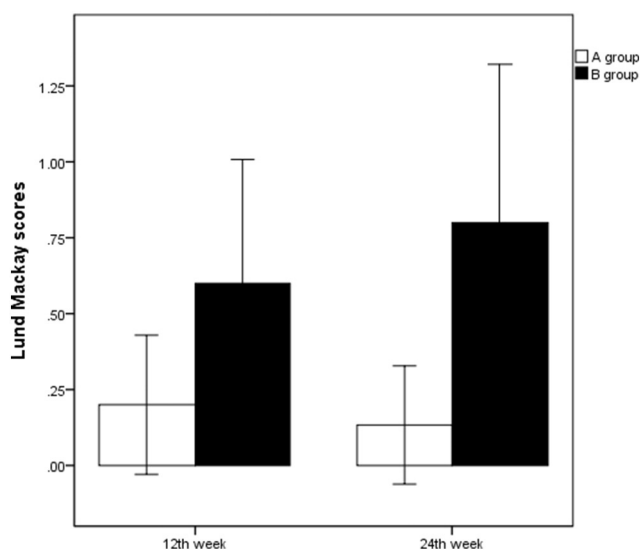


Fig. 2. Mean difference in computerized tomography scores (Lund-Mackay scores) at the 12th and 24th weeks of follow-up relative to baseline.

A review article [8] evaluated the literature regarding 6 different medical therapies for the management of postoperative AFRS and provided an evidence-based review with recommendations including oral steroids, topical nasal steroids, oral antifungals, topical antifungals, immunotherapy, and leukotriene modulators. The evidence supports the use of postoperative oral corticosteroids and, indirectly, topical corticosteroids in the postoperative management of AFRS patients. Oral antifungals and immunotherapy are therapeutic options for refractory postsurgical AFRS that are weakly supported by the literature. No evidence currently exists in the literature for the use of topical antifungals for AFRS patients. The use of leukotriene modulators has shown some positive effects on AFRS but requires more research before it can be recommended. Based on the findings of another systematic review of the literature [16], no convincing evidence exists to support the routine use of topical or oral antifungals for the treatment of patients with AFRS (or CRS).

Although these reviews have confirmed the important effects of steroids on AFRS patients, the use of steroids still has some problems including side effects. The early side effects of oral steroids include psychosis, insomnia, weight gain, poorer control of blood glucose (in diabetic patients) and blood pressure (in hypertensive patients), and gastric distress from peptic ulcer disease. The long-term adverse effects include Cushing's syndrome, adrenal insufficiency, accelerated osteoporosis, glaucoma, cataract formation, and avascular necrosis of the hip [17].

Except the therapies mentioned, budesonide nasal irrigations also did not seem to cause HPA axis suppression, but it depends on the concentration [18,19]. Ethan Soudry et al. [20] hold that long-term use of budesonide nasal irrigation is generally safe, but asymptomatic HPAA suppression may occur in selected patients. Kosugi and Kang et al. [21, 22] hold that nasal irrigation with budesonide is an effective postoperative treatment for difficult-to-treat CRS and chronic rhinosinusitis with asthma. However, Rawal et al. [23] compare normal saline (NS) vs. NS + budesonide irrigation in post-functional endoscopic sinus surgery (FESS) patients with chronic rhinosinusitis with polyposis (CRSwNP), and they found no evidence for NS + budesonide irrigation over NS irrigation alone. Therefore, controversy surrounding budesonide nasal irrigation remains.

The advantage of topical nasal steroid sprays over oral steroids lies in the ability of topical nasal steroids to achieve an effective drug concentration at the sinonasal mucosa without associated systemic side effects. Topical intranasal steroid sprays have been proven to be an effective treatment and can maintain a minimal risk profile [24]. As a consequence, we chose topical intranasal steroid sprays as the control group.

Möller et al. [25] confirmed that in contrast to nasal pump sprays, pulsating airflows can generate pressure gradients and have been shown to enhance ventilation efficiency and drug deposition in the paranasal sinus, allowing the delivery of significant doses into the posterior nasal spaces and paranasal sinuses to provide alternative therapeutic options before and after sinus surgery. Luo Zhang et al. [12,13] have shown that short-term budesonide transnasal nebulization is an effective and safe treatment option for patients with eosinophilic CRS with NPs. Steroid transnasal nebulization offers an alternative or a complementary treatment option to nasal sprays and nasal irrigation for the management of patients with CRS. Nebulized budesonide has also been shown to be an effective and safe alternative to systemic corticosteroids for the treatment of complications related to chronic obstructive pulmonary disease [11]. In our study, we aimed to compare the effect of budesonide transnasal nebulization with topical intranasal steroid sprays.

Although the TNSS was not found to be significantly different, the overall TNSS in group A was lower than that of group B. The Kupferberg NE grades were significantly different at the 4th week ($p = 0.041$). We observed two patients in group A with mucosal edema, 4 patients in group B with mucosal edema and 1 patient with polypoid edema; that budesonide transnasal nebulization may reduce mucosal edema to

some degree. The Lund-Mackay scores were also significantly different at the 24th week ($p = 0.036$). Patients with disease recurrence in the first 7.3 months had Lund-Mackay scores of 3, which were among the highest scores at the 24th week. The Lund-Mackay scores could be an indicator of recurrence. More attention should be paid to the CT scans during the follow-up. Recurrence was defined as a Lund-Mackay score >10 and a Kupferberg NE grade ≥ 2 . The recurrence times were 7.3, 14.2, 11.1, and 10.2 months, yielding a mean time of 11.18 ± 1.27 months in group B; 4 out of 15 (26.67%) patients in group B developed recurrent disease, while no patients in group A had recurrence. This difference was statistically significant ($p = 0.032$), which may show that budesonide transnasal nebulization can reduce the recurrence rate in AFRS patients. We also found that the patients with recurrence had bilateral involvement. Thus, the severity of AFRS also affects recurrence, and these patients should receive more positive therapy such as budesonide transnasal nebulization.

The potential for AFRS recidivism is well recognized and ranges from 10% [6] to nearly 100% [7]. However, the published rates of AFRS recurrence can be misleading and are highly dependent on the length of follow-up. To emphasize the importance of long-term surveillance, Kupferberg et al. [15] assessed the appearance of the sinonasal mucosa of 24 patients treated with combined medical and surgical therapy for AFRS. Nineteen of the 24 patients eventually developed disease recurrence after discontinuation of systemic corticosteroids, but they observed that endoscopic evidence of disease generally preceded the return of subjective symptoms. AFRS recidivism appears to be influenced by long-term postoperative therapy. Schubert et al. [26] reported the long-term clinical outcomes of 67 patients following initial surgical therapy for AFRS. Patients treated with at least 2 months of oral corticosteroids were compared to those who received no corticosteroids. At 1 year after the initial surgery, patients treated with oral corticosteroids were significantly less likely to have experienced recurrent AFRS (35%) than those who had not received oral corticosteroids (55%).

In our study, the median follow-up times were 18.72 ± 3.99 months (range 9.8–36.6 months) in group A and 18.45 ± 8.45 months (range 12.4–38.4 months) in group B. During our almost 2-year observation, the absence of recurrence in group A was confirmed to be an effect of budesonide transnasal nebulization. To the best of our knowledge, this is the first study to evaluate the effect of nebulized budesonide for AFRS recurrence and to compare it with topical intranasal steroid sprays. We suggest that budesonide transnasal nebulization can improve symptoms and reduce mucosal edema, thus reducing the recurrence of AFRS.

5. Conclusion

In conclusion, the results of this study indicate that budesonide transnasal nebulization is an effective and safe treatment in patients with AFRS following endoscopic sinus surgery, as evidenced by significant improvements in symptoms, NE grades at 4 weeks and Lund-Mackay scores at 24 weeks, as well as a reduced recurrence rate compared to the topical nasal steroids group.

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