Therapeutic potential of recombinant human basic fibroblast growth factor on postoperative patients with chronic rhinosinusitis with nasal polyps

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Abstract

Objectives: To explore the effect of intranasal administration of rh-bFGF on postoperative chronic rhinosinusitis with nasal polyps(CRSwNP) patients. Design: A prospective, randomized, controlled, double-blinded trial. Setting and Participants: 75 hospitalized patients who met the criteria of primary bilateral CRSwNP were enrolled from March 2020 to January 2021. Main outcome measures: Visual analogue scale, 22 item Sino-Nasal Outcome Test ,Lund-Kennedy system, and Scanning electron microscopy and Quantitative real-time PCR. Results: 75 patients with CRSwNP were randomly divided into three groups, and 72 patients completed the 1-month medication regimen and 1 year follow-up. Rh-bFGF nasal spray and drop application reduced general nasal VAS scores within two weeks after ESS compared to the control group. In contrast, only rh-bFGF nasal drops reduced SNOT-22 scores at 2 weeks and 1 year compared to the control group. A significant reduction in the endoscopic L-K score was observed in the rh-bFGF nasal spray and drop group compared to the control group. This is primarily because rh-bFGF promotes cilia growth in the nasal mucosal epithelium after the operation, as illustrated by scanning electron microscopy and expression of CP110, Tap73 and Foxj1 mRNA. For eosinophilic CRSwNP, the general VAS score of rh-bFGF nasal drops was more obviously reduced compared to the control group after ESS. A similar trend was observed for L-K score. Conclusions: Rh-bFGF nasal-drops and sprays can quickly and effectively relieve postoperative symptoms and improve long-term prognosis of patients with CRSwNP. Moreover, rh-bFGF nasal-drops are also an effective method for postoperative patients with eosinophilic CRSwNP.

ABSTRACT

Objectives: To explore the effect of intranasal administration of rh-bFGF on postoperative chronic rhinosinusitis with nasal polyps(CRSwNP) patients.

Design: A prospective, randomized, controlled, single-blinded trial.

Setting and Participants: 75 hospitalized patients who met the criteria of primary bilateral CRSwNP were enrolled from March 2020 to January 2021.

Main outcome measures: Visual analogue scale, 22 item Sino-Nasal Outcome Test ,Lund-Kennedy(L-K) system, and Scanning electron microscopy and Quantitative real-time PCR.

Results: 75 patients with CRSwNP were randomly divided into three groups, and 72 patients completed the 1-month medication regimen and 1 year follow-up. Rh-bFGF nasal-spray and drop application reduced

general nasal VAS scores within two weeks after ESS compared to the control group. In contrast, only rh-bFGF nasal-drops reduced SNOT-22 scores at 2 weeks and 1 year compared to the control group. A significant reduction in the endoscopic L-K score was observed in the rh-bFGF nasal-spray and drop group compared to the control group. This is primarily because rh-bFGF promotes cilia growth in the nasal mucosal epithelium after the operation, as illustrated by scanning electron microscopy and expression of CP110, Tap73 and Foxj1 mRNA. For eosinophilic CRSwNP, the general VAS score of rh-bFGF nasal-drops was more obviously reduced compared to the control group after ESS. A similar trend was observed for L-K score.

Conclusions: Rh-bFGF nasal-drops and sprays can quickly and effectively relieve postoperative symptoms and improve long-term prognosis of patients with CRSwNP. Moreover, rh-bFGF nasal-drops are also an effective method for postoperative patients with eosinophilic CRSwNP.

Keywords: eosinophilic chronic rhinosinusitis; nasal mucosa; rh-bFGF; nasal-spray; nasal-drop.

Key points

1. CRS is a common condition in most of the world, leading to a significant burden on society in terms of healthcare consumption and productivity loss.
2. Most current drugs are used to alleviate inflammation of the nasal mucosa, with no specific effect on promoting the epithelization or cilia growth of the nasal mucosa.
3. Rh-bFGF can promote division and maintain the growth of cells from various tissues. However, there is no research regarding the effect of rh-bFGF on the growth of nasal mucosa or cilia after sinusitis surgery.
4. Rh-bFGF nasal-drops and sprays can quickly and effectively relieve postoperative symptoms and improve long-term prognosis of patients with CRSwNP.
5. Rh-bFGF nasal-drops are also an effective method for postoperative patients with eosinophilic CRSwNP.

MAIN TEXT

Introduction

CRS is a common worldwide disease, which leads to an increase in medical consumption and a decrease in productivity, also brings a huge burden to the society[1,2,3]. The effect of CRS on quality of life is greater than that of coronary heart disease, myocardial infarction, rheumatism, hypertension and diabetes[4].

ESS is an important method for the treatment of CRS. Studies[9,10] have shown that the poor healing state of the nasal cavity after ESS is primarily characterized by high levels of mucosal edema, scarring and osteitis and eventually cause repeated symptoms and even recurrence. This is even more severe in eosinophilic or Th2 CRS[5,11-14]. Therefore, accelerating the process of nasal epithelialization and the growth rate of epithelial cilia is one of the important measures to improve symptoms and accelerate the recovery of patients after ESS.

Rh-bFGF is an active polypeptide that widely exists in the body. Previous studies found that rh-bFGF can promotes regeneration of tracheal epithelial tissues[15,16]. However, there is no research regarding the effect of rh-bFGF on the growth of nasal mucosa or cilia after sinusitis surgery.

In this study, we applied rh-bFGF to the nasal cavity after ESS to determine whether it promotes the epithelization of nasal mucosa and the growth of cilia. We focused on improvement of symptoms, the L-K endoscopic score and the growth rate of cilia by the intranasal use of rh-bFGF.

METHODS

Study design

This was a prospective, randomized, controlled, single-blinded trial which was approved by the hospital's ethical committee and registered on Chinese Clinical Trial Registry.

Setting and Participants

Patients between 18 and 75 years old who met the inclusion criteria were recruited into the study. They all voluntarily participated and signed the informed consent form. The admission criteria were consistent with primary bilateral CRSwNP from the EPOS 2020 guidelines[5]. Patients who had poor control of nasal symptoms after 6-12 weeks of drug therapy and needed surgical intervention were enrolled. Secondary CRS were excluded. Pregnant or breastfeeding women were not included in the study.

All patients were registered in the inpatient department from March 2020 to January 2021 and were randomly assigned to three groups. Patients in control group received conventional treatment (antibiotics for 3 days and nasal corticosteriod and irrigation for 1 month) and placebo (saline) nasal-spray twice per day after ESS. In the rh-bFGF nasal-spray group, patients received conventional treatment and rh-bFGF nasal-spray after ESS (4 sprays (1 spray=0.1 ml) twice per day). In the rh-bFGF nasal-drop group, patients received conventional treatment and rh-bFGF nasal-drops (0.4 ml twice per day). The patients in rh-bFGF nasal-drop group were required to keep the posture of Mygind during nasal-drops[17]. All enrolled patients received rh-bFGF treatment for 1 month and were followed up for 1 year.

Clinical evaluation

The VAS score was used to evaluate the subjective symptoms. Quality of life was evaluated by SNOT-22 score. The enrolled patients also underwent nasal endoscopy and scored with the L-K system.

Pathological examination

Hematoxylin and eosin staining was applied to detect whether the patient was eosinophilic CRSwNP which was defined as the amount of eosinophils in tissue exceeding 10% of the total number of inflammatory cells[18].

Scanning electron microscopy

Sinonasal mucosa specimens were dehydrated with different concentrations of graded ethanol for 10 minutes each. The dehydrated specimens were soaked in 100% acetone for 20 minutes and then in pure isoamyl acetate for 30 minutes. All samples were dried in a carbon dioxide critical point dryer, then sputtered with gold, and examined by SEM (QUANTA 2000; FEI; Czech republic) at the accelerated voltage of 10kV.

Quantitative real-time PCR

Total RNA was extracted from frozen sinonasal mucosa by using isolation kit ((DP431; Tiangen Biotech, Beijing, China). Total RNA was reverse transcribed with the TaqMan Reverse Transcription Reagents Kit (Applied Biosystems) based on the manufacturer's instruction. Then, quantitative real-time PCR analysis was performed on a Prism 7500 (Applied Biosystems, Foster City, California) to evaluate the expression levels of CP110, Foxj1 and Tap73. The relative fold increase of the three genes expression was calculated by using the comparative $2^{-[?][?]}$Ct methods, with the housekeeping gene Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as the reference.

Statistical analysis

The sample size was calculated by power analysis(α= 0.05 and 90% power), using the reduction of L-K score from our preliminary findings in a pilot study. SPSS v25.0 (IBM SPSS, Armonk, NY) and GraphPad Prism v8.0(GraphPad Inc, USA) were used for statistical analysis. Continuous data in accordance with the normal distribution were expressed as mean and standard deviation(SD) and analyzed by one-way ANOVA, while data with non-normal distribution were expressed as median and quartile rangetested by Kruskal-Wallis test. Pearson chi-square test was used to classify the data. P¡0.05 was considered to be statistically significant.

RESULTS

75 CRSwNP patients participated in the study. 2 patients in rh-bFGF nasal-spray group and 1 patient in rh-bFGF nasal-drop group lost follow-up. 72 patients completed 1 year follow-up(FigureS1). The baseline information of the three groups matched well(Table 1).

Symptom outcomes and quality of life

To assess the effect of rh-bFGF on the symptom outcomes and quality of life, VAS and SNOT-22 score were recorded. 2 weeks after ESS, the reduction in the VAS score for general symptoms in the rh-bFGF nasal-sprays and drops was significantly greater than that in control group(P_1=0.04,P_3=0.01,Figure1A). This trend was still obvious at 1 month. However, the difference was not significant(P_1=0.09,P_3=0.06,Figure1B). No significant difference was found among the three groups at 6 months and 1 year(Figure1C,D).

The symptom of nasal obstruction in rh-bFGF experimental groups was significantly relieved compared with the control group at 2 weeks and 1 month(FigureS2A,B). However, there was no difference at 6 months and 1 year(Figure S2C,D). For the rhinorrhea score, the reduction was significantly greater in the rh-bFGF nasal-drop group than in the control group at 2 weeks (P_3=0.01), 1 month (P_3=0.02) and 6 months(P_3=0.002,FigureS2E,F,G). However, symptoms of rhinorrhea were not relieved in the rh-bFGF nasal-spray group compared to the control group after ESS(FigureS2E-H). Regarding olfaction, facial pressure and headache, the rh-bFGF experimental groups did not show significant changes after ESS compared to the control group (P>0.05,FigureS2I-T).

We next assessed the SNOT-22 score, and the reduction was significantly greater in the rh-bFGF nasal-drop group than in the control group 2 weeks after ESS(P_3=0.03, Figure1E). However, there was no significant difference was found in nasal-spray group comparing with control group(P_1=0.25,Figure1E). The reduction of SNOT-22 score in rh-bFGF experimental groups was higher than that in control group, but the difference was not significant(P_1=0.15,P_3=0.06,Figure1E,F). There was a significant decrease in rh-bFGF experimental groups compared with control group at 6 months and 1 year, but the difference was statistically significant in nasal-spray group at 6 months and nasal-drop group at 1 year(Figure2G,H).

L-K score and nasal endoscopy

The reduction of L-K score in rh-bFGF nasal-drop group was significantly greater than in the control group 2 weeks(P_3=0.004), 1 month(P_3=0.004) and 1 year(P_3=0.02) after ESS(Figure1I,J,L). The decrease in nasal-drop group at 1 month was still obvious, but the difference was not statistically significantly compared with control group(P_3=0.09, Figure1K). The reduction of L-K score in rh-bFGF nasal-spray group was significantly greater than in the control group at 1 month(P_2=0.001), 6 months(P_2=0.02) and 1 year(P_2=0.03) after ESS(Figure1J-L). The decrease in nasal-spray group at 2 weeks was still obvious, but the difference was not statistically significantly compared with control group(P_2=0.13,Figure1I). Nasal endoscopy showed that reduced vesicles and purulent secretion occurred in the rh-bFGF experimental groups than that in control group at 2 weeks(Figure2B,G,L). This trend was even more pronounced 1 month after ESS. Partial nasal mucosal epithelialization was observed in rh-bFGF experimental groups(Figure2C,H,M). Rh-bFGF experimental groups almost eliminated edema and completed epithelialization at 6 months and 1 year(Figure2D,E,I,J,N,O).

Scanning electron microscopy

Sinonasal mucosa from preoperative patients in the three groups were poorly ciliated(Figure3A,D,G). 2 weeks after ESS, the mucociliary coverage of rh-bFGF experimental groups was significantly higher than control group(Figure 3B,E,H). The ciliary coverage in the control group increased at 1 month. However, it was still lower than the rh-bFGF experimental groups(Figure3C,F,I).

Ciliogenesis-associated markers

To further verify the effect of rh-bFGF on the cilia growth, the mRNA expression of CP110, Tap73 and Foxj1 was detected. The expression of CP110, Tap73 and Foxj1 in three groups before ESS was on the same level(Figure4A,D,G). The expression of CP110 and Tap73 of the rh-bFGF experimental groups was significantly lower than that of control group after ESS while no statistic difference was found between nasal-spray group and control group at 2 weeks(Figure4B,C,H,I). The expression of Foxj1 of the rh-bFGF experimental groups was significantly lower than that of control group after ESS. However, there was no difference between nasal-spray group and control group at 1 month(Figure4E,F).

Pathological features and clinical results of eosinophilic and non-eosinophilic CRSwNP

A total of 47.22% of patients were classified with eosinophilic CRSwNP in our study. For general VAS score in eosinophilic CRSwNP patients, the decrease in the rh-bFGF nasal-drop group was more obvious than that in the control group at 2 weeks (P_3=0.005), 1 month(P_3=0.04),6 months(P_3=0.001) and 1 year(P_3=0.04,Figure5A-D). The decrease in general VAS scores in the rh-bFGF nasal-spray group was more obvious than in the control group. However, statistical difference was only found at 6 months between nasal-spray and control group(P2=0.004,Figure5C). For non-eosinophilic CRSwNP patients, no significant difference was found among the three group after ESS, except for nasal-drop group at 1year(FigureS3A-D).

For SNOT-22 scores in eosinophilic CRSwNP patients, the reduction in rh-bFGF nasal experimental groups was greater than in control group. However, no significant difference was found(Figure5E-H). For non-eosinophilic CRSwNP patients, significant difference was only found between nasal-drop and control group at 2 weeks (P_1=0.15,P_3=0.04,FigureS3E). 1 month and 1 year after ESS, the SNOT-22 scores of nasal-spray was significant lower than that of control group(P_1=0.04,FigureS3F,H). As for other postoperative time points, there was no significant difference in SNOT-22 score among the three groups(FigureS3F-H).

For L-K score of eosinophilic CRSwNP patients, the reduction in the rh-bFGF nasal-spray group was more obvious than that of the control group at both 2 weeks (P_1=0.02) and 1 month(P_1=0.01,Figure5E,F). Moreover, a significant difference was found between the control and rh-bFGF nasal-drop groups at 1 month(P_3=0.01), 6 months(P_3=0.04) and 1 year(P_3=0.01), but no significant difference was observed at 2 weeks(P_3=0.43,Figure5E-H). However, for non-eosinophilic CRSwNP patients, only L-K score of nasal-drop group was significant lower than control group at 1 month(P_3=0.04, FigureS3I-L).

Safety analysis

Mild adhesion of the nasal cavity occurred in 3 patients in the control group, 3 patients in the rh-bFGF nasal-spray group and 2 patients in the rh-bFGF nasal-drop group. No significant difference in the adverse event rate was found among the three groups (P=0.86). No extensive adhesion and no major side effects were reported during the trial.

Discussion

The process of nasal epithelization after ESS is closely related to the recovery of symptoms. A previous study[19] showed that nasal irrigation with saline containing sodium hyaluronate improves postoperative nasal symptoms and accelerated the process of nasal epithelization. However, the evaluation indexes were subjective symptom score and endoscopic score in patients 6 weeks after the operation, with no direct evaluation of ciliary function recovery. In our study, we used subjective symptom score and endoscopic score in patients as the primary statistical index. We also collected the nasal mucosa of patients for SEM analysis as a direct index of mucosal epithelization and ciliary recovery. Our results showed the reduction of VAS, obstruction and rhinorrhea scores for general symptom in rh-bFGF nasal experimental group were significantly greater than in the control group, and SNOT-22 score reduction was significantly greater in the rh-bFGF nasal-drop group compared to the control group 2 weeks after ESS, indicating that intranasal use of rh-bFGF exerts obvious effects on rapid recovery of symptoms in ESS postoperative patients. What's more, a significant reduction was found in in rh-bFGF experimental groups at 6 months and 1 year which indicated that rh-bFGF may exert an persistent effect on its recovery. We performed a one-year recurrence and efficacy evaluation, considering that epithelial damage of the nasal cavity is an important factor causing the onset of sinusitis, we can predict that promoting epithelialization and ciliary growth during the early stage is helpful for reducing recurrence and polyp regeneration.

Th2-type CRS was associated with eosinophils and asthma. Studies[11,12] have shown that eosinophilic-associated CRS presents more severe postoperative mucosal edema and polypoid changes than non-eosinophilic CRS. In our study, one year follow-up data for the eosinophilic CRS patients showed that the reduction in VAS scores in the rh-bFGF nasal-drop group was greater than in the control group. Moreover, the reduction in the L-K score in the rh-bFGF nasal-spray group was greater than that in the control group.

This suggests that rh-bFGF may also contribute to the rapid recovery of eosinophilic sinusitis patients. However, this trend was not obvious in rh-bFGF experimental groups of non-eosinophilic patients compared with control group. We analyzed the reason for this difference between eosinophilic and non-eosinophilic CRSwNP, which was attributed to the poorer ciliary coverage and sever epithelial damage in eosinophilic CRSwNP. Therefore, we consider that rh-bFGF may improve the prognosis of patients with CRSwNP by promoting ciliary growth and epithelial repair.

To further verify the mechanism of rh-bFGF on the rapid recovery of ESS patients, epithelial cells of the experimental and the control groups were examined by SEM. 2 weeks and 1 month after ESS, rh-bFGF nasal-spray and rh-bFGF nasal-drop group exhibited a higher ciliary coverage compared with control group. CP110, Foxj1 and Tap73 have already been proven as ciliogenesis-associated makers[20]. The expression of these three genes has been marked decreased in rh-bFGF experimental groups compared with control group at 2 weeks and 1 month after ESS, which was consistent with the result of SEM. These results suggest that the outstanding improvement of postoperative nasal obstruction, rhinorrhea, as well as the endoscope L-K score, were also associated with rapid epithelialization and ciliary coverage.

The method of nasal administration is another highlight of our research design. Previous studies[21,22] have shown that changing the administration method of local nasal corticosteroids may affect the symptoms. Therefore, we designed a nasal-drop experiment group. The reduction in the VAS score for general symptoms in the rh-bFGF experimental groups was significantly greater than in the control group. In terms of epithelialization and ciliary growth post-operation, the rh-bFGF experimental groups may have the same effect on ethmoid mucosa cilia growth, whereas mucosa from patients in the control group had significantly less ciliated coverage. Therefore, the overall effect of the nasal-drop group was better than that of the nasal-spray group. This may be attributed to position drainage, which enables rh-bFGF to reach the mucous of the ethmoid roof and frontal recess.

Conclusions

Rh-bFGF nasal-sprays and drops quickly relieve postoperative symptoms and reduce L-K scores through promoting nasal epithelialization and cilia growth. In addition, the therapeutic effect of nasal-drops is better than that of nasal-sprays. Rh-bFGF nasal-sprays and drops can also improve long-term prognosis of patients with CRSwNP. Moreover, rh-bFGF nasal-drops are an effective method of administration in postoperative patients with eosinophilic CRSwNP.

Limitations

Firstly, we only conducted this study at a single center. Secondly, our enrolled patients were surgical patients with bilateral CRSwNP who had exhibited a poor response to adequate medication.

Abbreviations

CRS: Chronic Rhinosinusitis; CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; EPOS 2020: European position paper on rhinosinusitis and nasal polyps 2020 guidelines; SD: Standard Deviation; SNOT-22: 22-item Sino-Nasal Outcome Test; VAS: Visual Analog Scale; L-K: Lund-Kennedy; rh-bFGF: recombinant human-basic fibroblast growth factor. ESS: endoscopic sinus surgery. FESS: functional endoscopic sinus surgery.

References:

1. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in European underestimated disease. A GA(2)LEN study. Allergy 2011; 66:1216-23.

2. Hirsch AG, Stewart WF, Sundaresan AS, Young AJ, Kennedy TL, Scott GJ, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy 2017; 72:274-81.

3. Fokkens WJ. EPOS2020: a major step forward. Rhinology 2020; 58:1.

4. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital Health Stat 10 2014:1-161.

5. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy 2012; 67:91-8.

6. Samitas K, Carter A, Kariyawasam HH, Xanthou G. Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: The one airway concept revisited. Allergy 2018; 73:993-1002.

7. Frendo M, Hakansson K, Schwer S, Rix I, Ravn AT, Backer V, et al. Asthma in ear, nose, and throat primary care patients with chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy 2016; 30:67-71.

8. van der Veen J, Seys SF, Timmermans M, Levie P, Jorissen M, Fokkens WJ, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. Allergy 2017; 72:282-90.

9. Kule ZG, Habesoglu TE, Somay A, Deveci HS, Kule M, Gursel AO. Histopathological characteristics of nasal polyps in smokers and non-smokers. J Craniofac Surg 2014; 25:946-9.

10. Akbari E, Philpott CM, Ostry AJ, Clark A, Javer AR. A double-blind randomised controlled trial of gloved versus ungloved merocel middle meatal spacers for endoscopic sinus surgery. Rhinology 2012; 50:306-10.

11. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. J Allergy Clin Immunol 2003; 111:342-9.

12. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. J Allergy Clin Immunol 2011; 128:451-62, 463-4.

13. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. J Allergy Clin Immunol 2003; 111:342-9.

14. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. J Allergy Clin Immunol 2011; 128:451-62, 463-4.

15. Nakamura R, Katsuno T, Kitamura M, et al. Collagen sponge scaffolds containing growth factors for the functional regeneration of tracheal epithelium. J Tissue Eng Regen Med. 2019-05-01 2019;13(5):835-845.

16. Guan D, Mi J, Chen X, et al. Lung endothelial cell-targeted peptide-guided bFGF promotes the regeneration after radiation induced lung injury. Biomaterials. 2018-11-01 2018;184:10-19.

17. Hong SD, Jang JY, Kim JH, Jang SY, Kim HY, Dhong HJ, et al. The effect of anatomically directed topical steroid drops on frontal recess patency after endoscopic sinus surgery: a prospective randomized single blind study. Am J Rhinol Allergy 2012; 26:209-12.

18. Cao PP, Li HB, Wang BF, Wang SB, You XJ, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. J Allergy Clin Immunol 2009; 124:478-84, 481-4.

19. Xu W, Xu G, Zhou H. Effect of nasal flush combined growth factor on outcome of endoscopy surgery. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012; 26:999-1000.

20. Li YY, Li CW, Chao SS, Yu FG, Wang, DY. Impairment of cilia architecture and ciliogenesis in hyperplastic nasal epithelium from nasal polyps.J Allergy Clin Immunol 2014, 134(6): 1282-1292.

21. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev 2016; 4:D11993.

22. Wu YX, Wang M, Li H, Xing ZM, Shi MH, Huang SE, et al. Efficacy and safety of delivery of topical medication on to the frontal sinus at different head positions after frontal sinusotomy. Eur Arch Otorhinolaryngol 2020; 277:1361-8.

Figure and table legends

Table 1 Baseline information of participants, a Anova Analysis. b.Chi-square test. c.Kruskal-wallis analysis.

Figure 1 The reduction in symptom score: (A) The reduction in VAS score 2 weeks after ESS. (B)The reduction in VAS score 1 month after ESS. (C) The reduction in VAS score 6 months after ESS. (D)The reduction in VAS score 1 year after ESS. (E) The reduction in SNOT-22 score 2 weeks after ESS. (F)The reduction in SNOT-22 score 1 month after ESS. (G)The reduction in SNOT-22 score 6 months after ESS. (H)The reduction in SNOT-22 score 1 year after ESS. (I) The reduction in L-K score 2 weeks after ESS. (J)The reduction in L-K score 1 month after ESS. (K)The reduction in L-K score 6 months after ESS. (L) The reduction in L-K score 1 year after ESS. ESS, endoscopic sinus surgery.

Figure 2 Endoscopic photographs from one patient for each of the three groups. Figure(A,F,K)show the preoperative endoscopic condition of nasal cavity. Figure(B,G,L) show the postoperative ethmoid sinus cavity 2 weeks after ESS. Figure(C,H,M) show the postoperative ethmoid sinus cavity 1 month after ESS. Figure(D,I,N) show the postoperative ethmoid sinus cavity 6 months after ESS. Figure(E,J,O) show the postoperative ethmoid sinus cavity 1 year after ESS. ESS, endoscopic sinus surgery.

Figure 3 SEM photographs from one patient for each of the three groups. Figure(A,D,G)show the preoperative nasal mucosa. Figure(B,E,H) show the postoperative nasal mucosa 2 weeks after ESS. Figure(C,F,I) show the postoperative nasal mucosa 1 month after ESS. SEM, scanning electron microscope. ESS, endoscopic sinus surgery.

Figure 4 The mRNA expression of CP110, Foxj1 and Tap73. (A) The CP110 mRNA expression among control group, rh-bFGF nasal-spray and nasal-drop group before ESS. (B) The CP110 mRNA expression among the three groups 2 weeks after ESS. (C) The CP110 mRNA expression among the three groups 1 month after ESS. (D) The Foxj1 mRNA expression among the three groups before ESS.(E) The Foxj1 mRNA expression among the three groups 2 weeks after ESS.(F) The Foxj1 mRNA expression among the three groups 1 month after ESS. (G) The Tap73 mRNA expression among the three groups before ESS. (H)The Tap73 mRNA expression among the three groups 2 weeks after ESS. (I) The Tap73 mRNA expression among the three groups 1 month after ESS.

Figure 5 The reduction in VAS score, SNOT-22 and L-K score in eCRS of the three group. (a) The reduction in VAS score 2 weeks after ESS. (B)The reduction in VAS score 1 month after ESS. (C)The reduction in VAS score 1 month after ESS. (D)The reduction in VAS score 1 month after ESS.(E) The reduction in SNOT-22 score 2 weeks after ESS. (F)The reduction in SNOT-22 score 1 month after ESS. (G)The reduction in SNOT-22 score 6 months after ESS. (H)The reduction in SNOT-22 score 1 year after ESS. (I)The reduction in L-K score 2 weeks after ESS. (J) The reduction in L-K score 1 month after ESS. (K)The reduction in L-K score 6 months after ESS. (L)The reduction in L-K score 1 year after ESS. eCRS, eosinophil chronic rihnosinusitis. ESS, endoscopic sinus surgery.

Figure S1 Consort Flow Diagram: Flow diagram of participants enrolled in this study. Conventional treatment(antibiotics for 3 days and nasal corticosteriod and irrigation for 1 month).

Figure S2 The reduction of symptom score (A) The reduction in obstruction score 2 weeks after ESS. (B)The reduction in obstruction score 1 month after ESS. (C)The reduction in obstruction score 6 months after ESS. (D)The reduction in obstruction score 1 year after ESS. (E)The reduction in rhinorrhea score 2 weeks after ESS. (F)The reduction in rhinorrhea score 1 month after ESS. (G)The reduction in rhinorrhea score 6 months after ESS. (H)The reduction in rhinorrhea score 1 year after ESS.

(I)The reduction in olfactory score 2 weeks after ESS. (J)The reduction in olfactory score 1 month after ESS. (K) The reduction in olfactory score 6 months after ESS. (L)The reduction in olfactory score 1 year

after ESS. (M) The reduction in facial pressure score 2 weeks after ESS. (N)The reduction in facial pressure score 1 month after ESS. (O)The reduction in facial pressure score 6 months after ESS.(P)The reduction in facial pressure score 1 year after ESS. (Q)The reduction in headache score 2 weeks after ESS. (R)The reduction in headache score 1 month after ESS. (S)The reduction in headache score 6 months after ESS. (T)The reduction in headache score 1 year after ESS. ESS, endoscopic sinus surgery. ESS, endoscopic sinus surgery.

Figure S3 The reduction in VAS score, SNOT-22 and L-K score in non-eCRS of the three group. (a) The reduction in VAS score 2 weeks after ESS. (B)The reduction in VAS score 1 month after ESS. (C)The reduction in VAS score 1 month after ESS. (D)The reduction in VAS score 1 month after ESS.(E) The reduction in SNOT-22 score 2 weeks after ESS. (F)The reduction in SNOT-22 score 1 month after ESS. (G)The reduction in SNOT-22 score 6 months after ESS. (H)The reduction in SNOT-22 score 1 year after ESS. (I)The reduction in L-K score 2 weeks after ESS. (J) The reduction in L-K score 1 month after ESS. (K)The reduction in L-K score 6 months after ESS. (L)The reduction in L-K score 1 year after ESS. eCRS, eosinophil chronic rihnosinusitis. ESS, endoscopic sinus surgery.

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