doi.org/10.36721/PJPS.2025.38.3.REG.14312.1

Clinical efficacy and immunomodulatory mechanism of budesonide nasal spray combined with mucus promoter in patients with chronic sinusitis

Bo Luan[1], Dachen Huang[2], Qi Shen[1], Xiaoyan Wang[1], Li Ling[1], Jufang Shen[1], Jin Fang[1] and Kan Liu[*1]

[1]Department of ENT, Zhejiang Xin'an International Hospital, Jiaxing 314001, Zhejiang Province, China
[2]Department of ENT, Zhejiang Jiaxing Wangdian People's Hospital, Jiaxing 314001, Zhejiang Province, China

Abstract: Chronic rhinosinusitis (CR) seriously affects the patient's life quality, and current clinical treatment faces certain challenges. This study observed the effects of budesonide nasal spray combined with mucus promoter on the clinical efficacy and immunomodulatory mechanism of CR patients. 105 patients with CR from Zhejiang Xin'an International Hospital between January 2021 and January 2024 were categorized into EL group and BE group, both groups underwent mucus promoter intervention and BE group were added with budesonide nasal spray intervention. Inflammatory and immunity indicators ($CD4^+$ and $CD8^+$ Tcells percentage) and clinical efficacy were mainly assessed. Secondary results included Lund-Kenndey score, Lund-Mackey score, nasal ventilation function [DCAN, NCV, NMCA, and nasal airway resistance], clinical symptom scores, adverse effects incidences, and recurrence rates. After treatment, the indicators of the both groups were superior to pre-treatment (P<0.05). The $CD4^+$ Tcells percentage, $CD4^+/CD8^+$, NCV, NMCA, clinical symptom scores and clinical efficacy in BE group were markedly above the EL group, and inflammatory indicators, $CD8^+$ Tcells percentage, Lund-Kenndey score, Lund-Mackey score, DCAN, nasal airway resistance, adverse effects incidences and recurrence rate were markedly below the EL group (P<0.05). This combined therapy has a remarkable curative effect, which is worthy of popularizing and use in the clinic.

Keywords: Chronic rhinosinusitis; budesonide nasal spray; mucus promoter; immune indicator; inflammatory indicator

Submitted on 17-03-2025 – Revised on 05-04-2025 – Accepted on 15-05-2025

INTRODUCTION

Chronic rhinosinusitis (CR) as a common chronic disease of the nose, due to nasal polyps pus, redness and swelling of the inflammation, triggered by the eyes have a sense of pressure, can also cause visual impairment, dizziness and other problems, a small number of accompanied by allergies, asthma, the onset of its cause of respiratory tract infections, chills and fever, peripheral discomfort and other symptoms. Its long course, complex symptoms and easy to recur, seriously affecting the quality of life of patients (Bachert *et al.*, 2020). It has been found that long-term stimulation of the sinuses and nasal cavity by inflammatory factors can lead to significant proliferation of capillaries in the mucosa and bone, as well as an increase in the release of inflammatory substances, leukocyte infiltration and cytokines in the inflamed tissues (Kato *et al.*, 2022). The pathogenesis of CR involves chronic inflammation of the nasal sinus mucosa, imbalance of immune regulation, and microbial infection, etc. Among them, cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) play an important role in inflammation, and are involved in the development of CR through the mechanisms of regulating inflammation, promoting cell proliferation and migration, etc. (Cho *et al.*, 2020). Currently, there are various clinical treatments available, including drug therapy, surgical treatment and postoperative management, but single therapies are often difficult to achieve ideal therapeutic effects, especially for symptomatic relief and prevention of recurrence in postoperative patients, which is still an unresolved problem (Albu, 2020). Therefore, it is of great clinical value to explore safe and effective combined treatment options to optimize postoperative management of CR, reduce recurrence, and improve patients' quality of life.

Glucocorticoids show an inflammatory factor inhibitory effect and can inhibit the inflammatory response of the diseased tissues effectively, thereby ameliorating the edema of the mucosal tissues (Reichardt *et al.*, 2021). Nasal glucocorticoids can reduce the infiltration of inflammatory cells and the release of cytokines in the nasal mucosa, can effectively inhibit the production of inflammatory mediators, and mainly act locally, with low systemic bioavailability and minimal adverse effects (Wijnants *et al.*, 2022). It has been shown that nasal mucosal epithelial cells recovered significantly after glucocorticoid inhalation in patients with nasal inflammation (Mygind *et al.*, 2001). Budesonide is a kind of adrenal glucocorticoid drug, and is commonly used in the treatment of chronic rhinitis and postoperative sinusitis, which reduces the inflammatory response of the body by inhibiting vasodilatation, decreasing edema, improving vascular permeability, and other physiological mechanisms, to achieve the effect of promoting mucosal epithelialization and accelerating mucosal healing. It

*Corresponding author: e-mail: yhgfiyt@hotmail.com

possesses good anti-allergic and anti-inflammatory effects, can bind to glucocorticoid receptors, has suitable water solubility and high lipophilicity and high affinity (Heo, 2021). The application of budesonide nasal spray in rhinitis patients can promote the reduction of local eosinophils as well as mast cell infiltration, which in turn inhibits the production and release of inflammatory factors (Lin *et al.*, 2020). Budesonide Nasal Spray uses the nasal cavity as the route of administration, which enables the drug effect to be exerted more rapidly, improves the utilization rate and concentration of the drug locally, and facilitates the rapid relief of nasal mucosal symptoms, and at the same time, compared with systemic medication, there are fewer adverse reactions, and the dosage of medication is also reduced, which improves the safety to a large extent (Zieglmayer *et al.*, 2020).

According to the guidelines for the clinical diagnosis and treatment of chronic rhinosinusitis, mucus promoters can thin nasal and sinus secretions and improve the activity of nasal mucosal cilia, and have the effect of promoting mucus drainage and contributing to the restoration of the physiological function of the nasal cavity and sinuses, and are recommended for use (Kardos *et al.*, 2020). The main components of eucalyptol, limonene and pinene enteric capsules are composed of the extracts of Eucalyptus spp. of the Myrtaceae family and the extracts of Orange spp. of the Rutaceae family and Pine spp. of the Pinaceae family, and the pharmacological effects of the different components are antipyretic, anti-inflammatory, cough-suppressant, expectorant and anti-fungal effects respectively (He *et al.*, 2024). The three active ingredients act on the mucus cilia clearance system of the nasal mucosa, restoring cilia activity and facilitating mucus discharge, which in turn restores the function of the mucus cilia clearance system and rebuilds the clearance defense mechanism of the whole system, thus solving the inflammatory reactions of the upper respiratory tract, such as rhinitis, sinusitis, bronchitis, etc., at the root (Peric *et al.*, 2021). It has also been reported in the literature that the drug reduces mucosal edema in the treatment of otitis media, synergizes the effect of antibiotics, and opens drainage, thus shortening the course of inflammation and improving symptoms (Liao *et al.*, 2022).

Currently, there are fewer relevant reports on the combination of budesonide nasal spray with mucus promoters for the treatment of CR. In view of the respective advantages of budesonide nasal spray and eucalyptol, limonene and pinene enteric capsules in the treatment of CR, the present study was designed to observe the clinical efficacy of the combination of the two for the treatment of CR, and to analyze the inflammatory indicators and immunity indicators, in order to provide more therapeutic choices for the clinic.

MATERIALS AND METHODS

Study Design and Participants

This study is a systematic evaluation and integration aimed at comparatively analyzing the clinical efficacy of budesonide nasal spray combined with mucus prokinetic agents in the treatment of patients with CR, and further evaluating its effects on the expression of inflammatory factors and the level of immune function in patients. The design of this study was a retrospective clinical controlled trial, and 105 patients with CR admitted from January 2021 to January 2024 were selected and divided into two groups, EL group and BE group, according to the interventions. The flow chart of this study is illustrated in fig. 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) meet the diagnostic criteria of CR (Saltagi *et al.*, 2021); (2) age 18-65 years old; (3) all have symptoms such as profuse pus and nasal congestion; (4) decreased sense of smell and localized inflammatory changes in the mucosa of the sinuses; (5) those who can tolerate the medications involved in this study; (6) the patients have good communication skills and good adherence; (7) the patients and their families were informed and executed the informed consents documents.

Exclusion criteria: (1) cardiovascular disease, neurological or other serious organ function damage; (2) the presence of malignant tumor history; (3) the combination of other chronic diseases; (4) the combination of serious infections or rheumatic diseases; (5) suffering from serious infectious diseases and taking medications for the treatment of CR; (6) have undergone nasal surgery; (7) allergic to the components of the medicines used in this experiment; (8) those who have recently received the same kind of drug treatment, which makes it difficult to judge the efficacy of the drug; (9) other conditions affecting the follow-up observation index.

Ethical approval

The study was performed in compliance with the Declaration of Helsinki and hospital ethical guideline and was endorsed by Zhejiang Xin'an International Hospital ethical committee. (No. XA-K-2024-026)

Interventions

Both groups were treated with eucalyptol, limonene and pinene enteric capsules (Manufacturer: Beijing Jiuho Pharmaceuticals, National Drug Code H20070006) orally, 0.12 mg/times, 2 times/d, for 12 weeks.

The BE group added budesonide nasal spray treatment on top of this (Manufacturer: McNeil Sweden AB, National Drug Code HJ20171311, 64 μg/spray), 1 spray for each bilateral nasal cavity each time, 2 times/d, and continued treatment for 12 weeks.

Observational indicators

Primary indicators

Inflammation indicators

Referring to the research method of Kanlioglu et al. (Kanlioglu Kuman *et al.*, 2021), 5 mL of fasting venous blood was drawn from patients pre- and post-treatment, centrifuged and processed, and then stored in cold storage to be detected, and serum IL-6, ultrasensitive C-reactive protein (hs-CRP), and TNF-α levels were measured using enzyme-linked immunosorbent assay.

The kits used were Human IL-6 ELISA kit (Item No.: ml027379，Shanghai Enzyme-linked Biotechnology Co., Ltd.), Human hs-CRP ELISA kit (Item No.: ml106583，Shanghai Enzyme-linked Biotechnology Co., Ltd.) and Human TNF-α ELISA kit (Item No.: ml077385，Shanghai Enzyme-linked Biotechnology Co., Ltd.).

Immunity indicators

Immune indicators were observed in both groups, and the percentage of $CD4^+$ and $CD8^+$ T cells in peripheral blood samples were measured using enzyme-linked immunosorbent assay (Aljabr *et al.*, 2022).

The kits used were Human $CD4^+$ T cells ELISA kit (JKbio 14552, Shanghai Jingkang Bioengineering Co., Ltd.) and Human $CD8^+$ T cells ELISA kit (JKbio 14553, Shanghai Jingkang Bioengineering Co., Ltd.).

Clinical efficacy

The Clinical effectiveness was observed and documented. Obvious effect: clinical symptoms disappeared, no purulent secretions and mucosal edema, and the sinuses were open. Effective: clinical symptoms improved, but the sinus openings were not completely open and accompanied by a small amount of purulent secretions. Ineffective: clinical symptoms did not improve or worsened. Total effective rate = (obvious effect + effective) / total × 100%.

Secondary indicators

Scoring of nasal mucosal structure and degree of sinusitis

The nasal mucosal structure and the degree of sinusitis were scored in both groups (Lee *et al.*, 2021). Nasal mucosal structure score was analyzed by Lund-Kenndey score of nasal endoscopy, including 5 items of nasal mucosa, including scar, polyp, crust, nasal leakage and edema, 2 items of scar and crust were excluded due to the lack of surgical treatment in this study, and the other 3 items were counted, with 0-6 points on each side and a total score of 0-12, with lower scores representing the less severe inflammation of the nasal mucosa. The degree of sinusitis score was analyzed using the Lund-Mackey score, including 6 items for the front group of sieve sinuses, the back group of sieve sinuses, frontal sinus, pterygoid sinus, maxillary sinus, and sinus-oral-nasal tract complex, with 0~12 points on each side and a total score of 0~24 points, with lower scores representing the better recovery of the sinuses.

Nasal ventilation function

Nasal acoustic reflectometer and anterior nasal manometer were used to measure before and after the treatment, respectively (Ma *et al.*, 2021), and the indexes included: minimum cross-sectional distance from nostril to nasal cavity (DCAN), nasal cavity volume (NCV), nasal minimum cross-sectional area (NMCA), and nasal airway resistance.

Clinical symptoms score

The clinical symptoms such as headache, nasal leakage and nasal congestion were assessed using visual analog scoring pre- and poet-treatment in the both groups (Shukla *et al.*, 2020), with 10 being the total score, and more scores representing more seriousness.

Adverse reaction

These include nasolacrimal duct obstruction, nasal adhesions, decreased sense of smell, and nasal bleeding.

Recurrence rate

Record the recurrence rate at 6-month follow-up after the end of treatment.

Follow-Up Visits

This study was primarily scheduled for a 6-month post-treatment follow-up to assess the durability of the effect and to address any potential adverse reactions or problems. These follow-up visits are essential to assess the long-term efficacy and safety of budesonide nasal spray combined with mucus promoter in the treatment of CR.

Sample size calculation

Sample size was based on a power analysis performed with G*Power 3.1.9.7 computer software to determine the sample size required to detect a statistically significant difference. The sample size was calculated based on the primary outcome of the inflammation indicator (Preethi *et al.*, 2023). Considering an α level of 0.05 and 85% efficacy, we calculated that a sample size of 41 patients was required for each group. Considering the potential uncertainties, the sample sizes chosen for this study were EL group (n=50) and BE group (n=55), and we believe that the sample sizes in this study are capable of drawing reliable conclusions.

STATISTICAL ANALYSIS

SPSS27.0 statistics software was applied for analysis of the data. Measurements that conform to normally distributed value are represented as ($\bar{x}$±s), and comparisons among groups adopts act independently pattern t examination, and counting data is expressed as rate (%) using x^2 test, with P<0.05 indicating a statistical significance of the difference.

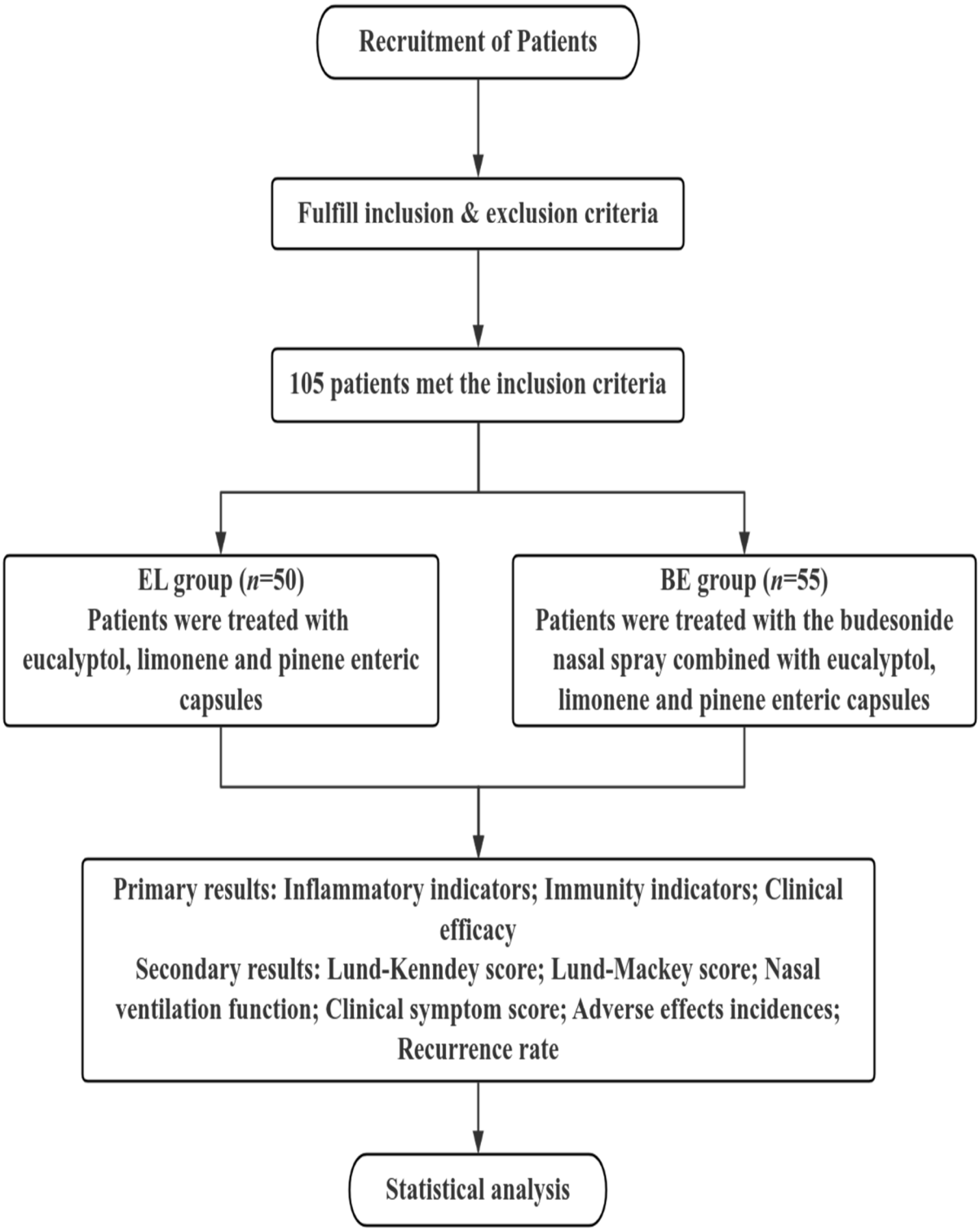

Fig. 1: Flow chart

RESULTS

Basic information

This study was conducted at Zhejiang Xin'an International Hospital between January 2021 and January 2024, 105 CR patients were randomized to EL group (n=50) and BE group (n=55) according to different interventions. The baseline demographic and baseline characteristics of the both groups of patients are shown in table 1, and these features were not markedly different among the both groups (P>0.05). Thus, the randomization process achieved the important goal of randomly assigning participants to both groups, the two groups were comparable at the pretreatment level, and confounding by demographic/clinical factors did not affect the analysis of results.

Primary results

Inflammatory indicators

Detection of inflammatory indicators in patients with CR helps to assess the effectiveness of patient treatment, and the results of the comparison of inflammatory indicators among the both groups are showed in table 2. Before treatment, the hs-CRP, TNF-α and IL-6 levels in the both groups were not statistically different compared among the groups (P>0.05). After treatment, the levels of inflammatory indicators were 4.02 ± 0.49 ng/L, 2.38 ± 0.36 ng/L, and 12.22 ± 1.92 ng/L in patients of the EL group,

Table 1: Patient demographics and baseline disease characteristics

Parameter	EL group (n=50)	BE group (n=55)	t/x^2	P
Age/ (year)	46.62±11.22	46.45±10.74	-0.079	0.937
Gender/ (male/female)	21/29	25/30	0.127	0.722
Height/ (year)	159.95±6.20	159.47±5.64	-0.415	0.679
Weight/ (kg)	63.03±8.14	62.77±8.67	-0.158	0.875
Disease duration/ (year)	6.27±1.58	6.24±1.30	-0.107	0.915
Body mass index/ (kg/m^2)	22.58±2.62	22.71±2.46	0.262	0.794
Smoking/ (Yes/no)	26/24	29/26	0.006	0.941
Alcohol consumption/ (Yes/no)	28/22	31/24	0.001	0.970
Hypertension/ (Yes/no)	23/27	27/28	0.100	0.751
Diabetes/ (Yes/no)	26/24	28/27	0.012	0.911
Temperature/ (℃)	36.51±0.28	36.58±0.26	1.328	0.187
Breathing/ (breaths/min)	17.19±1.75	16.86±1.66	-0.991	0.324
Heart rate/ (beat/min)	75.26±7.30	75.34±6.92	0.058	0.954
Systolic blood pressure/ (mmHg)	120.46±6.31	120.19±7.81	-0.194	0.847
diastolic blood pressure/ (mmHg)	76.99±5.46	77.10±6.44	0.094	0.925

Table 2: Comparisons of inflammation indicators ($\bar{x}$±s，ng/L)

norm	time	EL group	BE group	t	P
hs-CRP	Pre-treatment	6.18±0.42	6.13±0.39	-0.633	0.529
	Post-treatment	4.02±0.49*	3.34±0.35*	-8.238	<0.001
TNF-α	Pre-treatment	5.02±0.52	5.03±0.46	0.105	0.917
	Post-treatment	2.38±0.36*	1.66±0.55*	-7.851	<0.001
IL-6	Pre-treatment	15.72±2.55	15.84±3.30	0.207	0.836
	Post-treatment	12.22±1.92*	6.59±1.51*	-16.778	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, P<0.05.

Table 3: Immune function indicators ($\bar{x}$±s)

norm	time	EL group	BE group	t	P
CD4$^+$ T cells (%)	Pre-treatment	13.61±2.13	13.64±2.22	0.071	0.944
	Post-treatment	16.25±2.14*	18.35±2.07*	5.109	<0.001
CD8$^+$ T cells (%)	Pre-treatment	21.82±2.58	21.77±2.69	-0.097	0.923
	Post-treatment	19.48±1.66*	17.71±1.59*	-5.579	<0.001
CD4$^+$/CD8$^+$	Pre-treatment	0.61±0.11	0.62±0.15	0.386	0.700
	Post-treatment	0.89±0.15*	1.05±0.18*	4.921	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, P<0.05.

Table 4: Clinical efficacy analysis

Group	Obvious effect (*n*)	Effective (*n*)	Ineffective (*n*)	Total efficacy rate (*n*, %)
EL group	18	22	10	40 (80.00)
BE group	23	28	4	51 (92.73)
x^2			7.236	
P			<0.05	

Table 5: Nasal mucous membrane structure and sinusitis degree score ($\bar{x}$±s, score)

norm	time	EL group	BE group	*t*	*P*
Lund-Kenndey	Pre-treatment	8.46±1.27	8.47±1.20	0.042	0.967
	Post-treatment	6.58±1.25*	5.24±0.96*	-6.192	<0.001
Lund-Mackey	Pre-treatment	7.86±1.42	7.79±1.34	0.260	0.796
	Post-treatment	4.62±0.87*	3.44±0.72*	-7.597	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 6: Comparison of nasal ventilation function ($\bar{x}$±s)

norm	time	EL group	BE group	*t*	*P*
DCAN (cm^2)	Pre-treatment	1.67±0.26	1.62±0.32	-0.873	0.385
	Post-treatment	1.09±0.11*	0.82±0.15*	-10.430	<0.001
NCV (cm^2)	Pre-treatment	10.24±0.73	10.37±0.75	0.898	0.371
	Post-treatment	13.42±1.56*	17.10±2.30*	9.499	<0.001
NMCA (cm^2)	Pre-treatment	0.49±0.20	0.47±0.17	-0.554	0.581
	Post-treatment	0.55±0.17*	0.71±0.13*	5.446	<0.001
nasal airway resistance [kPa/(L·s)]	Pre-treatment	2.70±0.40	2.71±0.34	0.138	0.890
	Post-treatment	1.84±0.22*	1.06±0.14*	-21.874	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 7: Clinical symptom scores ($\bar{x}$±s, score)

norm	time	EL group	BE group	*t*	*P*
Headaches	Pre-treatment	4.33±1.25	4.45±1.35	0.471	0.639
	Post-treatment	2.04±0.89*	0.74±0.34*	-10.059	<0.001
Nasal leakage	Pre-treatment	6.29±1.63	6.16±1.62	-0.409	0.683
	Post-treatment	2.41±0.64*	1.42±0.55*	-8.522	<0.001
Nasal congestion	Pre-treatment	6.67±2.43	6.66±2.07	-0.023	0.982
	Post-treatment	2.56±0.37*	1.35±0.27*	-19.262	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 8: Incidence of adverse reactions

Group	Nasolacrimal duct obstruction	Nasal adhesions	Decreased sense of smell	Nasal bleeding	Total incidence (*n*, %)
EL group	2	3	2	1	8 (16.00)
BE group	1	1	1	0	3 (5.45)
x^2			6.438		
P			<0.05		

and 3.34 ± 0.35 ng/L, 1.66 ± 0.55 ng/L, and 6.59 ± 1.51 ng/L in patients of the BE group, which were all markedly decreased compared with the pre-treatment levels. The BE group was markedly below the EL group ($P<0.05$). It indicated that the levels of inflammatory indexes were markedly reduced in both groups post-treatment, and the patients in the BE group showed better improvement in blood inflammatory response.

Immune indicators

CR and immune response are closely related. We analyzed and compared the results of the immune function indicators

of the both groups are demonstrated in table 3. Before treatment, no remarkable discrepancy was found among the both groups in immune indicators (P>0.05). After treatment, the percentage of $CD4^+$ T cells and $CD4^+/CD8^+$ in EL group were 16.25 ± 2.14% and 0.89 ± 0.15, respectively, and those of BE group were 18.35 ± 2.07% and 1.05 ± 0.18, respectively, which were markedly increased compared with pre-treatment (P<0.05). The $CD8^+$ T cells percentage in EL group was 19.48 ± 1.66% and 17.71 ± 1.59% in BE group, both of which were markedly below that of pre-treatment (P<0.05). The changes of immune indicators in BE group were superior to EL group (P<0.05). It indicated that the immunity indicators of patients in both groups improved remarkably post-treatment, and the improvement of immune function in the BE group was more remarkable.

Clinical efficacy

We analyzed the clinical efficacy of the two groups of patients by combining the effects of the two groups of patients, and the results of the analysis are demonstrated in table 4. The total efficacy rate of the EL group patients was 80.00% (40/50), and the total efficacy rate of the BE group patients was 92.73% (51/55), which was statistically significant compared with the group (P<0.05). The results showed that the efficacy of BE group patients was better, indicating that budesonide nasal spray combined with mucus promoter had better clinical efficacy than mucus promoter alone in CR.

Nasal mucosa structure and sinusitis scores

The nasal mucosal structure and sinusitis degree scores of the both groups pre- and post-treatment were comparatively analyzed as presented in table 5. Before treatment, no remarkable discrepancy was found among the Lund-Kenndey and Lund-Mackey scores of the both groups (P>0.05). After treatment, the Lund-Kenndey and Lund-Mackey scores of patients in the EL group were 6.58 ± 1.25 score and 4.62 ± 0.87 score, respectively, and those of patients in the BE group were 5.24 ± 0.96 score and 3.44 ± 0.72 score, respectively, which were markedly reduced from pre-treatment. The scores of BE group patients were remarkably below EL group (P<0.05). It indicated that the improvement of nasal mucosa structure and degree of sinusitis was better in BE group.

Nasal ventilation function

The results of comparative analysis of nasal ventilation function of the both groups of patients are presented in table 6, and no obvious discrepancy was found in the comparison of the both groups of patients pre-treatment (P>0.05). After treatment, the DCAN and nasal airway resistance of patients in EL group were 1.09 ± 0.11 cm^2 and 1.84 ± 0.22 kPa/(L·s), respectively, and those of BE group were 0.82 ± 0.15 cm^2 and 1.06 ± 0.14 kPa/(L·s), respectively, which were obviously below the pre-treatment (P<0.05). The NCV and NMCA of patients in the EL group were 13.42 ± 1.56 cm^2 and 0.55 ± 0.17 cm^2, respectively, and those in the BE group were 17.10 ± 2.30 cm^2 and 0.71 ± 0.13 cm^2, respectively, which were markedly above pre-treatment (P<0.05). The changes in nasal ventilation function indicators in the BE group were superior to the EL group (P<0.05). It indicates that the nasal ventilation function of both groups improved markedly after treatment, and the BE group patients had a better improvement effect.

Clinical symptom scores

The results of the clinical symptom scores of the both groups of patients after treatment are presented in table 7. Before treatment, no statistical discrepancy was found in

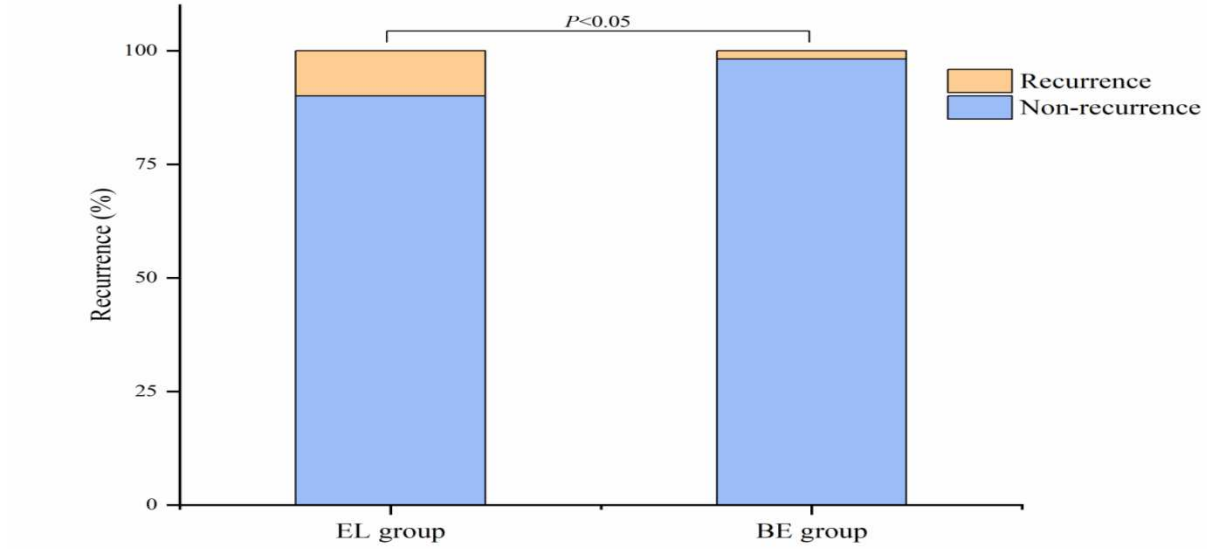

Fig. 2: Recurrence

the headache, nasal leakage and nasal congestion levels among the both groups of patients (P>0.05). After treatment, the clinical symptom scores of patients in the EL group were 2.04 ± 0.89 score, 2.41 ± 0.64 score and 2.56 ± 0.37 score, respectively, and those of the BE group were 0.74 ± 0.34 score, 1.42 ± 0.55 score and 1.35 ± 0.27 score, respectively, all of which were markedly decreased the pre-treatment. The BE group was markedly below the EL group (P<0.05). It indicated that the clinical symptoms of patients in both groups improved post-treatment, and the clinical symptoms of patients in BE group improved better.

Adverse reactions

We followed up the patients to observe the adverse reactions. Adverse reactions of varying degrees such as nasolacrimal duct obstruction during treatment in both groups are presented in table 8. The total incidence of adverse reactions in patients in the EL group was 16.00% (8/50), and that in the BE group was 5.45% (3/55), and the total incidence in the BE group was markedly below the EL group (P<0.05). It indicated that the therapeutic effect of the treatment used in BE group patients was better and safer.

Recurrence rate

We recorded the recurrence of patients in the both groups during the follow-up period, as shown in fig. 2, the recurrence rate in the EL group was 10.00% (5/50) markedly above the BE group's 1.82% (1/55), and the difference was statistically significant (P<0.05). It shows that the combined treatment method used in this study can effectively reduce the recurrence rate of patients after treatment.

DISCUSSION

CR is a chronic inflammatory condition, a symptom that develops over time from chronic inflammation of the nasal cavity and paranasal sinuses. The pathogenesis consists of problems such as nasal polyps, turbinate hypertrophy, nasal stones, and nasal septal deviation that impede nasal respiratory function, affecting the patient's quality of life, and causing respiratory infections at severe levels (Bleier and Paz Lansberg, 2021). Patients with CR mainly present with nasal congestion, pus-filled rhinorrhea, dizziness, headache, and decreased sense of smell. The course of the disease is relatively long, and patients are prone to recurrent episodes that last for a long time (Hirsch *et al.*, 2020). CR is first treated with medication, diagnosis of CR, no obvious anatomical abnormality is found, deviated nasal septum, then medication can be applied first, medication for 3-6 months, the patient's symptoms do not improve or the improvement is not obvious, then CT is needed to determine, if the patient is found to have sinus sinus opening blockage or small polyps, then surgical treatment is taken. Although surgery can remove the diseased tissue and improves ventilations and drainages in the nasal and sinus cavities, the damage and inflammation in the operative cavity are long-lasting (Kolkhir *et al.*, 2023).

Pharmacologic treatment of CR usually includes glucocorticoids, mucolytic pro-eliminators, and antihistamines (Patel *et al.*, 2020). Nasal glucocorticosteroids: Nasal glucocorticosteroids are clinically recommended as the first-line treatment of choice for CR (Bernstein *et al.*, 2023). CR treatment guidelines state that preoperative nasal glucocorticosteroids in patients with CR can improve symptoms and reduce surgical bleeding, and postoperative glucocorticosteroids can reduce recurrence. Nasal glucocorticosteroids are usually used 1-2 times per day, and their efficacy can be maintained with long-term use for sustained symptomatic relief (Tamene *et al.*, 2023). Budesonide or mometasone furoate are often used as nasal sprays, and inflammatory factors can be reduced by the use of hormones to reduce the production and aggregation of inflammatory factors in the patient's nose. Nasal glucocorticoids are safe and well tolerated, with a low incidence of localized adverse effects (Macias Valle and Psaltis, 2021). Mucus promoters are often used as adjuncts to the treatment of CR in clinical practice (Cartagena *et al.*, 2023). Mucus and purulent secretions are common signs of CR, and the smooth expulsion of mucus or purulent mucus is critical for disease regression and recovery of ventilation. Mucus promoters can help expulsion by changing the viscosity of secretions to normal levels, and can also be regulated to improve mucociliary clearance or stimulate the cough reflex to help the clearance of secretions (Kostić *et al.*, 2020). When patients with CR have clinical concomitant allergic rhinitis, they often exhibit allergic reactions such as sneezing and clearing of nasal mucus in addition to the typical symptoms of CR, and their clinical symptoms are relatively severe and more complex. In response to these allergic reactions, antihistamines can be used in combination, and either oral or nasal sprays can effectively alleviate the symptoms, and the duration of treatment is often more than two weeks, whereas when CR patients with bronchial asthma, aspirin intolerance, or eosinophilia are encountered clinically, adverse reactions will exist (Hanson and Lepule, 2021; Shirindza and Bronkhorst, 2024). Therefore, in this study, we chose the combination of nasal glucocorticoids and mucus promoters for the treatment of CR in order to observe the clinical efficacy.

It has been established that an imbalance in the distribution of T-cell subsets is the main trigger for the development of CR. Both helper T cells (Th) and cytotoxic T cells (Tc) are involved in the pathogenesis (Cao *et al.*, 2019). $CD4^+$ is a surface marker for Th cells and $CD8^+$ for Tc cells. The former are able to differentiate into Th1 and Th2 under the influence of cytokines and antigens and can contribute to the involvement of T cells in the regulation of the immune system. The latter eliminates virus-infected cells and tumor cells in the body with cytotoxic effects, but impairs the function of the immune system (Ganji *et al.*, 2020). In

addition, inflammatory factors are distributed in the epithelium, vascular endothelium, glands and inflammatory cells of the nasal mucosa, and under normal conditions, the concentration in the body is low and has a certain protective effect on the body, but if too much can cause local inflammation and damage (Kaliniak *et al.*, 2024). The results of this study showed that the inflammatory indexes and immune indexes of the both groups improved markedly after treatment, and the improvement of patients in the BE group was better the EL group, and the clinical efficacy of patients in the BE group was above to the EL group, indicating that the therapeutic effect of budesonide nasal spray combined with mucus promoter was better than that of mucus promoter alone in CR. This may be due to the fact that the combination of the two drugs may produce a synergistic effect that enhances the local anti-inflammatory and immunomodulatory effects, resulting in more effective control of inflammation and promoting clinical efficacy. Some studies have reported that glucocorticoids can significantly reduce the levels of inflammatory factors in patients with allergic rhinitis (Wang *et al.*, 2020), which is consistent with the findings of the present study.

The Lund-Kenndey and Lund-Mackey are scales designed to evaluate the nasal mucosal structure and the severity of sinusitis, scoring the pus filling in the sinuses, the structure of the nasal mucosa, and the degree of inflammation in order to determine the severity of the condition (Taheri *et al.*, 2024; Tsuda *et al.*, 2024). After treatment, the scores of both groups decreased, and the BE group patients had significantly better scores. The evaluation of nasal ventilation function is helpful in the diagnosis and treatment of CR, and the results of the study showed that the DCAN and nasal airway resistance of patients in the BE group were below to EL group, and the NCV and NMCA were above to the EL group (P<0.05). In addition, patients in the BE group showed better clinical symptom improvement, and patients in the BE group had lower rates of adverse reactions and recurrence. The reason may be because the combination of budesonide nasal spray and mucus promoter reduced the inflammatory response and improved the ability of immune regulation, which improved the blood circulation of the nasal mucosa, facilitated the discharge of secretions, accelerated the recovery of nasal ventilation, further improved the clinical symptoms, and reduced the rate of adverse reactions and recurrence. Chen et al. reported similar findings in a randomized trial comparing the combination of montelukast and budesonide in the treatment of allergic rhinitis (Chen *et al.*, 2021). These results suggest that the combination of the two can effectively improve the inflammatory response of patients, improve the recovery of immune function, and have a high safety profile and a low recurrence rate, which also provides more scientific basis and therapeutic strategies for clinical treatment.

This study has some limitations. The sample size was relatively small and failed to cover the different conditions of all CR patients, which may lead to biased findings and affect the extrapolation and reliability of the conclusions.

The limitation of the single-center study is that there are differences in the patients' own underlying conditions, which may affect the generalizability of the findings. In addition, the relatively short follow-up period did not allow for adequate assessment of the long-term effects and safety of the treatment. Therefore, future studies should further expand the sample size and extend the follow-up time to more comprehensively assess the efficacy and safety of the combination of budesonide nasal spray and mucus promoter for the treatment of CR.

CONCLUSION

In this study, we analyzed the effects of budesonide nasal spray combined with mucus promoter on the clinical efficacy and immunomodulatory mechanism of CR patients, in order to provide a new drug pathway for the treatment of this type of disease. The results showed that post-treatment, all the indexes of patients in both groups improved. The percentage of $CD4^+$ T cells and $CD4^+/CD8^+$, NCV, NMCA, improvement of clinical symptoms and clinical efficacy in the BE group were remarkably above the EL group. Inflammatory indexes, $CD8^+$ T cells percentage, Lund-Kenndey score, Lund-Mackey score, DCAN, nasal airway resistance, adverse effects and recurrence rate were markedly below the EL group in the BE group. It indicates that budesonide nasal spray combined with mucus promoter has significant efficacy in the treatment of CR, which can effectively reduce the inflammatory response and improve the immune function, as well as improve the clinical efficacy, which provides a new reference method for the clinical treatment of related diseases. However, the present study has a small sample size and a short course of clinical medication, failing to observe the long-term effectiveness of this method of treatment. Due to the limitation of conditions, more specific indexes such as others could not be added. Multi-center, large-sample, high-quality clinical studies can be carried out in the later stage for validation.

Conflict of interest

There is no conflict of interest.

REFERENCES

Albu S (2020). Chronic rhinosinusitis: An update on epidemiology, pathogenesis and management. *J. Clin. Med.*, **9**(7): 2285.

Aljabr W, Al Amari A, Abbas B, Karkashan A, Alamri S, Alnamnakani M and Al Qahtani A (2022). Evaluation of the levels of peripheral CD3, CD4 and CD8 T cells and IgG and IgM antibodies in COVID-19 patients at different stages of infection. *Microbiol. Spectr.*, **10**(1):

e00845-00821.

Bachert C, Marple B, Schlosser RJ, Hopkins C, Schleimer RP, Lambrecht BN, Bröker BM, Laidlaw T and Song WJ (2020). Adult chronic rhinosinusitis. *Nat. Rev. Dis. Primers.*, **6**(1): 86.

Bernstein JA, White AA, Han JK, Lang DM, Elkayam D and Baroody FM (2023). Review of evidence supporting the use of nasal corticosteroid irrigation for chronic rhinosinusitis. *Ann. Allergy Asthma Immunol.*, **130**(1): 46–57.

Bleier BS and Paz Lansberg M (2021). Acute and chronic sinusitis. *Med. Clin. North Am.*, **105**(5): 859–870.

Cao P, Wang Z, Schleimer RP and Liu Z (2019). Pathophysiologic mechanisms of chronic rhinosinusitis and their roles in emerging disease endotypes. *Ann. Allergy Asthma Immunol.*, **122**(1): 33–40.

Cartagena MB, Acosta RM, Piñero AG, Ferrer MS, Díaz PG, Mezquida JR, Muñoz IP and Jover AS (2023). P099 Effect of a mucolytic agent delivered through sinus pulsating aerosol system (SPAS) device on sinonasal symptoms and patient report outcomes in people with cystic fibrosis (PwCF). *J. Cyst. Fibros.*, **22**: S94.

Chen H, Zhang L, Lou H, Wang Y, Cao F and Wang C (2021). A randomized trial of comparing a combination of montelukast and budesonide with budesonide in allergic rhinitis. *Laryngoscope.*, **131**(4): E1054–E1061.

Cho SH, Hamilos DL, Han DH and Laidlaw TM (2020). Phenotypes of chronic rhinosinusitis. *J. Allergy Clin. Immunol. Pract.*, **8**(5): 1505–1511.

Ganji A, Farahani I, Khansarinejad B, Ghazavi A and Mosayebi G (2020). Increased expression of CD8 marker on T-cells in COVID-19 patients. *Blood Cells Mol. Dis.*, **83**: 102437.

Hanson C and Lepule K (2021). Management of acute and chronic sinusitis. *S. Afr. Pharm. J.*, **88**(5): 22–28.

He B, Yang J, Dang L, Sun M, Liu J and Xin W (2024). Eucalyptol, limonene and pinene enteric soft capsules relieve otitis media with effusion in mice based on AQP5-TLR4/MyD88/NF-κB pathway. *Drug Eval. Res.*, **47**(8): 1820–1826.

Heo YA (2021). Budesonide/glycopyrronium/formoterol: A review in COPD. *Drugs.*, **81**(12): 1411–1422.

Hirsch AG, Nordberg C, Bandeen Roche K, Tan BK, Schleimer RP, Kern RC, Sundaresan A, Pinto JM, Kennedy TL and Greene JS (2020). Radiologic sinus inflammation and symptoms of chronic rhinosinusitis in a population-based sample. *Allergy.*, **75**(4): 911–920.

Kaliniak S, Fiedoruk K, Spałek J, Piktel E, Durnaś B, Góźdź S, Bucki R and Okła S (2024). Remodeling of paranasal sinuses mucosa functions in response to biofilm-induced inflammation. *J. Inflamm. Res.*, **21**: 1295–1323.

Kanlioglu Kuman N, Kozaci LD, Sen S, Senturk E, Cokpinar S, Yaman E, Kilicaslan N and Karadag F (2021). Prognostic significance of inflammatory markers IL-6, sP-selectin, TNF-α, BNP-32, and procalcitonin levels in thoracic surgery. *Indian J. Surg.*, **83**(3): 740–748.

Kardos P, Dinh Q, Fuchs KH, Gillissen A, Klimek L, Koehler M, Sitter H and Worth H (2020). German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough. *Respir. Med.*, **170**: 105939.

Kato A, Schleimer RP and Bleier BS (2022). Mechanisms and pathogenesis of chronic rhinosinusitis. *J. Allergy Clin. Immunol.*, **149**(5): 1491–1503.

Kolkhir P, Akdis CA, Akdis M, Bachert C, Bieber T, Canonica GW, Guttman-Yassky E, Metz M, Mullol J, Palomares O, Renz H, Ständer S, Zuberbier T and Maurer M (2023). Type 2 chronic inflammatory diseases: targets, therapies and unmet needs. *Nat. Rev. Drug Discov.*, **22**(9): 743–767.

Kostić M, Ivanov M, Babić SS, Petrović J, Soković M and Ćirić A (2020). An up-to-date review on bio-resource therapeutics effective against bacterial species frequently associated with chronic sinusitis and tonsillitis. *Curr. Med. Chem.*, **27**(41): 6892–6909.

Lee HY, Pyo JS and Kim SJ (2021). Distinct patterns of tissue remodeling and their prognostic role in chronic rhinosinusitis. *ORL.*, **83**(6): 457–463.

Liao Z, Tu B, Sun L, Dong C, Jiang H and Hu G (2022). Interleukin-33 and thymic stromal lymphopoietin are primary cytokines involved in the Th1/Th2 inflammatory response in chronic secretory otitis media. *Eur. J. Inflamm.*, **20**: 1721727X221094158.

Lin L, Lan J, Dai F, Wei J, Chen Z and Sun G (2020). Efficacy of budesonide nasal spray on neutrophilic chronic rhinosinusitis with nasal polyps: a combined clinical and experimental study. *Int. Arch. Allergy Immunol.*, **181**(7): 551–562.

Ma S, Lei X, Tu J, Tian C, Lian G, Li W and Wang D (2021). Effect of glucocorticoids infiltration on CRSwNP after endoscopic sinus surgery and the curative efficacy of nasal ventilation function and mucociliary clearance. *Am. J. Transl. Res.*, **13**(4): 3826.

Macias Valle L and Psaltis A (2021). A scholarly review of the safety and efficacy of intranasal corticosteroids preparations in the treatment of chronic rhinosinusitis. *Ear Nose Throat J.*, **100**(5): 295–301.

Mygind N, Nielsen LP, Hoffmann HJ, Shukla A, Blumberga G, Dahl R and Jacobi H (2001). Mode of action of intranasal corticosteroids. *J. Allergy Clin. Immunol.*, **108**(1): S16–S25.

Patel GB, Kern RC, Bernstein JA, Hae Sim P and Peters AT (2020). Current and future treatments of rhinitis and sinusitis. *J. Allergy Clin. Immunol. Pract.*, **8**(5): 1522–1531.

Peric A, Soklic TK, Aleksic A, Kopacheva Barsova G and Peric AV (2021). Efficacy and safety of Myrtol® standardized in the treatment of acute and chronic rhinosinusitis: A review of literature. *J. Clin. Pract. Res.*, **43**(1): 3.

Preethi A, Venkatraman R, Karthika U and Rangapriya A (2023). Evaluation of the efficacy of magnesium sulfate

in reducing blood loss in functional endoscopic sinus surgery: a randomized double-blinded controlled trial. *Cureus.*, **15**(5): e38636.

Reichardt SD, Amouret A, Muzzi C, Vettorazzi S, Tuckermann JP, Lühder F and Reichardt HM (2021). The role of glucocorticoids in inflammatory diseases. *Cells.*, **10**(11): 2921. doi:10.3390/cells10112921

Saltagi MZ, Comer BT, Hughes S, Ting JY and Higgins TS (2021). Diagnostic criteria of recurrent acute rhinosinusitis: a systematic review. *Am. J. Rhinol. Allergy.*, **35**(3): 383–390.

Shirindza N and Bronkhorst E (2024). Management of allergy and sinusitis. *S. Afr. Pharm. J.*, **91**(3): 13–18. Shukla RH, Nemade SV and Shinde KJ (2020). Comparison of visual analogue scale (VAS) and the nasal obstruction symptom evaluation (NOSE) score in evaluation of post septoplasty patients. *WJOHNS.*, **6**(1): 53–58.

Taheri A, Shahzamani A and Asadi M (2024). Diagnostic accuracy of sino-nasal outcome test-22 and Lund-Kennedy endoscopic score for chronic rhinosinusitis in pre-bone marrow transplantation assessment. *J. Res. Med. Sci.*, **29**(1): 67.

Tamene S, Dalhoff K, Schwarz P, Backer V and Aanaes K (2023). Systemic corticosteroids in treatment of chronic rhinosinusitis—a systematic review. *Eur. Clin. Respir. J.*, **10**(1): 2240511.

Tsuda T, Takeda K, Terada R, Tanaka S, Waki S, Akama T and Nishimura H (2024). Osteitis in eosinophilic chronic rhinosinusitis. *Ear Nose Throat J.*, **103**(12): NP741–NP748.

Wang H, Zuo Y, Li J and Wang W (2020). Effects of glucocorticoid therapy on nasal conditions and inflammatory factors in patients with allergic rhinitis. *Int. J. Clin. Exp. Med.*, **13**(4): 2154–2162.

Wijnants D, Stalmans I and Vandewalle E (2022). The effects of intranasal, inhaled and systemic glucocorticoids on intraocular pressure: A literature review. *J. Clin. Med.*, **11**(7): 2007.

Zieglmayer P, Schmutz R, Lemell P, Unger Manhart N, Nakowitsch S, Goessl A, Savli M, Zieglmayer R and Prieschl-Grassauer E (2020). Fast effectiveness of a solubilized low-dose budesonide nasal spray in allergic rhinitis. *Clin. Exp. Allergy.*, **50**(9): 1065–1077.