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Original Research

Herbal Drug BNO 1016 Versus Fluticasone Propionate Nasal Spray in the Treatment of Chronic Rhinosinusitis without Nasal Polyps: A Preliminary Report

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ABSTRACT

Objective: Current evidence supports the use of herbal drugs in the reduction of symptoms of acute (ARS) and chronic rhinosinusitis (CRS). Intranasal corticosteroids are the first line treatment option for treating CRS with or without nasal polyps. This study was designed to compare the safety and efficacy of plant medication BNO 1016 and fluticasone propionate nasal spray (FPNS) for treating CRS without nasal polyps (CRSsNP).

Methods: Forty subjects with CRSsNP were randomly divided into two treatment groups that comprised 20 patients each. The patients from Group 1 were treated with herbal drug BNO 1016, tablets of 160 mg, 3×1/d per os, for 28 d. The patients from Group 2 used FPNS 200 µg once daily, 2 puffs in each nostril in the morning for 28 d. We evaluated the nasal total symptom score (TSS), individual scores for each symptom (nasal congestion/obstruction, rhinorrhea/postnasal discharge, facial pain with the sense of pressure, headache, loss of the sense of smell), total endoscopic score (TES), and individual endoscopic signs (edema of the nasal mucosa, nasal secretion, and nasal crusting), before and after the therapy.

Results: TSS was lower on Day 7 ($p=0.008$), Day 14 ($p=0.004$), Day 21 ($p<0.001$), and Day 28 ($p=0.002$) in patients treated with BNO 1016. Moreover, the TES was lower on Day 21 ($p=0.001$) and Day 28 ($p=0.002$) in subjects who were on therapy with BNO 1016. No adverse events were noted in Group 1; however, in patients treated with intranasal glucocorticoids, 2 patients reported mild nasal bleeding, and 1 reported a sense of dryness in the nose.

Conclusion: BNO 1016 could be a good alternative to intranasal corticosteroids in the treatment of CRSsNP without adverse events.

Keywords: Glucocorticoids, ınflammation, plants, medicinal, rhinitis, sinusitis

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa, with complaints (nasal congestion/obstruction, rhinorrhea/postnasal discharge, facial pain with the sense of pressure, headache and loss of the sense of smell) that persist for >12 wk. In addition to the symptoms, diagnosis is also based on signs of mucosal edema with or without nasal polyps during a nasal endoscopy. Furthermore, computed tomography (CT) scan of the paranasal sinuses might show changes within the ostiomeatal complex or the sinuses (1, 2).

The etiology of CRS remains unknown. The mechanisms involved in the translation from acute rhinosinusitis (ARS) to CRS are debatable. Repeated viral, bacterial, and fungal infections; cigarette smoking; air pollution; allergic reactions of the nasal mucosa; neurogenic inflammation; as well as innate and adaptive immune dysfunction are the focus of discussion (3, 4).

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The prevalence of CRS in Europe is estimated to be 7%–27% (around 11%). This disease considerably affects the quality of life. The first option in the pharmacological treatment of CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) is the use of intranasal corticosteroids; other medications, such as macrolide antibiotics, nasal irrigation with sea water isotonic and hypertonic solutions, systemic glucocorticoids, antihistamines, and biological drugs are also used (1, 2, 5).

The efficacy of the herbal medicinal product BNO 1016 that is available as tablet, syrup, and drops, has been assessed in several studies for the treatment of acute upper-airway infections (6-9). However, two controlled studies have evaluated the efficacy of BNO 1016 in the treatment of CRS (10, 11). The main constituents are the extracts of the following five medicinal plants: gentian (*Gentiana lutea*, root); primrose (*Primula veris*, flower); common sorrel (*Rumex acetosa*, herb); elder (*Sambucus nigra*, flower); and European vervain (*Verbena officinalis*, herb). Previous reports have shown clear mucolytic, secretomotoric, anti-inflammatory, virostatic, and bacteriostatic effects of these extracts (6-12). We aimed to investigate the safety and efficacy of BNO 1016 in comparison to that of corticosteroid fluticasone propionate nasal spray (FPNS) in the treatment of CRSsNP. To the best of our knowledge, this is the first study to compare the effects of BNO 1016 and intranasal glucocorticoid in CRS patients without nasal polyps.

METHODS

Participants

Adult patients diagnosed with CRSsNP were eligible for this randomized, non-inferiority, open-label, parallel arm, prospective study. The study period was May 2019 to October 2019 as per the principles of the Helsinki Declaration. The Ethics Committee of the Military Medical Academy, Belgrade, Serbia approved the protocol for investigation (Approval No. 05/2019). Written informed consent was obtained from all the subjects who participated in the study.

Main Points:

- This is the first study designed to compare the effects of herbal drug BNO 1016 and intranasal corticosteroid in the therapy of patients with CRSsNP.
- Our results demonstrated better efficacy of BNO 1016 on nasal congestion/obstruction, facial pain with the sense of pressure, headache, and loss of the sense of smell in comparison to fluticasone propionate nasal spray (FPNS).
- The endoscopic findings in CRSsNP patients were superior after the therapy with BNO 1016.
- No adverse events were noted in patients treated by BNO 1016, however, in patients treated with intranasal corticosteroids, 2 patients reported mild nasal bleeding, and 1 reported a sense of dryness in the nasal cavity.
- BNO 1016 could be a good alternative to intranasal corticosteroids in the treatment of CRSsNP without adverse events.

CRS was diagnosed as per the criteria of the International Consensus Statement on Allergy & Rhinology: Rhinosinusitis (ICAR 2016) (1) and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) (2). Only patients with nasal symptoms that had lasted for >12 wk, with specific endoscopic findings without features of nasal polyps and with findings on paranasal sinuses CT scans were enrolled. CT scan was performed for all the participants before the start of therapy as per the Lund-Mackay scoring system (13). We did not perform post-treatment CT scans owing to the limitations noted in the local Ethics Committee Approval. Patients with CRSwNP, bronchial asthma, and non-steroid anti-inflammatory drug-exacerbated respiratory disease (N-ERD) were excluded from the study by the experienced rhinologist, allergist, and pulmonologist as per clinical findings, prior history of reaction to non-steroid anti-inflammatory drugs, and pulmonary function results.

Other exclusion criteria were as follows: age <18 years, age > 65 years; ARS; presence of choanal polyps and hamartomatous lesions in the nasal cavities; deformations of the nasal septum and hypertrophy of the inferior and/or middle turbinate that significantly impaired the nasal airflow and the application of nasal sprays; systemic diseases that affected nasal function, such as Churg-Strauss syndrome, primary ciliary dyskinesia, and granulomatosis with polyangiitis; allergies to medications used in the study; use of antibiotics, antihistamines, and glucocorticoids in the form of drops, sprays, or oral tablets within 4 wk before study initiation; pregnancy or lactation; previous paranasal sinus surgery; and cigarette smoking.

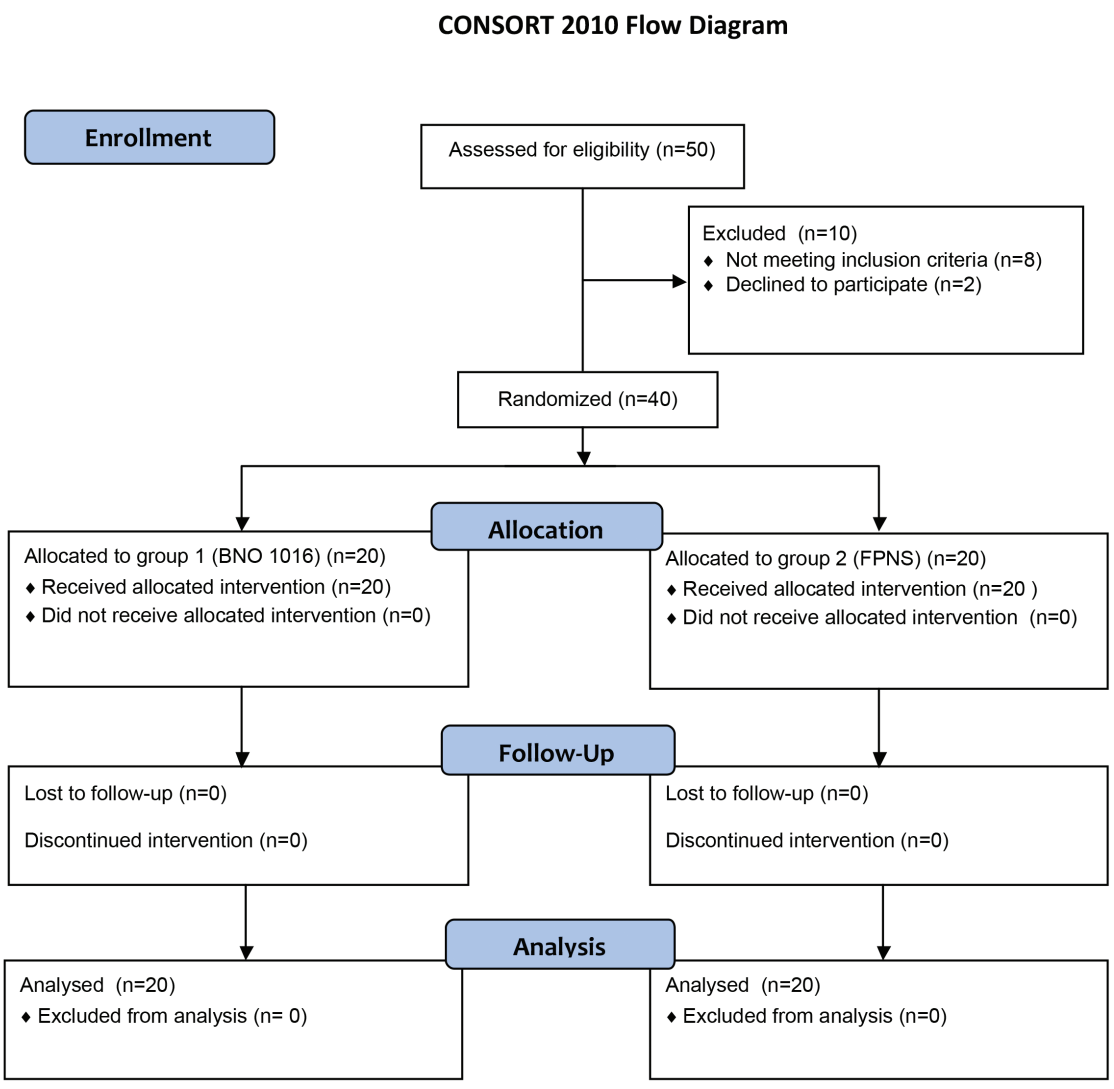
Treatment

We randomly divided CRSsNP patients into the following two study groups. Group 1 patients (n=20) were treated for 28 days with a herbal medicinal product BNO 1016 (Sinupret® forte, Bionorica, Neumarkt, Germany), oral tablets of 160 mg (Flixonase®), 3×1/day. The subjects from Group 2 (n=20) used FPNS (Glaxo Smith Kline Pharmaceuticals S.A., Burgos, Spain) 200 µg/day in the morning, two sprays in each nostril for 28 days, and these patients were informed about the correct application of INCS. Both, the investigators and the patients were aware of the drug being given. The patients did not use other medications simultaneously with herbal drug or intranasal corticosteroid.

Clinical Evaluation (Primary Outcomes)

The intensity of five nasal symptoms (nasal congestion/obstruction, rhinorrhea/postnasal discharge, facial pain with a sense of pressure, headache, and loss of the sense of smell) was evaluated by the patients on Day 0 and during Days 7, 14, 21, and 28 following treatment initiation. They used a visual analog scale (VAS) (0–10 cm; from 0=the absence of symptoms to 10=symptoms of maximal level). A 10-cm VAS was applied and explained for use in patients by the nurse following randomization. During the investigation, patients recorded their symptom scores and noted the use of medications on diary cards after taking the medications, and the investigator recorded the scores at the visits. The investigator evaluated treatment compliance based on the information in the diary cards.

Figure 1. Flow diagram, presented as per the CONSORT statement. Fifty patients (n=50) were involved in this study. Two (n=2) did not consent to participate, and eight (n=8) did not meet the inclusion criteria. Finally, 40 patients were recruited and assigned to Group 1 (n=20) and Group 2 (n=20)



An experienced rhinologist performed the nasal endoscopic examination at each visit using a 4 mm 0° and 30° endoscope (Karl Storz SE & Co., Tuttlingen, Germany) to assess the value of edema of the nasal mucosa, nasal secretion, and nasal crusting. Thereafter, the patients' local findings were scored as per the Likert endoscopic scoring system (14) as follows: 0, none; 1, mild; 2, moderate; 3, moderately severe; and 4, severe.

The parameters of clinical efficacy (main endpoints) were as follows: total symptom score (TSS; sum of the scores for nasal symptoms), individual symptom score (score for individual nasal symptom), total endoscopic score (TES; sum of the scores for all endoscopic signs – edema of the nasal mucosa, nasal secretion, nasal crusting), and individual endoscopic score for each endoscopic sign during Days 0, 7, 14, 21, and 28 following treatment initiation.

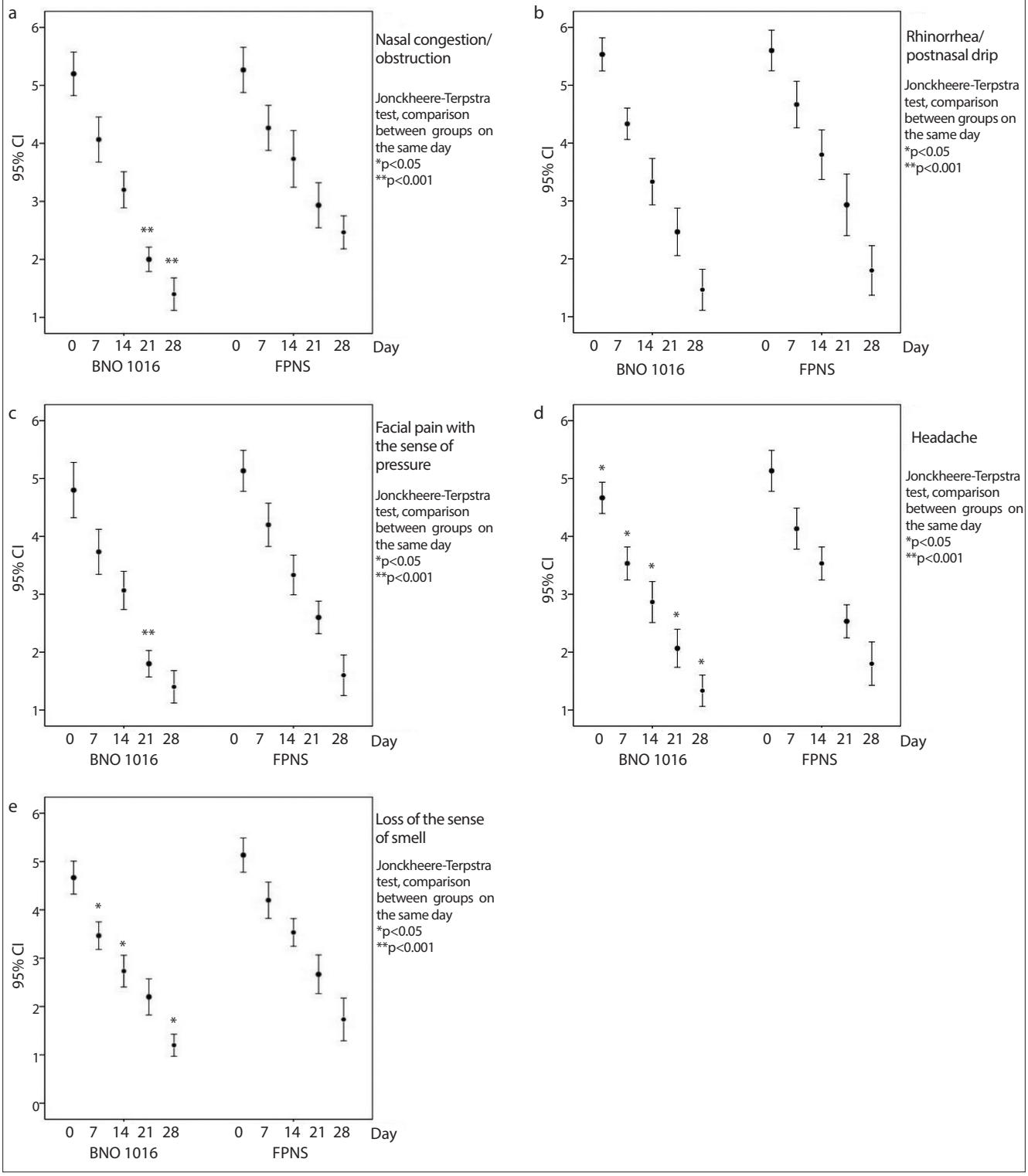
Safety

The reported adverse events were recorded throughout the study period, with severity grades classified as mild, moderate, and severe. At visits, nasal examination, laboratory tests, and vital signs assessment were performed. All the patients were aware of the potential adverse effects of both the medications.

Randomization

Randomization was performed as per the CONSORT statement. Fifty patients (n=50) with CRSsNP who were examined and treated at two hospitals were selected for the study. Two patients refused study participation, and eight did not meet the inclusion criteria. Thus, finally, 40 patients were included and divided into Group 1 (n=20) and Group 2 (n=20). The simple computer-generated procedure for participant randomization was used to allocate the patients into the study groups. The patients' eligibility was decided by

Figure 2. a-e. Comparison of the individual scores for nasal symptoms during treatment with two different medications: (a) Nasal congestion/obstruction; (b) Rhinorrhea/postnasal drip; (c) Facial pain with the sense of pressure; (d) Headache; and (e) Loss of the sense of smell. The levels of statistical significance: *p<0.05, **p<0.001

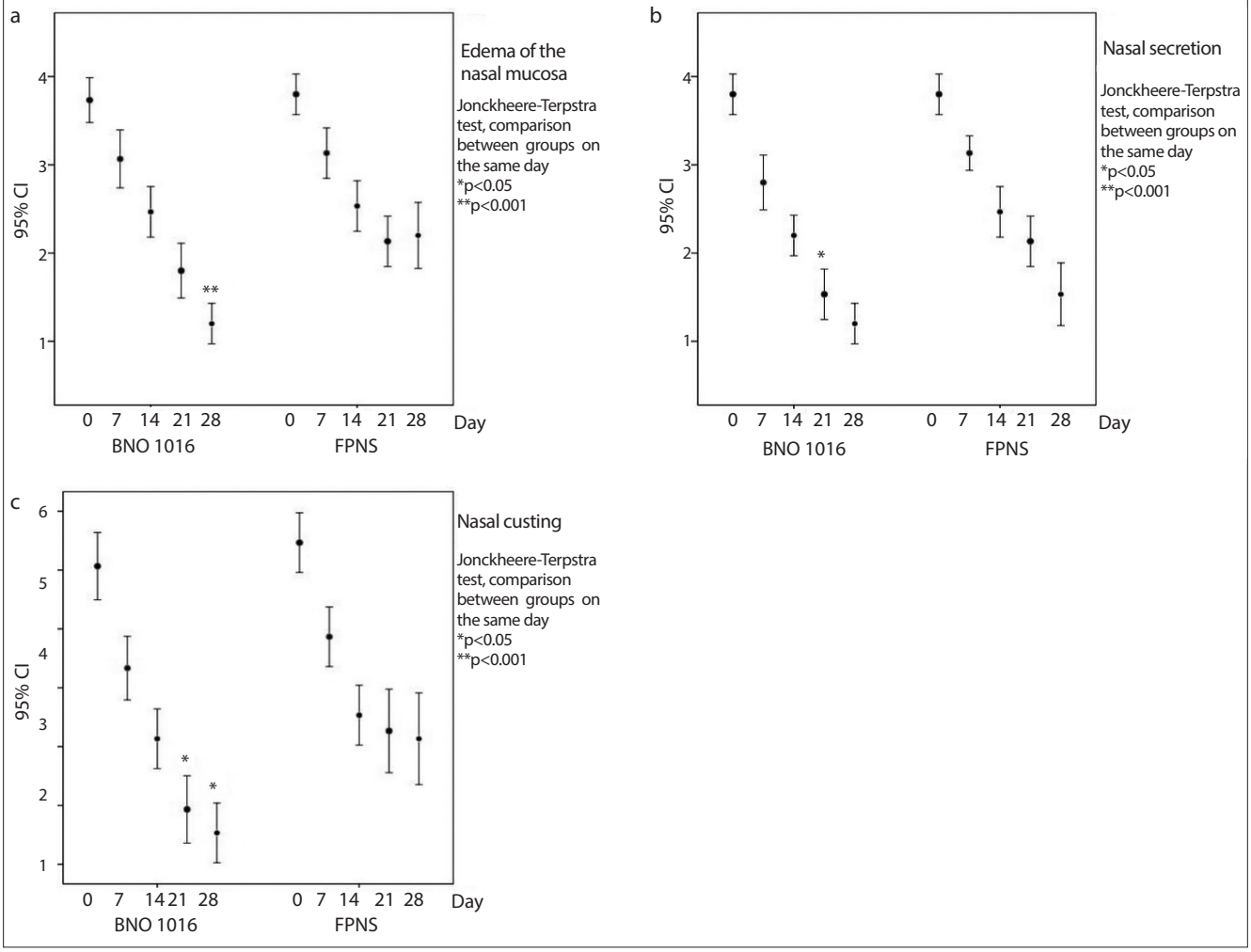


the investigator who then informed the nurse about the eligibility; thereafter, the nurse assigned the participants to either of the two study groups using computer-generated random allocation. The study profile has been presented in Figure 1.

Power of the Study and Statistical Analyses

A study power analysis indicated that 20 subjects would be required in each study group to reach a power level of at least 80% and a significance level of 5%. In our literature review,

Figure 3. a-c. Comparison of the individual scores for nasal endoscopic findings during treatment with two different medications: (a) Edema of the nasal mucosa; (b) Nasal secretion; and (c) Nasal crusting. The levels of statistical significance were as follows: *p<0.05, **p<0.001



we found no studies that have investigated the minimally import and difference in the symptom scores, assessed using the VAS for CRS patients; however, Devillier et al. (15) found that this value in patients with perennial allergic rhinitis could be rounded up to –1 unit for convenience. Therefore, the sample size was calculated as per the clinically relevant change for symptom scores and endoscopic scores of 1 point (IQR 1). The study parameters were expressed as median with interquartile range (IQR) values because the main variables were not distributed normally. We had several independent samples and assumed that they were arranged orderly; we used the nonparametric Jonckheere-Terpstra test for between-group comparisons of clinical median parameters on Days 0, 7, 14, 21, and 28 after treatment initiation. For paired comparisons within a group between the parameters of two successive visits (e.g. Day 0 *vs*. Day 7), for before-after effect and matched paired samples, we used the nonparametric Marginal Homogeneity test. We considered p-values <0.05 as statistically significant. For the statistical analysis, we used SPSS software (Statistical Package for the Social Sciences, version 15.0, (SPSS Inc.; Chicago, IL, USA).

RESULTS

Twenty patients who provided informed consent were enrolled in each group. There were no dropouts during the study period. Total 40 adult patients (23 men and 17 women, aged 25–61 y) who were diagnosed with CRSsNP were enrolled. We found no significant differences in the age and the pre-treatment Lund-Mackay CT score (p=0.587; p=0.482, respectively) (Table 1).

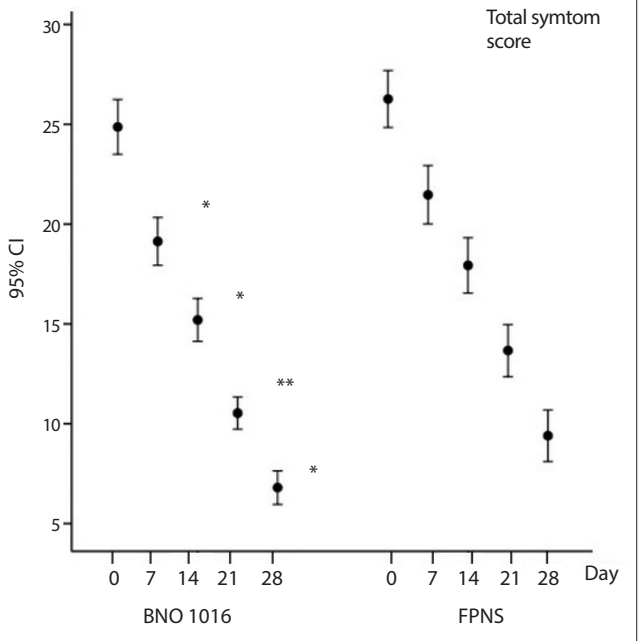
When we compared the individual symptom scores of the two groups, we found that Group 1 had significantly lower scores for nasal congestion/obstruction on Day 21 (p<0.001) and on Day 28 (p<0.001), significantly lower score for facial pain with the sense of pressure on Day 21 (p<0.001), lower scores for headache on Days 0, 7, 14, 21, and 28 (p=0.041; p=0.014; p=0.008; p=0.038; p=0.046, respectively), and lower scores for loss of the sense of smell during Day 7 (p=0.006), Day 14 (p=0.002), and Day 28 (p=0.039). The scores for rhinorrhea/postnasal discharge were not significantly different between the study groups from the start to the end of the investigation (Table 2, Figure 2 a-e).

Table 1. Baseline demographic characteristics and pre–treatment Lund–Mackay CT score of the study subjects

Characteristics	BNO 1016	FPNS	p
Patients	20		20
Age, years	44 (23)	46 (16)	0.587
Females	9 (45%)	8 (40%)	
Males	11 (55%)	12 (60%)	
Lund– Mackay CT score	11 (4)	9 (4)	0.482

Age: median (interquartile range – IQR)
Abbreviation: FPNS – fluticasone propionate nasal spray; CT – computed tomography

Figure 4. Comparison of total symptom score (TSS) during treatment with two different medications. Note the significantly lower TSS in Group 1 on Day 7 (p=0.009), Day 14 (p=0.003), Day 21 (p<0.001), and Day 28 (p<0.001)



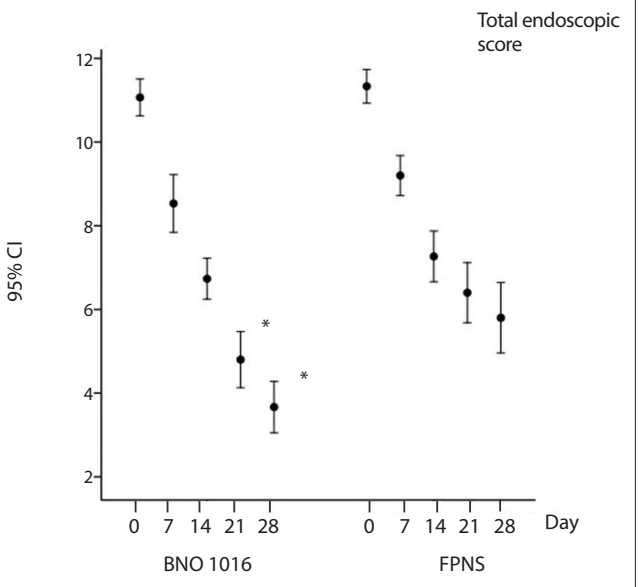
Jonckheere-Terpstra test, comparison between groups on the same day
*p<0.05 **p<0.001

Comparing the individual endoscopic scores, we found that Group 1 had a significantly lower score for edema of the nasal mucosa on Day 28 (p<0.001), lower score for nasal secretion on Day 21 (p=0.007), and lower scores for nasal crusting on Day 21 (p=0.008) and Day 28 (p=0.003) (Table 2, Figure 3a-c).

Finally, we found significantly lower TSS in Group 1 during Day 7 (p=0.008), Day 14 (p=0.004), Day 21 (p<0.001), and Day 28 (p=0.002) (Table 2, Figure 4). We found significantly lower TES in Group 1 on Day 21 (p=0.001) and Day 28 (p=0.002) (Table 2, Figure 5).

With respect to paired comparisons within a group between the parameters of two successive visits, we found significantly

Figure 5. Comparison of the total endoscopic score (TES) during treatment with two different medications. Note the significantly lower TES in Group 1 on Day 21 (p=0.002) and Day 28 (p=0.001)



Jonckheere-Terpstra test, comparison between groups on the same day
*p<0.05

decreased levels from Day 0 to Day 28 for individual symptom scores, individual endoscopic scores, TSS, and TES, except for nasal secretion and nasal crusting in Group 1 between the visits on Day 21 and Day 28 (p=0.061; p=0.087, respectively). Further, we found no significant differences in Group 2 for mucosal edema between the visits on Day 21 and Day 28 (p=0.618), for nasal crusting in the same group between the visits on the Day 14 and Day 21 (p=0.329), and between the visits on the Day 21 and Day 28 (p=0.583). All these results are presented in Table 3.

Group 1 patients exhibited no adverse events; however, Group 2 patients reported mild epistaxis, and one patient in Group 2 reported dryness in the nose.

DISCUSSION

To the best of our knowledge, only one study by Passali et al. has compared the efficacy and safety of BNO 1016 with intranasal corticosteroid in ARS treatment (16). The authors demonstrated better efficacy and safety of BNO 1016 in terms of the nasal symptoms and quality of life in comparison to that with fluticasone furoate nasal spray (16). Regarding the CRSsNP, only two randomized studies with BNO 1016 have been performed. The first randomized, placebo-controlled trial investigated 31 patients who had CRSsNP and were treated with BNO 1016 for 28 d (10). Of the 16 patients in the BNO 1016 group, 15 showed improvement in the radiological findings. However, of the 15 patients in the placebo group, only 6 showed improvement on paranasal sinus radiographies (10). In a recent, double blind, placebo-controlled study, Palm et al. (11) demonstrated that BNO 1016 can be recommended for the treatment of CRS patients for 3 mon with 3 times higher concentrations of drug constituents.

Table 2. Clinical parameters of the patients enrolled in this study. For between-group comparisons, we used a Jonckheere-Terpstra test

Parameter	BNO 1016 (N=20) Nr (%)/Median (IQR)	FPNS (N=20) Nr (%)/Median (IQR)	p
Nasal congestion/obstruction (Day 0)	5 (1)	5 (1)	0.782
Nasal congestion/obstruction (Day 7)	4 (1)	4 (1)	0.436
Nasal congestion/obstruction (Day 14)	3 (1)	4 (1)	0.072
Nasal congestion/obstruction (Day 21)	2 (0)	3 (1)	<0.001
Nasal congestion/obstruction (Day 28)	1 (1)	2 (1)	<0.001
Rhinorrhea/postnasal drip (Day 0)	6 (1)	6 (1)	0.564
Rhinorrhea/postnasal drip (Day 7)	4 (1)	5 (1)	0.113
Rhinorrhea/postnasal drip (Day 14)	3 (1)	4 (1)	0.057
Rhinorrhea/postnasal drip (Day 21)	2 (1)	3 (2)	0.151
Rhinorrhea/postnasal drip (Day 28)	1 (1)	2 (1)	0.226
Facial pain/sense of pressure (Day 0)	5 (1)	5 (1)	0.81
Facial pain/sense of pressure (Day 7)	4 (1)	4 (1)	0.083
Facial pain/sense of pressure (Day 14)	3 (0)	3 (1)	0.232
Facial pain/sense of pressure (Day 21)	2 (0)	3 (1)	<0.001
Facial pain/sense of pressure (Day 28)	1 (1)	2 (1)	0.388
Headache (Day 0)	5 (1)	5 (1)	0.041
Headache (Day 7)	4 (1)	4 (1)	0.014
Headache (Day 14)	3 (1)	4 (1)	0.008
Headache (Day 21)	2 (0)	3 (1)	0.038
Headache (Day 28)	1 (1)	2 (1)	0.046
Loss of the sense of smell (Day 0)	5 (1)	5 (1)	0.063
Loss of the sense of smell (Day 7)	3 (1)	4 (1)	0.006
Loss of the sense of smell (Day 14)	3 (1)	4 (1)	0.002
Loss of the sense of smell (Day 21)	2 (1)	3 (1)	0.121
Loss of the sense of smell (Day 28)	1 (0)	2 (1)	0.039
Edema of the nasal mucosa (Day 0)	4 (1)	4 (0)	0.682
Edema of the nasal mucosa (Day 7)	3 (0)	3 (0)	0.761
Edema of the nasal mucosa (Day 14)	2 (1)	3 (1)	0.731
Edema of the nasal mucosa (Day 21)	2 (1)	2 (0)	0.107
Edema of the nasal mucosa (Day 28)	1 (0)	2 (1)	<0.001
Nasal secretion (Day 0)	4 (0)	4 (0)	1.000
Nasal secretion (Day 7)	3 (1)	3 (0)	0.072
Nasal secretion (Day 14)	2 (0)	2 (0)	0.133
Nasal secretion (Day 21)	2 (1)	2 (0)	0.007

Table 2. Clinical parameters of the patients enrolled in this study. For between–group comparisons, we used a Jonckheere–Terpstra test (Continued)

Parameter	BNO 1016 (N=20) Nr (%)/Median (IQR)	FPNS (N=20) Nr (%)/Median (IQR)	p
Nasal secretion (Day 28)	1 (0)	1 (1)	0.112
Nasal crusting (Day 0)	4 (1)	4 (1)	0.264
Nasal crusting (Day 7)	3 (1)	3 (0)	0.139
Nasal crusting (Day 14)	2 (0)	2 (1)	0.248
Nasal crusting (Day 21)	1 (1)	2 (1)	0.008
Nasal crusting (Day 28)	1 (1)	2 (1)	0.003
Total symptom score (Day 0)	24 (4)	27 (2)	0.118
Total symptom score (Day 7)	18 (3)	23 (2)	0.008
Total symptom score (Day 14)	16 (2)	18 (4)	0.004
Total symptom score (Day 21)	10 (2)	14 (4)	<0.001
Total symptom score (Day 28)	6 (2)	9 (4)	0.002
Total endoscopic score (Day 0)	11 (1)	11 (1)	0.348
Total endoscopic score (Day 7)	8 (1)	9 (1)	0.112
Total endoscopic score (Day 14)	7 (1)	7 (2)	0.221
Total endoscopic score (Day 21)	5 (2)	6 (2)	0.001
Total endoscopic score (Day 28)	3 (1)	6 (2)	0.002

Abbreviations: IQR – interquartile range; FPNS – fluticasone propionate nasal spray

Our study showed that 1-month therapy with FPNS reduces the symptoms and local clinical signs in CRSsNP patients. We also demonstrated that treatment with herbal drug BNO 1016 leads to slightly more reduction in almost all symptoms and improved endoscopic findings. Thus, TSS is significantly lower after BNO 1016 treatment than after FPNS monotherapy on Days 7, 14, 21, and 28.

BNO 1016 is prepared using a mixture of the following five herbal extracts: gentian, primrose, common sorrel, elder, and European vervain. BNO 1016 is a drug with strong anti-inflammatory effects. In an experiment, the pleuritis was artificially induced in rats. The rats that were administered BNO 1016 extracts showed less pleural effusion and impaired neutrophil infiltration of the pleural tissue owing to the effects of polysaccharides and tannins from sorel and iridoids from vervain (17). BNO 1016 is shown to exert a strong virostatic effect against rhinoviruses, adenoviruses, respiratory syncytial virus, coxackie virus, influenza, and parainfluenza virus due to the inhibition of the enzyme neuraminidase, resulting in the inhibition of viral replication (6, 12). Therefore, BNO 1016 exerts antibacterial effects against Gram positive and Gram-negative bacteria (7). These anti-inflammatory and antimicrobial effects of BNO 1016 cause greater reduction in nasal symptoms and more improvement in the endoscopic findings compared to FPNS.

However, although significant improvement was observed in the rhinorrhea/postnasal discharge score for subjects in both the study groups from the start to the completion of treatment, there was no significant between-group difference in terms of the symptoms at all 4 time-points during the treatment period. This finding is in contrast to the lower endoscopically evaluated nasal secretion score in the BNO 1016 group. This interesting phenomenon could be attributed to the strong secretolytic and secretomotoric activity of BNO 1016. Dysfunction of mucociliary clearance is caused by chronic inflammation. Transport of the mucus that covers the respiratory epithelium is influenced by the transepithelial secretion of ions, especially chloride ions (Cl-). Cl- ion channels are dysfunctional in the respiratory epithelium of patients with ARS, CRS, and cystic fibrosis, and this disturbance in Cl- ion transport leads to impaired mucociliary clearance of pathogenic microorganisms and inflammatory products (18). Bioflavonoids, the main pharmacological component in BNO 1016, strongly activate transepithelial Cl- ion secretion, enhance Na+ ion and water molecule secretion, and increase ciliary beat frequency, resulting in hydration of nasal secretion and reduction of the viscosity of nasal fluid (18, 19). In contrast, intranasal corticosteroid application leads to decreased secretion in the nasal mucosal glands due to an anti-inflammatory effect (20). Thus, in patients treated with BNO 1016, accelerated nasal fluid clearance and decreased nasal secretion viscosity decreased the

Table 3. P–values (differences) for the comparison of clinical parameters in the same group of patients on consecutive visits during treatment with BNO 1016 (a) and fluticasone propionate nasal spray (b). For paired comparison within the group, we used a Marginal Homogeneity test

(a) Group 1 (BNO 1016)

Parameters/Day	Day 0 vs. Day 7	Day 7 vs. Day 14	Day 14 vs. Day 21	Day 21 vs. Day 28
Nasal congestion/obstruction	0.000	0.003	0.001	0.007
Rhinorrhea/postnasal discharge	0.000	0.001	0.003	0.001
Facial pain with the sense of pressure	0.000	0.002	0.000	0.014
Headache	0.000	0.002	0.005	0.002
Loss of the sense of smell	0.000	0.001	0.011	0.001
Edema of the nasal mucosa	0.002	0.003	0.004	0.003
Nasal secretion	0.000	0.003	0.004	0.061
Nasal crusting	0.000	0.003	0.007	0.087
Total symptom score	0.000	0.000	0.000	0.000
Total endoscopic score	0.000	0.000	0.001	0.003

(b) Group 2 (Fluticasone propionate nasal spray)

Parameters/Day	Day 0 vs. Day 7	Day 7 vs. Day 14	Day 14 vs. Day 21	Day 21 vs. Day 28
Nasal congestion/obstruction	0.000	0.005	0.001	0.008
Rhinorrhea/postnasal discharge	0.000	0.000	0.002	0.001
Facial pain with the sense of pressure	0.000	0.000	0.001	0.001
Headache	0.000	0.003	0.001	0.001
Loss of the sense of smell	0.000	0.002	0.003	0.001
Edema of the nasal mucosa	0.002	0.003	0.034	0.618
Nasal secretion	0.002	0.002	0.025	0.007
Nasal crusting	0.001	0.004	0.329	0.583
Total symptom score	0.001	0.000	0.000	0.000
Total endoscopic score	0.000	0.001	0.007	0.029

sense of rhinorrhea/postnasal discharge that is of similar intensity to the sense of nasal discharge in patients treated with FPNS.

There were no adverse effects in patients from the BNO 1016 group as compared to that in two subjects of the FPNS group who reported mild epistaxis and sensation of dryness in the nose. The use of 200 μg of FPNS daily in the morning during the 1-month therapy may theoretically cause the formation of small areas of atrophy in the nasal epithelium and mild nasal bleeding. The results of an experimental animal study that was conducted by Cho et al. (21) in a rabbit model of CRS showed that dry extracts from BNO 1011 suppress the atrophic changes of the ciliated epithelium and improve the histological characteristics of the lamina propria. This could explain the protective role of BNO 1016 in the human nasal mucosa.

The present study has certain limitations, such as a relatively small sample size. Further, we did not include the peak nasal inspiratory flow or other objective measurements of nasal patency. These parameters can increase the quality of results because the symptom scores are dependent on the subjective sensation of the patients. Although our study employed a prospective and randomized design, it was an open-label study wherein both, the researchers and participants were aware of which treatment was being administered. Thus, there is a need to further align herbal medicine with the requirements of evidence-based medicine, especially by organizing double blind, placebo-controlled studies that could provide better evidence of the efficacy of BNO 1016.

CONCLUSION

Our results demonstrated better efficacy of BNO 1016 on nasal congestion/obstruction, facial pain with the sense of pressure, headache, and loss of the sense of smell. The endoscopic findings in CRSsNP patients were superior after BNO 1016 treatment than after FPNS treatment. The absence of adverse events sug-

gests better safety of BNO 1016 treatment as compared to that of nasal corticosteroid monotherapy in CRSsNP patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Military Medical Academy, Belgrade, Serbia (Approval No. 05/2019).

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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