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Multicenter, Randomized, Open-Label, Comparative Study of Therapeutic Efficacy, Safety and Tolerability of a Herbal Medicinal Product with the Gentian Root (Radih Gentanye); Primrose Flowers with Calyx (*Primulae flos* Cum Calycibus), Vervain Herb (Verbenae Herba), Common Sorrel Herb (Rumex Herba); Flowers of Elderberry (*Sambuci flos*) in the Delayed Antibiotic Prescription Method in Patients with Acute Rhinosinusitis

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Abstract

Introduction: Acute Rhinosinusitis (ARS) includes viral and post-viral (in the USA non-viral) forms. Only about 0.5% to 5% of ARS may be characterized as Acute Bacterial Rhinosinusitis (ABRS). Thus, not more than 5% of patients with ARS require antimicrobial therapy. The objective of the study was to determine the efficacy of phytoneering extract BNO-1012 (Sinupret®) in the delayed antibiotic prescription approach in patients with acute rhinosinusitis.

Methods: In the multicenter, randomized, open-label, comparative study 292 children were randomized, where 275 ones with ARS aged 6 years to 11 years who received phytoneering extract of five herbs BNO-1012 (Sinupret®) in addition to standard symptomatic therapy or standard therapy, completed a study.

Assessment Criteria: Reduction of nasal congestion, rhinorrhoea, post-nasal drip, assessed by a physician on a 4-point scale at each visit compared with the 1st visit, dynamics of rhinorrhoea self-scoring, headache on a 10-point visual analogue scale, frequency of antibiotic prescription, "Therapeutic benefit" in days from the use of BNO-1021 (Sinupret®).

Results: The use of BNO-1012 (Sinupret®) in addition to the standard symptomatic treatment of acute viral and post-viral rhinosinusitis provides a clinically significant, adequate reduction in the severity of rhinorrhoea, nasal congestion and post-nasal drip, assessed by a physician for V2 ($p<0.005$). Significant differences were noted in the patient's self-scoring of rhinorrhoea on the second or third day for viral, from the fourth to the eighth day in post-viral RS, headache on the fourth day in acute viral rhinosinusitis, and from the third to the fifth day of post-viral RS treatment ($p<0.005$). Symptoms of similar intensity in control group were observed at V3. Thus, in the first week of treatment, the treatment group compared to the control one showed a “therapeutic benefit” of three days. The use of BNO-1021 in the delayed antibiotic prescription method in patients with acute viral rhinosinusitis can reduce the justified prescription of antibacterial drugs by 2.7 times, post-viral by 1.4 times. No, on-treatment side effects were observed in any patients.

Conclusion: BNO-1012 (Sinupret®) is a safe and effective drug for the treatment of acute rhinosinusitis in children aged 6 years to 11 years, which provides a significant “therapeutic benefit” when administered in addition to standard symptomatic therapy, reducing the need for antibiotic use.

Keywords: Acute rhinosinusitis; Sinupret; Delayed antibiotic therapy

Introduction

Acute Rhinosinusitis (ARS) refers to acute respiratory infections, is the most common disease, and in addition to discomfort and reduce the patient's quality of life, is of great social and economic importance. This group of diseases is one of the key factors of a significant number of day's absence from school in children [1]. The concept of "Rhinosinusitis" was introduced in the recent years as inflammatory process had been proved to occur simultaneously in the nose and paranasal sinuses. Each case of viral infection of the upper respiratory tract with rhinitis symptoms should be regarded as ARS. ARS is defined as a sudden appearance of two or more typical clinical symptoms, one of which should be either nasal congestion or nasal obstruction, or nasal discharge (rhinorrhoea or post-nasal drip), as well as ± facial pressure/pain and ± reduction or loss of smell, and children cough (day and night) within <12 weeks. Other symptoms include fever, fatigue and headache [1].

ARS includes viral (common cold) and post-viral forms. In Europe, acute viral rhinosinusitis is defined as acute corresponding symptoms within up to 10 days without their aggravation in 5 days. Acute post-viral rhinosinusitis is diagnosed by aggravation of symptoms in 5 days or symptoms saving in 10 days [1]. In USA, acute post-viral rhinosinusitis is diagnosed by aggravation of symptoms in 5 days or symptoms saving in 10 days [2]. Thus, the terms "acute post-viral RS" and "acute non-viral RS" in Europe (EPOS 2012) and USA guidelines were chosen to indicate that most of the cases of ARS are not bacterial. Only about 0.5% to 5% of ARS may be characterized as Acute Bacterial Rhinosinusitis (ABRS).

Until now, there is not a single standard parameter for the differential diagnosis among viral, post-viral and bacterial ARS. Based on the complex differentiation between viral and bacterial aetiology, criteria have been proposed that assess the presence or absence of a number of anamnestic data and clinical symptoms. These include aggravation of symptoms after initial improvement, hyperthermia above 38°C, severe local pain and nasal discharge (mostly purulent) [1,2].

The primary cause of ARS in the first 10 days of the disease is usually various viruses (rhinovirus, parainfluenza virus type 1 and type 2, coronavirus, influenza virus). All of them increase the concentration of proinflammatory cytokines and the number of neutrophils [3]. Their activity leads to mucociliary clearance disorders as a result of ciliated epithelium damage, as well as increased viscous secretion. These changes lead to degradation of the osteomeatal complex, ventilation disorders and impaired drainage from the paranasal sinuses. A similar reaction is observed with a bacterial infection. As a result, ARS can most likely be mistakenly diagnosed as a bacterial infection, as a result of which antibacterial therapy will be unreasonably carried out, which does not contribute to recovery at this stage of the disease.

However, acute rhinosinusitis is one of the most frequent diagnoses for antibiotic prescription, although there are no evidences that antibacterial therapy reduces the disease duration. In Ukraine, pediatricians prescribe antibiotics in 32%, general practitioners in 54%, and otolaryngologists in 77% of ARS cases [4]. In other countries, antibiotics are also prescribed for acute respiratory infections 4 times to 9 times more often than proposed by therapeutic recommendations [5].

One of the strategies to reduce the number of unnecessary prescriptions is delayed antibiotic prescription. The specialist assumes that the immediate prescription of an antibiotic is not necessary, expecting that the symptoms will be eliminated without their use, but leaves the possibility of prescription if the patient's condition does not meet the criteria of positive dynamics. Patients and physicians may be more likely to agree with such a cycle of treatment, compared with immediate or no prescription of antibiotics in people with respiratory tract infections [6].

The key factors for the possibility of implementing a delayed antibiotic prescription method are the prescription of evidence-based treatment. According to the recommendations, symptomatic pharmacotherapy of acute rhinosinusitis includes therapeutic irrigations with isotonic solution of sea salt and non-steroidal anti-inflammatory or antipyretic drugs. However, these symptom relieving drugs do not cover the whole spectrum of the pathogenetic mechanisms of ARS, and the prescription of such widely used drugs as nasal decongestants, antihistamines, homoeopathic medicine and mucolytics in acute rhinosinusitis is not justified, since their use has not yet been proven [2,3]. The low treatment efficacy, especially in the early days, is the main reason for the prescription of antibiotics on revisits. Based on this, there is a need to use drugs with a comprehensive effect on the pathogenesis base units and proven efficacy.

In light of these data, the use of herbal medicinal products could be interesting, because according to the study they can influence a number of pathological processes [7]. The most studied is Pelargonium sidoides, which has shown efficacy in treatment of cold symptoms [8]. The fewness of studies that meet GCP standards is associated with the difficulties of standardization of herbal medicinal products and thus, the study of their efficacy and safety using the tools of evidence-based medicine. However, the situation has changed after the issue of the corresponding recommendations [9].

In clinical practice, an aqueous alcoholic extract of BNO-1012 (Sinupret®) is used, which includes the standardized content of key biologically active substances *Gentiana lutea* (bitterroot), *Primula veris* (primrose flowers), *Rumex acetosa* (sorrel herb), *Sambucus nigra* (elder flowers), *Verbena officinalis* (verbena herb). It is proved that this herbal medicinal product intensifies ciliary activity *in vitro* and has an anti-inflammatory activity in animal experiments [10,11]. It has a wide range of pharmacological activity including mucolytic, secretomotor, antiviral, anti-inflammatory and immunomodulatory effect. It has been shown that BNO-1012 in combination with standard antibacterial therapy significantly reduces the acute symptoms and signs of sinusitis [12].

Jund et al., [13] conducted a randomised double-blind placebo-controlled efficacy study with the involvement of 386 adult patients with acute viral rhinosinusitis. The active treatment group received monotherapy with herbal medicinal product in a daily dose of 3 mg × 160 mg for 15 days. The active treatment group showed a more significant improvement compared to placebo group based on the results of sinonasal test including total index, nasal symptoms, rhinogenous symptoms and overall life quality.

The components of the drug have a complex therapeutic activity, which is presented in secretolytic (fluidifying sputum) effect, as well as anti-inflammatory, anti-oedema, antiviral and immunostimulating effects, and indications for use are "chronic or acute inflammation of paranasal sinuses". However, in the scientific literature there are no valid reports of GCP compliance - the standards of efficacy study of

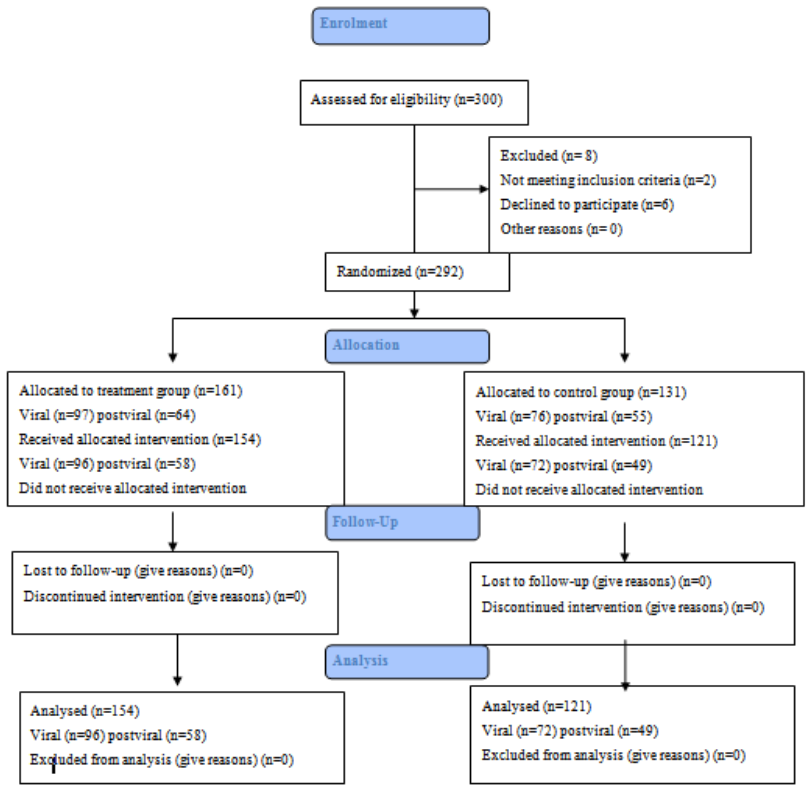

Figure 1: Patients included in screening, randomization and excluded from the study.

BNO-1021 in the treatment of acute viral and post-viral rhinosinusitis.

The objective of this study was to evaluate the efficacy of phytoneering extract BNO-1021 for use in the delayed antibiotic prescription method in children of school age (6 years to 11 years) compared to patients receiving standard symptomatic ARS therapy according to national guidelines [14].

Materials and Methods

Trial design: Open-label, exploratory, comparative, multicenter, randomized, prospective, parallel-group study was performed in six outpatient institutions of Ukraine from October 2015 to February 2016. The study was performed in accordance with the GCP standards and the Declaration of Helsinki. The study was approved by the Ethics Committee in all study sites. The parents of each child gave written consent to participate in the study.

Participants: A 300 subjects were enrolled, 292 outpatient subjects aged 6 years to 11 years diagnosed with acute rhinosinusitis were randomized. Depending on the diagnosis, all patients were divided into two categories: acute viral rhinosinusitis (n-173) and acute post-viral rhinosinusitis (n-119). 161 patients were randomized into the treatment group: viral RS (n- 97) and post-viral RS (n- 64) patients taking BNO-1012, a standardized extract of five medicinal herbs (Sinupret®) in addition to standard therapy. The 131 patients were randomized into the control group: viral RS (n-76) and post-viral RS (n-55). Patients in the control group received standard symptomatic therapy.

Among randomized patients with acute viral rhinosinusitis (n-173), 54 (55.7%) boys and 43 (44.3%) girls were in the treatment group (n-97), 54 (55.7%) boys and 43 (44.3%) girls were in the control group (n-76). The average age of patients with viral rhinosinusitis was 8.17 ± 3.29 years.

Among randomized patients with acute post-viral rhinosinusitis (n-119), 34 (53.1%) boys and 30 (46.9%) girls were in the treatment group (n-64), 30 (54.5%) boys and 25 (45.5%) girls were in the control group (n-55). The average age of patients with post-viral rhinosinusitis was 9.41 ± 3.21 years.

Diagnostic and differential diagnostic criteria for acute rhinosinusitis were assessed in accordance with the recommendations provided in European and national clinical Guidelines [2,13]. The clinical diagnosis of ARS was based on the presence of two or more typical clinical symptoms, one of which should be either nasal congestion or nasal obstruction, or nasal discharge (anterior rhinorrhoea or post-nasal drip), as well as ± facial pressure/pain and ± cough (day and night) within <12 weeks.

The diagnosis of viral rhinosinusitis is determined in case of corresponding symptoms for up to 10 days without their aggravation in 5 days, post-viral rhinosinusitis - if symptoms persist for more than 10 days, or the symptoms of rhinosinusitis aggravate in 5 days.

Inclusion criteria: Male and female subjects aged 6 years to 11 years who are on outpatient treatment with acute rhinosinusitis, the willingness and ability of the patient and/or parents to comply with the requirements of the study protocol, signed informed consent. The following three key symptoms were rated by the physician with 0 points to 4 points according to the major sinusitis severity score (MSS score): nasal discharge (rhinorrhoea), nasal congestion, post-nasal drip. The scale of the scores is as follows: 0-absent, 1-slight, 2-moderate, 3-severe, 4-very severe.

Withdrawal criteria: The decision of the patient and/or parents to discontinue participation in the study and withdrawal of written informed consent; loss of contact with the patient, individual intolerance to the study drug and the reference treatment regimen, the occurrence of serious and/or unforeseen adverse events/reactions in the patient during the study; significant reduced general condition, the development of complications of the underlying disease, which in the physician's opinion require patient's withdrawal from the study; patient's violation of the procedures provided by the Protocol.

Exclusion criteria: The use of one dosage form of the studied herbal medicinal product for 30 days before the onset of rhinosinusitis, indications for the immediate start of systemic antibiotic therapy, the diagnosis of allergic rhinosinusitis, the use of systemic antibacterial or antifungal drugs, topical and systemic glucocorticosteroids, cytostatics for the last 14 days; intolerance or individual idiosyncrasy to any of the components of the study drug and the reference treatment regimen, chronic pathology and anatomical anomalies of the osteomeatal complex, which may affect the outcome of the disease.

The patients of two groups were of similar sex, age, clinical manifestations of the disease ($p<0.05$).

Interventions: From the moment of randomization, all patients received therapeutic irrigation of the nasal cavity with isotonic seawater solution 4 times a day and (if indicated) symptomatic medication (paracetamol).

Patients of the treatment group received adjunctive complex herbal medicinal product BNO-1012 (Sinupret®) per os, one batch, in the following dosage strength: 3.5 ml 3 times a day for children aged 6 years to 11 years (total 10.5 ml), after meals.

BNO-1012 per os syrup as a standardized extract. Active ingredients: 100 g of syrup contains 10 g of extract (1:11):

Bitterroot (Radix Gentianae), Primrose flowers with flower cup (Flores Primulae cum Calycibus), Verbena herb (Herba Verbenae), Sorrel herb (Herba Rumicis), Elder flowers (Flores Sambuci) in a ratio of 1:3:3:3:3 59% v/v ethanol extraction solvent, Percipients: purified water, cherry odour, maltitol liquid. The ethanol content is 8% v/v.

Name and address of the manufacturer: Bionorica SE, Kerschensteinerstrasse, 11 to 15, 92318, Neumarkt, Germany.

The drug is registered in Ukraine and available OTC. Therefore, formulation, manufacturing process, packaging and labeling of the drug comply with GMP and current national requirements of Ukraine. A detailed description of all aspects of the quality and safety of BNO-1012 is part of the corresponding product characteristics. In Ukraine, the approved indications for use are acute and chronic diseases of the paranasal sinuses. ENT practitioners with experience of at least 5 years were involved in the study.

Outcome measures: All data were evaluated at the baseline and within 10 days (Table 1). Symptoms were assessed by physicians and patients. At each visit, physicians evaluated three principal symptoms according to the MSS scale: (0 points to 4 points for each symptom): Nasal congestion, rhinorrhoea, post-nasal drip. In addition, patients and their parent's daily assessed complaints in a diary (rhinorrhoea, headache) in points on a 10-point visual analogue scale.

On visit 2 (V2), the physician assessed the patient's condition according to the evaluation criteria, self-scoring and, together with the patient and/or his/her parents, made a decision on the need of antibiotic therapy.

Table 1: Schedule of assessments.

V1					V2		V3			V4
day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10
Treatment group										
Reference treatment + Sinupret										
Control group										
Reference treatment										

V1 day 0 Screening, randomization, prescription of treatment
V2 day 5 ± 1 Status evaluation, possible prescription of antibiotics
V3 day 7 ± 1 Evaluation of treatment efficacy
V4 day 10 ± 1 Evaluation of treatment efficacy, end of treatment

Table 2: Allocation of patients according to sex.

Nosology	Group	Statistical indicators		
		n	Boys	Girls
Viral RS (n- 168)	Treatment	96	54 (56.2 %)	42 (43.8 %)
	Control	72	39 (54.2 %)	33 (45.8 %)
Post-viral RS (n- 107)	Treatment	58	31 (53.4 %)	27 (46.6 %)
	Control	49	27 (55.1 %)	22 (44.9 %)
Total		275	151 (54.9 %)	124 (45.1 %)

Table 3: Allocation of patients according to age.

Parameter	Group	Statistical indicators			
		n	M ± SD	p-value	Homogeneity of the groups*
Age, Years	Viral RS	168	8.17 ± 3.219	0.071	Homogeneous
	Post-viral RS	107	9.46 ± 3.296		

*The conclusion is drawn at the significance level of 0.05

Efficacy key factor: Decrease in major symptoms of the disease, assessed on a scale according to the MSS scale, at each visit compared with the 1st visit, the dynamics of self-scoring of the symptoms of acute rhinosinusitis, the frequency of antibiotics prescription, "therapeutic benefit" in days.

Sample size: A clinical study has been developed to obtain a reliable description of the *in vivo* efficacy of active (additional) use of the extract of five medicinal herbs BNO-1012 compared to the standard treatment only under the method of delayed antibiotic prescription. Depending on findings, several trial descriptive and statistical evaluations were performed so that a biometric estimate of the sample size is not required. However, in order to guarantee a sufficient sample size for data analysis, the sample size N=300 was chosen.

Randomization: The clinical part of the randomized study is open, without a blinding procedure. Subjects with ARS symptoms are randomized to one of two possible treatments according to the basic randomization list. Randomization was performed using the software [StatSoft is a random number generator]. Randomization was performed for each patient who signed an informed consent. Patients with ARS who undergo a randomization procedure are additionally divided into two categories: acute viral rhinosinusitis and acute post-viral rhinosinusitis.

Statistical methods: In order to analyze homogeneity of groups, descriptive statistics methods were used for description of the baseline condition of the treatment and control group (for quantitative

Table 4: Severity of the on-treatment principal symptoms in points, evaluated by a physician in patients with viral RS.

Parameter	Visit (V)	Treatment group			Control group		
		n	Arithmetical mean	Standard deviation	n	Arithmetical mean	Standard deviation
Rhinorrhoea	V 1	97	3.35	0.778	76	3.34	0.793
	V 2	97	1.89	1.019	76	2.46	0.916
	V 3	96	0.32	0.641	72	0.49	0.839
	V 4	96	0.04	0.248	72	0.11	0.491
Nasal congestion	V 1	97	3.18	0.764	76	2.96	1.113
	V 2	97	1.15	1.112	76	1.46	1.089
	V 3	96	0.2	0.515	72	0.29	0.542
	V 4	96	0.05	0.266	72	0.08	0.325
Post-nasal drip	V 1	97	2	1.479	76	1.79	1.552
	V 2	97	1.02	1.181	76	1.51	1.438
	V 3	96	0.23	0.492	72	0.19	0.521
	V 4	96	0.03	0.227	72	0	0

Table 5: Comparison of the dynamics of symptoms assessed by a physician in patients with viral RS.

Parameter	T	Mann-Whitney U-test	Wilcoxon W	Z-statistics	p-value (two-sided)	Significant differences*
Rhinorrhoea	T1	3679	6605	-0.024	0.981	Non-significant
	T2	2478.5	7231.5	-3.92	0	Significant
	T3	3495	8248	-0.76	0.447	Non-significant
	T4	3369	8025	-0.805	0.421	Non-significant
Nasal congestion	T1	3433.5	6359.5	-0.821	0.412	Non-significant
	T2	3063	7816	-1.99	0.047	Significant
	T3	3389	8142	-1.33	0.183	Non-significant
	T4	3360.5	8016.5	-0.785	0.433	Non-significant
Post-nasal drip	T1	3400.5	6326.5	-0.898	0.369	Non-significant
	T2	3000	7753	-2.224	0.026	Significant
	T3	3444	6370	-1.126	0.26	Non-significant
	T4	3384	6012	-1.228	0.219	Non-significant

*The conclusion is drawn at the significance level of 0.05

parameters-n, mean arithmetic, median, standard deviation, minimum and maximum values; for qualitative parameters-incidence and share as %). Verification of normality of data distribution in groups was performed for quantitative parameters using Shapiro-Wilk test. If the data in groups showed normal distribution according to certain parameters, the groups were compared by these parameters *via* Student's test for in-dependent samples. Otherwise (if the data distribution was different from normal), comparison of groups was performed according to Mann-Whitney test. For categorical parameters, the groups were compared using Pearson's chi-squared test or Fisher's exact test.

For analysis of efficacy, descriptive statistics parameters were calculated in each group (n, mean arithmetic, median, standard deviation, minimum and maximum values) for all visits in accordance with patients' examination scheme.

Analysis of dynamics of the said parameters in each group was performed *via* two-way Analysis of Variance (ANOVA) according to the following scheme: "Visit" factor is fixed (levels: visit 1…visit n); "Subjects" factor is random. Results of the subsequent visits were compared against the data of visit 1 *via* contrast analysis using simple contrasts.

Comparison between groups in dynamics of tested parameters was performed by differences dTi=(TVisit n-TVisit 1) of assessed parameters using Mann-Whitney test. The level of confidence for Shapiro-Wilk test was accepted equal to 0.01, and for the rest of the criteria it was accepted equal to 0.05. The analysis was performed in software environment IBM SPSS 22.0.

Results

Study sample: The 300 patients aged 6 years to 11 years were enrolled in the study (Figure 1). Of the 300 patients enrolled, 8(2.6%) were not included in the study. The reason was the non-compliance with the study inclusion criteria: age non-compliance (n=2) and the unwillingness of the patient and/or his/her parents to comply with the protocol requirements (n=6). The rest 292 patients were randomized either to the viral rhinosinusitis group: n-173 (treatment group n-97, control group n-76), or post-viral rhinosinusitis group: n-119 (treatment group n-64, control group n-55), 17(5.8%) randomized patients were excluded from the study: n-7 from the treatment group (n-1 from the viral RS group and n-6 from the post-viral RS group) and n-10 from the control group (n-4 from the viral RS group and n-6 from the post-viral RS group). The reason was a protocol violation. These patients' data were excluded from the analysis.

Table 6: Severity of the on-treatment principal symptoms in points, evaluated by a physician in patients with post-viral RS.

Parameter	Visit	Treatment group			Control group		
		n	Arithmetical mean	Standard deviation	n	Arithmetical mean	Standard deviation
Rhinorrhoea	V1	64	3.88	0.333	55	3.87	0.336
	V2	63	1.49	1.045	55	2.29	0.994
	V3	58	0.12	0.329	49	0.27	0.531
	V4	58	0	0	49	0	0
Nasal congestion	V1	64	3.77	0.427	55	3.78	0.417
	V2	63	1.4	0.993	55	2.27	0.912
	V3	58	0.07	0.256	49	0.18	0.486
	V4	58	0	0	49	0	0
Post-nasal drip	V1	64	2.86	0.56	55	2.73	0.651
	V2	63	0.83	0.943	55	1.33	0.862
	V3	58	0	0	49	0	0
	V4	58	0	0	49	0	0

Table 7: Comparison of the dynamics of symptoms assessed by a physician in patients with post-viral RS.

Parameter	T	Mann–Whitney U-test	Wilcoxon W	Z-statistics	p-value (two-sided)	Significant differences*
Rhinorrhoea	T1	1756	3296	-0.037	0.97	Non-significant
	T2	964.5	2980.5	-4.39	0	Significant
	T3	1299	3010	-1.439	0.15	Non-significant
	T4	1450	2725	0	1	Non-significant
Nasal congestion	T1	1731.5	3811.5	-0.209	0.834	Non-significant
	T2	855	2871	-5.028	0	Significant
	T3	1343	3054	-1.257	0.209	Non-significant
	T4	1450	2725	0	1	Non-significant
Post-nasal drip	T1	1628	3168	-0.896	0.37	Non-significant
	T2	1088.5	3104.5	-3.883	0	Significant
	T3	1450	2725	0	1	Non-significant
	T4	1450	2725	0	1	Non-significant

*The conclusion is drawn at the significance level of 0.05

Thus, from October 2015 to February 2016, 275(94.1%) of 292 patients completed the study in full and were analysed: n-154 in the treatment group (n-96 viral RS and n-58 post-viral RS) and n-121 in the control group (n-72 viral RS and n-49 post-viral RS).

Table 2 presents sex distribution of patients in both groups who completed the study. A 96 of 168 patients with viral RS were included in the treatment group, where 54(56.2%) were boys and 42(43.8%) were girls. A 72 patients of the control group: 39 boys (54.2%), 33 girls (45.8%). A 58 out of the 107 patients with post-viral RS were included in the treatment group, where 31(53.4%) were boys and 27(46.6%) were girls. 49 patients of the control group: 27 boys (55.1%), 22 girls (44.9%).

In general, there were slightly more boys than girls (54.9% *vs.* 45.1%) among patients enrolled in the study.

Table 3 presents age distribution of patients in both groups: average age of patients with viral RS was 8.17 ± 3.219 years, with post-viral RS is 9.46 ± 3.296. In general, there were no significant differences in demographic characteristics among patients with viral and post-viral RS in the treatment and control groups at the baseline (Day 1).

Outcomes and estimation: Typical objective clinical symptoms of ARS, both viral and post-viral, are nasal discharge (rhinorrhoea or post-nasal drip), nasal congestion/obstruction associated with mucosal oedema. Table 4 presents the severity of the principal symptoms in points, evaluated by a physician on a 4-point scale in patients with viral rhinosinusitis.

When the physician assessed the symptom of nasal discharge (rhinorrhoea), both groups showed comparable severity indicators during V1: 3.35 points in the treatment group and 3.34 points in the control group. In the course of treatment on V2, regression of rhinorrhoea was observed in patients of both groups: 3.35 points to 1.89 points in the treatment group and 3.34 points to 2.46 points in the control group. On V3 there is a further regression of rhinorrhoea in patients of both groups: 0.32 points in the treatment group and 0.49 in the control group. On V4, the severity of rhinorrhoea was 0.04 points in the treatment group and 0.11 points in the control group. There is a tendency to more pronounced regression of the symptom in the treatment group (Table 4).

Table 5 presents on-treatment comparative assessment of the severity of principal symptoms evaluated by the physician in patients with viral RS with the Mann-Whitney test. Comparison of regression

Table 8: Symptom self-scoring in points in patients with viral RS.

Parameter	Day	Treatment group			Control group		
		n	Arithmetical mean	Standard deviation	n	Arithmetical mean	Standard deviation
Rhinorrhoea	Day 1	97	5.46	1.888	76	4.96	1.851
	Day 2	97	5.22	1.821	76	4.99	1.77
	Day 3	97	4.4	1.897	76	4.21	1.746
	Day 4	97	3.71	1.814	76	3.58	1.543
	Day 5	97	2.7	1.98	76	3.18	1.547
	Day 6	97	2.04	1.876	73	2.3	1.381
	Day 7	97	1.23	1.777	73	1.62	1.36
	Day 8	96	0.82	1.465	72	0.97	1.265
	Day 9	96	0.45	1.035	72	0.65	1.135
	Day 10	96	0.17	0.735	72	0.38	1.013
Headache	Day 1	97	2.11	1.999	76	2.08	1.486
	Day 2	97	1.96	2.14	76	1.92	1.403
	Day 3	97	1.25	1.768	76	1.29	1.441
	Day 4	97	0.62	1.35	76	0.79	1.17
	Day 5	97	0.43	1.189	76	0.55	0.985
	Day 6	97	0.29	0.889	73	0.41	0.796
	Day 7	97	0.21	0.763	73	0.33	0.751
	Day 8	96	0.13	0.567	72	0.31	0.729
	Day 9	96	0.06	0.431	72	0.17	0.56
	Day 10	96	0.04	0.408	72	0.03	0.237

of rhinorrhoea symptoms between groups shows significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$).

When the physician assessed the symptom of nasal congestion in patients with viral RS, both groups showed comparable severity indicators during V1: 3.18 points in the treatment group and 2.96 points in the control group (Table 4). In the course of treatment on V2, regression of nasal congestion was observed in patients of both groups: 3.18 points to 1.15 points in the treatment group and 2.96 points to 1.46 points in the control group. On V3, there is a further regression of nasal congestion in patients of both groups: 0.20 points in the treatment group and 0.29 points in the control group. On V4, the severity of nasal congestion was 0.05 points in the treatment group and 0.08 points in the control group. There is a tendency to more pronounced regression of the symptom in the treatment group (Table 4).

Table 5 shows a comparative assessment of the regression of the nasal congestion symptom between groups using the Mann-Whitney test. Significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$) are shown.

When the physician assessed the symptom of post-nasal drip both groups with viral RS showed comparable severity indicators during V1: 2.00 points in the treatment group and 1.79 in the control group (Table 4). In the course of treatment on V2, regression of post-nasal drip was observed in patients of both groups: 2.00 points to 1.02 points in the treatment group and 1.79 points to 1.51 points in the control group. On V3 there is a further regression of post-nasal drip in patients of both groups: 0.23 points in the treatment group and 0.19 points in the control group. On V4, the severity of post-nasal drip was 0.03 points in the treatment group and 0.00 points in the control group. There is a tendency to more pronounced regression of the symptom in the treatment group (Table 4).

In on-treatment comparative assessment of the severity of post-nasal drip in patients with viral RS using the Mann-Whitney test, significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$) are shown (Table 5).

Table 6 presents the severity of the principal symptoms in points, evaluated by a physician on a 4-point scale in patients with post-viral rhinosinusitis.

When the physician assessed the symptom of nasal discharge (rhinorrhoea), both groups showed comparable severity indicators during V1: 3.88 points in the treatment group and 3.87 points in the control group. In the course of treatment on V2, regression of rhinorrhoea was observed in patients of both groups: 3.88 points to 1.49 points in the treatment group and 3.87 points to 2.29 points in the control group. On V3, there is a further regression of rhinorrhoea in patients of both groups: 0.12 points in the treatment group and 0.27 points in the control group. On V4, the severity of rhinorrhoea was 0.00 points in the treatment group and 0.00 points in the control group (Table 6).

Table 7 presents on-treatment comparative assessment of the severity of the principal symptoms evaluated by the physician in patients with post-viral RS with the Mann-Whitney test. Comparison of regression of rhinorrhoea symptoms between groups shows significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$).

When the physician assessed the symptom of nasal congestion,

Table 9: Comparison of the dynamics of symptoms self-scoring in patients with viral RS.

Parameter	Day	Mann–Whitney U-test	Wilcoxon W	Z-statistics	p-value (two-sided)	Significant differences*
Rhinorrhoea	Day 1	3324	8077	-1.153	0.249	Non-significant
	Day 2	2926	7679	-2.399	0.016	Significant
	Day 3	2809	7562	-2.474	0.013	Significant
	Day 4	3181.5	7934.5	-1.142	0.254	Non-significant
	Day 5	3179	7835	-0.944	0.345	Non-significant
	Day 6	3244	7900	-1.266	0.206	Non-significant
	Day 7	3471	8224	-0.679	0.497	Non-significant
	Day 8	3355	8108	-1.045	0.296	Non-significant
	Day 9	3458	8211	-0.759	0.448	Non-significant
	Day 10	3258	8011	-1.621	0.105	Non-significant
Headache	Day 1	3298	8051	-1.658	0.097	Non-significant
	Day 2	3359	8112	-1.587	0.113	Non-significant
	Day 3	3262.5	8015.5	-1.566	0.117	Non-significant
	Day 4	3093	7846	-2.213	0.027	Significant
	Day 5	3223.5	7879.5	-1.527	0.127	Non-significant
	Day 6	3396	8052	-0.206	0.837	Non-significant
	Day 7	3681	6607	-0.017	0.987	Non-significant
	Day 8	3465	8218	-0.78	0.436	Non-significant
	Day 9	3435	8188	-0.938	0.348	Non-significant
	Day 10	3513	8266	-0.7	0.484	Non-significant

*The conclusion is drawn at the significance level of 0.05

Table 10: Symptom self-scoring in points in patients with post-viral RS.

Parameter	Day	Treatment group			Control group		
		n	Arithmetical mean	Standard deviation	n	Arithmetical mean	Standard deviation
Rhinorrhoea	Day 1	64	3.88	0.333	55	3.85	0.356
	Day 2	64	3.69	0.531	55	3.73	0.592
	Day 3	64	2.89	0.645	55	3.11	0.712
	Day 4	64	2.14	0.753	55	2.62	0.871
	Day 5	63	1.37	1.005	55	2.24	1.036
	Day 6	58	0.57	0.624	49	1.49	0.767
	Day 7	58	0.14	0.348	49	0.76	0.723
	Day 8	58	0.03	0.184	49	0.18	0.441
	Day 9	58	0	0	49	0.06	0.242
	Day 10	58	0	0	49	0.02	0.143
Headache	Day 1	64	2.17	0.808	55	2.15	0.841
	Day 2	64	1.84	0.877	55	1.94	0.842
	Day 3	64	1.17	1.001	55	1.53	0.973
	Day 4	64	0.61	1.033	55	1.04	1.126
	Day 5	63	0.36	1.029	55	0.62	1.197
	Day 6	58	0.02	0.131	49	0.09	0.282
	Day 7	58	0	0	49	0.04	0.204
	Day 8	58	0	0	49	0.02	0.146
	Day 9	58	0	0	49	0	0
	Day 10	58	0	0	49	0	0

both groups showed comparable severity indicators during V1: 3.77 points in the treatment group and 3.78 in the control group (Table 6).

In the course of treatment on V2, regression of nasal congestion was observed in patients of both groups: 3.77 points to 1.40 points in the

Table 11: Comparison of the dynamics of symptoms self-scoring in patients with post-viral RS.

Parameter	Day	Mann–Whitney U-test	Wilcoxon W	Z-statistics	p-value (two-sided)	Significant differences*
Rhinorrhoea	Day 1	1724	3264	-0.325	0.745	Non-significant
	Day 2	1656	3736	-0.733	0.463	Non-significant
	Day 3	1453.5	3533.5	-1.849	0.065	Non-significant
	Day 4	1220.5	3300.5	-3.136	0.002	Significant
	Day 5	912.5	2928.5	-4.599	0	Significant
	Day 6	604	2315	-5.534	0	Significant
	Day 7	777	2488	-4.97	0	Significant
	Day 8	1267	2978	-2.245	0.025	Significant
	Day 9	1363	3074	-1.883	0.06	Non-significant
	Day 10	1421	3132	-1.077	0.281	Non-significant
Headache	Day 1	1670	3101	-0.151	0.88	Non-significant
	Day 2	1565.5	3645.5	-0.755	0.45	Non-significant
	Day 3	1287	3367	-2.403	0.016	Significant
	Day 4	1248.5	3328.5	-2.685	0.007	Significant
	Day 5	1439	3519	-1.962	0.047	Significant
	Day 6	1300	3011	-1.59	0.112	Non-significant
	Day 7	1334	3045	-1.562	0.118	Non-significant
	Day 8	1363	3074	-1.099	0.272	Non-significant
	Day 9	1368	2544	0	1	Non-significant
	Day 10	1392	2568	0	1	Non-significant

*The conclusion is drawn at the significance level of 0.05

treatment group and 3.78 points to 2.27 points in the control group. On V3, there is a further regression of nasal congestion in patients of both groups: 0.07 points in the treatment group and 0.18 points in the control group. On V4, the severity of nasal congestion was 0.00 points in the treatment group and 0.00 points in the control group. There is a tendency to more pronounced regression of the symptom in the treatment group (Table 6).

Table 7 shows a comparative assessment of the regression of the nasal congestion symptom between groups of patients with acute post-viral RS using the Mann-Whitney test. Significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$) are shown.

When the physician assessed the symptom of post-nasal drip both groups with post-viral RS showed comparable severity indicators during V1: 2.86 points in the treatment group and 2.73 points in the control group (Table 6). In the course of treatment on V2, regression of post-nasal drip was observed in patients of both groups: 2.86 points to 0.83 points in the treatment group and 2.73 points to 1.33 points in the control group. On V3 and V4, there is a regression of post-nasal drip in patients of both groups: 0.00 points in the treatment group and 0.00 points in the control group (Table 6).

In on-treatment comparative assessment of the severity of post-nasal drip in patients with post-viral RS using the Mann-Whitney test, significant differences in V2 ($p<0.05$) and not significant differences among groups in V1, V3 and V4 ($p>0.05$) are shown (Table 7).

Patients individually or with the help of parents evaluated the main complaints daily in the diary on a ten-point visual-analogue scale. Table 8 presents the dynamics of self-scored symptoms of rhinorrhoea and headache in patients with viral RS.

According to the self-scoring, there is a regression of rhinorrhoea in patients of both groups: 5.46 points to 5.22 points on the second day and to 4.40 points on the third day in patients of the treatment group. Patients in the control group had 4.96 points to 4.99 points on the second day and up to 4.21 points on the third day. From day 8, symptoms of rhinorrhoea were practically absent in patients of both groups: 0.82 points in the treatment group and 0.97 points in the control group.

Dynamics of self-scoring on the symptom of headache has been studied. Patients in the treatment group had 2.11 points to 1.96 points on the second day and up to 1.25 points on the third day. Patients in the control group had 2.08 points to 1.92 points on the second day and up to 1.29 points on the third day. Headache was practically absent in patients of both groups starting from day 4:0.62 points in the treatment group and 0.79 points in the control group (Table 8).

Comparison of rhinorrhoea regression according to patient's self-scoring between groups using the Mann-Whitney test shows significant differences on the second and third day, and headache on the fourth day of treatment ($p<0.05$) (Table 9).

Table 10 presents the dynamics of self-scored symptoms of rhinorrhoea and headache in patients with post-viral RS.

According to the self-scoring, there is a regression of rhinorrhoea in patients of both groups: 3.88 points to 3.69 points on the second day and to 2.89 points on the third day in patients of the treatment group. Patients in the control group had 3.85 points to 3.73 points on the second day and up to 3.11 points on the third day. Symptoms of rhinorrhoea were practically absent in patients of the treatment group from day 9 and were 0.02 points on the tenth day in the control group.

Table 12: Prescription of antibiotics in patients with acute RS.

Nosology	Group	n	Prescription of antibiotics	
			n	%
Viral RS (n- 168)	Treatment	96	2	2.08 %
	Control	72	4	5.55 %
Post-viral RS (n- 107)	Treatment	58	5	8.62 %
	Control	49	6	12.24 %

Dynamics of self-scoring on the symptom of headache has been studied in patients with post-viral RS. Patients in the treatment group had 2.17 points to 1.84 points on the second day and up to 1.17 points on the third day. Patients in the control group had 2.15 points to 1.94 points on the second day and up to 1.53 points on the third day. Headache was absent in patients of the treatment group starting from day 7 and day 9 in the control group (Table 10).

Comparison of rhinorrhoea regression according to patient's self-scoring between groups using the Mann-Whitney test shows significant differences from the fourth to the eighth day, and headache from the third to the fifth day of treatment ($p<0.05$) (Table 11).

According to the study design on V2 (the fifth day of treatment), a comprehensive evaluation of the patient's condition was made and the decision was made on the need for antibiotic therapy. Table 12 presents data on the prescription of antibiotics in patients with acute RS.

Antibiotic therapy was prescribed to 17 out of 275(6.18%) patients with ARS. Antibiotic was prescribed to 6(3.57%) out of 168 patients with acute viral RS, to 11(10.28%) out of 107 patients with post-viral RS. A 2 out of 96 patients (2.08%) with acute viral RS in the treatment group were prescribed antibacterial therapy, and 4 out of 72(5.55%) in the control group. The 5 patients out of 58(8.62%) with acute post-viral RS required antibiotic therapy in the treatment group, and 6 out of 49(12.24%) in the control group.

Safety and tolerability: An analysis of the tolerability assessment findings showed that the treatment was well tolerated or very well tolerated in all cases. No, on-treatment side effects were observed in any patients.

Discussion

Acute rhinosinusitis includes viral (common cold) and post-viral/non-viral forms. The term "post-viral ARS" was chosen to indicate that the most ARS cases are not bacterial. Only about 0.5% to 5% of ARS may be characterized as Acute Bacterial Rhinosinusitis (ABRS). Thus, not more than 5% of patients with ARS require antimicrobial therapy. However, antibiotics are also prescribed for acute respiratory infections 4 times to 9 times more often than recommended by clinical guidelines [5]. One of the strategies to reduce the number of unnecessary prescriptions is delayed antibiotic prescription.

From the point of view of the delayed antibiotic prescription method, the initial treatment should be highly effective, especially in the first days after its administration. With a lack of efficacy of initial treatment, when re-examining, it is always necessary to prescribe antibacterial drugs.

In this study, it was demonstrated that the use of the phytotherapeutic drug BNO-1021 in addition to the standard symptomatic therapy of acute rhinosinusitis has a proven therapeutic benefit in the first days of treatment.

Patients with acute viral rhinosinusitis in BNO-1021 group demonstrated a clinically significant, adequate reduction in the severity of local symptoms (rhinorrhoea, nasal congestion and post-nasal drip), assessed by a physician on V2 ($p<0.005$). Significant differences were noted in the patient's self-scoring of the severity of rhinorrhoea on a 10-point scale on the second or third day of treatment ($p<0.005$).

Patients with acute post-viral rhinosinusitis in BNO-1021 group demonstrated a clinically significant, adequate reduction in the severity of local symptoms (rhinorrhoea, nasal congestion and post-nasal drip), assessed by a physician on V2 on a 4-point scale ($p<0.005$). Significant differences were noted in the patient's self-scoring of the severity of rhinorrhoea on a 10-point scale from the fourth to the eighth day of treatment ($p<0.005$).

Symptoms similar in severity, both assessed by a physician and based on the results of self-scoring in patients of the control group, were achieved on V3, i.e. by the seventh day of observation, when the difference in the symptom intensity scores was not reliable ($p>0.005$). Thus, during the seven-day observation period, the treatment group compared to the control group showed a "therapeutic benefit" of three days.

Our findings reflect the few literature data, which demonstrate that Sinupret® is effective for acute rhinosinusitis in adults [12,13]. The results obtained in these studies demonstrated that in the active treatment group, by the 10th day, according to the sinonasal test, including total index, nasal symptoms and the overall quality of life, such acute rhinosinusitis symptoms improvement occurred, which was observed in the placebo group only by day 14. Similar results were obtained in paediatric study [15,16].

The possibility of Sinupret influence on the local symptoms of ARS is confirmed by the previously obtained data that this herbal medicinal product enhances the activity of the ciliary epithelium *in vitro* [10].

One of the diagnostically important symptoms of ARS is headache. In viral rhinosinusitis, this is mainly due to the toxic effect of viruses and mucosal oedema; in case of post-viral rhinosinusitis, it is associated with oedematous-inflammatory changes of the mucous membrane of the sinuses and blockade of fistulas. Our study showed significantly better dynamics of headache reduction according to the patient's self-scoring on a 10-point scale in the treatment group compared to the control group on the fourth day with acute viral rhinosinusitis and from the third to the fifth day of treatment with post-viral RS ($p<0.005$). This clinical effect confirms previously obtained data on the anti-inflammatory properties of Sinupret in an *in vivo* study [11].

Thus, an important and interesting conclusion of the study is that the use of BNO-1021 in patients with acute rhinosinusitis leads to a pronounced, significant regression of such important local symptoms as rhinorrhoea, post-nasal drip, nasal congestion and headache by the first control (V2) patient visit ($p<0.005$).

Many researchers have expressed the opinion that the presence or weak dynamics of rhinorrhoea regression, post-nasal drip, nasal congestion and headache in patients with acute rhinosinusitis is a driving factor in the unjustified prescription of antibiotics among both physicians and the desire for antibiotic therapy among patients themselves, which is one of the primary causes of the global problem of antibiotic resistance [17]. The proven efficacy of BNO-1021 is an

important argument for reducing the desire of patients and physicians to prescribe antibiotics due to unexpressed symptom regression, especially in the first days of treatment.

According to the study design, patients with diagnostic criteria for acute non-bacterial (viral and post-viral) RS not requiring the immediate prescription of antibiotic therapy were enrolled. The decision on prescription of antibiotics was made after evaluation the dynamics of symptom regression on V2. In such cases, antibiotic therapy was considered reasonable because the treatment assigned on V1 was ineffective.

Antibiotics were prescribed for 17(6.18%) of 275 patients with ARS, which is consistent with existing recommendations for antibiotic therapy for ARS [2,3,6]. 7 out of 154 patients (4.54%) in the treatment group were prescribed antibacterial therapy, and 10 out of 121(8.26%) in the control group. Thus, the use of BNO-1021 in the delayed antibiotic prescription method in patients with acute rhinosinusitis can reduce the justified prescription of antibacterial drugs by 1.81 times.

ARS includes viral (common cold) and post-viral forms. In viral RS, it is relatively easy for a physician to establish a connection with viral infection and to avoid the prescription of antibiotics. Consequently, out of 168 patients with acute viral RS, reasonable antibacterial therapy was prescribed only to 6 patients (3.57%). 2 out of 96 patients (2.08%) in the treatment group were prescribed antibacterial therapy, and 4 out of 72(5.55%) in the control group. The use of BNO-1021 in the delayed antibiotic prescription method in patients with acute viral rhinosinusitis can reduce the justified prescription of antibacterial drugs by 2.7 times.

It is much more difficult to avoid prescription of antibiotics in case of aggravation of symptoms after 5 days or if they persist after 10 days of illness. In present guidelines, the term "post-viral ARS" has been chosen to indicate that most cases of ARS are not bacterial. In our study, 11(10.28%) out of 107 patients with post-viral RS were prescribed reasonable antibiotic therapy. About 5 patients out of 58(8.62%) in the treatment group required antibiotic therapy and 6 out of 49(12.24%) in the control group. The use of BNO-1021 in the delayed antibiotic prescription method in patients with acute post-viral rhinosinusitis can reduce the justified prescription of antibacterial drugs by 1.4 times.

An important conclusion of the study is that the use of BNO-1021 in patients with acute rhinosinusitis almost twice reduces the need for reasonable antibacterial therapy as part of delayed antibiotic prescription method. However, according to literature data, unreasonable antibacterial therapy is prescribed from 54% to 77% of cases of ARS [5,6]. The proven high efficacy of acute rhinosinusitis treatment in terms of severe regression of symptoms in the first days after its administration will allow it to more widely implement the delayed antibiotic prescription method and multiply reduce the number of unreasonable antibiotic prescription at the first visit of the patient.

The efficacy of BNO-1021, described in this study, generally confirms the results of earlier studies in patients with acute rhinosinusitis [13,14]. However, its advantage is the diagnosis of acute viral and post-viral rhinosinusitis, established according to accepted criteria. The groups of randomized patients, homogeneous in terms of diagnosis and clinical manifestations, made it possible to draw reasonable conclusions regarding the evaluation of treatment results. The number of patients with viral and post-viral RS responded to treatment on V2 was significantly higher in treatment groups compared with control.

The design involved a comparative study that did not allow for a placebo control. However, the comparison was made with the treatment according to the clinical guidelines, which provide for mandatory prescription of only symptomatic therapy using irrigation therapy and, if indicated, paracetamol [2,15]. The effect of symptomatic therapy can be considered equivalent in groups. Consequently, all the differences in treatment results can be attributed to the clinical effects of BNO-1021, since the group characteristics were comparable.

Conclusion

It was shown that in addition to standard symptomatic therapy, the use of phytoneering drug BNO-1021 (Sinupret®) for the treatment of acute rhinosinusitis provides a significant clinical effect in the first 3 days to 4 days of treatment. Reliably compared with the control, the clinical symptoms of the disease are reduced; the self-scoring of symptoms and general condition of the patients improves. The therapeutic benefit in the first days of treatment reduces the need for antimicrobial drugs. The inclusion of the drug in the treatment regimen may be recommended for patients with acute rhinosinusitis as part of a delayed antibiotic prescription method.

The prospect of further studies is to study the drug efficacy in patients with bacterial rhinosinusitis.

Trial Registration

This trial was registered in German Clinical Trials Register retrospectively 27th March 2018. Trial Acronym ARSiCh DRKS-ID: DRKS00000765.

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