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An open-label, multicentre, randomized comparative study of efficacy, safety and tolerability of the 5 plant - extract BNO 1012 in the Delayed Antibiotic Prescription Method in children, aged 6 to 11 years with acute viral and post-viral rhinosinusitis

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ABSTRACT

Acute rhinosinusitis (ARS) can be characterized as bacterial (ABRS) and require antibiotic therapy only in 0.5–5% of cases. In most cases, the disease is in a viral and post-viral form, which requires pathogenetic and symptomatic treatment.

The study objective was to determine the efficacy of BNO 1012 extract in the technology of delayed antibiotic prescribing in children with acute rhinosinusitis.

Methods: 292 children aged 6 to 11 years with ARS were randomized in the multicenter, comparative study. They received an extract of five medicinal plants in addition to standard symptomatic therapy or standard therapy only.

Evaluation criteria: reduction of the sinusitis severity according to a 4-point medical assessment scale (nasal congestion, severity of anterior and posterior rhinorrhea) at each visit, dynamics of self-scoring of rhinorrhea and headache (according to a 10-point visual analogue scale), “therapeutic benefit” in days, frequency of antibiotic prescriptions due to the use of an extract of five plants.

Results: The use of the 5-plant extract BNO 1012 in addition to the standard symptomatic treatment of acute rhinosinusitis provides a clinically significant, adequate reduction in the severity of rhinorrhea, nasal congestion and post-nasal drip, assessed by a physician at V2 ($p < 0.005$). Significant differences are noted in the patient's self-scoring of rhinorrhea on the second or third day in viral RS, and from the fourth to the eighth day in post-viral RS. 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 1012 in patients with acute rhinosinusitis can 1.81-fold reduce the prescription of antibacterial drugs.

Conclusion: The combination of five medicinal plants is effective for the treatment of acute rhinosinusitis in children aged 6 to 11 years. Its use provides a significant “therapeutic benefit” when administered in addition to standard symptomatic therapy, reducing the need for antibiotic use.

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1. Introduction

Acute rhinosinusitis (ARS) is one of the most frequent upper respiratory tract diseases which is the key cause of absence from school among children [1].

Depending on the disease course, ARS can be regarded as acute viral rhinosinusitis (AVRS) and post-viral rhinosinusitis (PVRS). In Europe, acute viral rhinosinusitis is defined as acute corresponding symptoms within up to 10 days without their aggravation after the 5th day. Post-viral rhinosinusitis is diagnosed while symptoms persist > 10 days or they aggravate after the 5th day [2]. In the United States, this form of the disease is defined as acute non-viral rhinosinusitis [3]. Only 0.5% to 5% of ARS cases are caused by bacterial infection and may be characterized as acute bacterial rhinosinusitis (ABRS) that requires prescription of antibiotics.

As a rule, the most common cause of ARS within the first 10 days of the disease is various respiratory viruses. All of them increase the concentration of proinflammatory cytokines and the number of neutrophils [4]. Their activity leads to mucociliary clearance disorders because of ciliated epithelium damage and a significant increase in the viscous secretion. These changes lead to ventilation disorders and impaired drainage from the paranasal sinuses. A similar reaction is observed with a bacterial infection. As a result, ARS can be mistakenly diagnosed as a bacterial infection with the following unreasonable prescription of antibacterial therapy, which is not appropriate at this stage of the disease.

Although there are no evidences that antibiotic use is beneficial, acute rhinosinusitis is one of the leading diagnoses for which antibacterial therapy is unreasonably prescribed. Thus, in Ukraine, paediatricians prescribe antibiotics in 32%, general practitioners in 54%, and otolaryngologists in 77% of ARS cases [5]. In European countries, antibiotics are also prescribed for this nosology 4–9 times more often than recommended by guidelines [6].

One of the strategies to reduce the number of unnecessary prescriptions of antibiotics is to prescribe treatment without antibiotics in cases where there are no absolute indications for their prescription. The specialist does not resort to the immediate prescription of an antibiotic expecting that the patient's condition will improve under the influence of pathogenetic therapy, but leaves the possibility for prescribing antibacterial therapy if there is no positive dynamics [7].

The main condition for the possibility of implementing such a strategy is the prescription of evidence-based treatment. However, such widely used drugs as nasal decongestants, antihistamines, homeopathic medicine and mucolytics in acute rhinosinusitis have not proven their efficacy [2,3]. Many researchers have expressed the opinion that the weak dynamics of rhinorrhea 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, which is one of the primary causes of the global problem of antibiotic resistance [8].

According to the recommendations, pharmacotherapy of acute rhinosinusitis includes therapeutic irrigations with isotonic saline solution of sea salt and non-steroidal anti-inflammatory or antipyretic drugs, topical corticosteroids (in case of post – viral RS). Efficacy in treating sinusitis symptoms has been proven for Pelargonium sidoides, standardized myrtol [9,10]. The fewness of studies with herbal medicinal products 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 [11].

In clinical practice in Ukraine and several other countries, the standardized aqueous alcoholic extract BNO 1012 (Sinupret® syrup, Bionorica SE, Germany) is used and includes the standardized content of key biologically active substances Gentian root (Gentianae radix), Primrose flowers with calyx (Primulae flos cum calycibus), Common sorrel herb (Rumex herba), Elder flowers (Sambuci flos), Vervain herb (Verbenae herba). The complex medicinal product based on the extract of the specified herbal combination has a wide spectrum of pharmacological activity, including mucolytic, secretomotor, antiviral and anti-inflammatory effect. In vitro studies have shown that this product enhances the hydration of the airway secretion, enhances the activity of the ciliate epithelium [12] and exhibits anti-inflammatory properties in animal experiments [12,13]. Other studies have shown the ability of plant flavonoids in the complex herbal formulation to suppress the replication of respiratory viruses in a dose-dependent manner [14].

Several clinical studies have shown good results. A randomized, double-blind, placebo-controlled efficacy study of the dry phytoextract containing the components of the specified medicinal plants has shown its high efficacy in the treatment of acute viral rhinosinusitis. According to the sinonasal test, including total index, nasal symptoms and overall quality of life, such acute rhinosinusitis symptoms improvement occurred in adult patients in the active treatment group by Day 10, but in the placebo group only by Day 14 [15]. Similar results were obtained in a study among children with acute rhinosinusitis [16,17].

The use of phytoextract in combination with standard antibacterial therapy significantly reduces the acute symptoms and signs of sinusitis [18].

However, in the scientific literature there are no valid reports of GCP compliance — the standards of efficacy study of a five-component phytoextract to prevent the unreasonable use of antibiotic therapy in patients with acute rhinosinusitis.

The study objective was to evaluate the efficacy of the extract of five medicinal plants BNO 1012 to prevent unreasonable prescription of antibiotics in children aged 6–11 years compared to patients receiving standard symptomatic ARS therapy according to the recommendations of national guidelines [19].

2. Materials and methods

2.1. Study design

Open-label, multicenter, randomized, exploratory, comparative, prospective, parallel-group study was conducted in six outpatient institutions in Ukraine. The study duration was from October 2015 to February 2016. The study was approved by the Ethics Committee at each site and conducted in accordance with the GCP standards and the Declaration of Helsinki. The parents/official representatives of each child gave their written informed consent to participate in the study.

2.2. Participants

To evaluate the possible participation in the study, 304 outpatient subjects were enrolled; 292 outpatient subjects aged 6–11 years diagnosed with acute rhinosinusitis were randomized.

Diagnostic and differential diagnostic criteria for acute rhinosinusitis were evaluated in accordance with the recommendations made in European and national clinical guidelines [2,19].

The diagnosis of viral rhinosinusitis is determined in the case of relevant symptoms (nasal congestion, or nasal obstruction, or nasal discharge (anterior rhinorrhea or post-nasal drip), as well as face pressure/pain and cough (day and night) for up to 10 days without exacerbating them for 5 days, post-viral rhinosinusitis - if symptoms persist for > 10 days, or rhinosinusitis symptoms worsen after 5 days.

Depending on the treatment received, all patients were allocated into two groups: treatment group and control group.

Of the 168 patients with viral RS, 96 were included in the treatment group, where 54 (56.2%) were boys and 42 (43.8%) were girls. 72 patients in the control group: 39 boys (54.2%), 33 girls (45.8%). Of 107 patients with post-viral RS, 58 were included in the treatment group, where 31 (53.4%) were boys and 27 (46.6%) were girls. 49 patients in the control group: 27 boys (55.1%), 22 girls (44.9%). In general, there

Table 1
Schedule of visits and 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
Therapeutic irrigation + Sinupret syrup – 10 days

Control group
Therapeutic irrigation – 10 days
V1 day 0 Screening, randomization, prescription of treatment
V2 day 5 ± 1 Assessment of symptoms dynamics and indications for antibiotics prescription.
V3 vday 7 ± 1 Assessment of treatment efficacy
V4 day 10 ± 1 Assessment of treatment efficacy, end of treatment

were fewer boys than girls (54.9% versus 45.1%) among those patients who completed the study.

The average age of patients with viral RS was 8.17 and 3.219 years, and with post-viral MS 9.46 and 3.296 years.

In general, there were no significant differences in demographic characteristics among patients with viral and post-viral RS in the treatment and control groups.

Inclusion criteria:

- Male and female subjects aged 6 to 11 years undergoing outpatient treatment for acute rhinosinusitis,
- the willingness and ability of the patient and/or parents to comply with the requirements of the study protocol,
- signed informed consent.

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 a patient during the study; significantly 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 of the dosage forms 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 ($p < 0.05$).

2.3. Interventions

All patients received therapeutic irrigation of the nasal cavity with isotonic seawater solution 4 times daily and, in addition, symptomatic medications acetaminophen:

Patients of the treatment group additionally received the standardized extract of five medicinal plants BNO 1012 per os from one batch at a dose of 3.5 mL 3 times daily after meals. The treatment duration was 10 days.

The standardized extract BNO 1012 (trade name Sinupret® syrup) includes the fixed combination of five medicinal plants. Active ingredients: 100 g of syrup contains 10 g of extract (1:11):

Gentian root (*Gentianae radix*)
Vervain herb (*Verbenae herba*)
Elder flowers (*Sambuci flos*)
Common sorrel herb (*Rumex herba*)
Primrose flowers with calyx (*Primulae flos cum calycibus*) *in the ratio 1:3:3:3:3*

Ethanol extraction solvent 59% (v/v); excipients: purified water, cherry odour, maltitol liquid.

The ethanol content is 8% v/v.

Name and address of the manufacturer: Bionorica SE, Neumarkt, Germany.

The drug is registered in Ukraine and available OTC. Formulation, manufacturing process, packaging and labelling of the drug comply with GMP and current national requirements of Ukraine. 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.

2.4. Outcome measures

The symptom dynamics in patients was evaluated within four consecutive visits during 10 days (Table 1).

Additionally, if the patient's condition required it, an unscheduled visit was conducted.

At each visit, physicians evaluated three principal symptoms according to the MSS scale: (0 to 4 points for each symptom): Nasal congestion, rhinorrhea, post-nasal drip. In addition, patients and their parents daily assessed complaints in a diary (rhinorrhea, headache) in points using a 10-point visual analogue scale.

On Visit 2 (V_2), a decision on the need of antibiotic therapy was made based on the assessment of the patient's condition according to the established criteria and self-scoring and, together with the patient and/or his/her parents.

The efficacy key factor was: decrease in major symptoms of the disease, assessed according to the MSS scale, at each visit compared with the Visit 1, the dynamics of self-scoring of the symptoms of acute rhinosinusitis, the frequency of antibiotics prescription.

2.5. Sample size

A clinical study has been developed to obtain reliable data on the

efficacy of use of the extract of five medicinal plants in addition to the standard treatment compared to the standard treatment alone. 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.

2.6. Randomization

The clinical part of the randomized study is open, without a blinding procedure. After signing the informed consent, the patients were randomized to treatment groups according to the basic randomization list using a random number generator [StatSoft software]. In order to obtain objective data of statistical analysis, the patients were further divided into two subgroups depending on the diagnosis: acute viral rhinosinusitis and acute post-viral rhinosinusitis.

2.7. Statistical methods

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.

3. Results

3.1. Study sample

304 patients aged 6 to 11 years were enrolled in the study (Fig. 1).

Of the 304 patients enrolled, 12 (3.9%) were not included in the study. The reason was non-compliance with the study inclusion criteria: age non-compliance (n = 2) and the unwillingness of a patient and/or his/her parents to comply with the protocol requirements (n = 10). The rest 292 patients were randomized either to the viral rhinosinusitis subgroup: n – 173 (treatment group n – 97, control group n – 76), or to the post-viral rhinosinusitis subgroup: 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 subgroup and n – 6 from the post-viral RS subgroup) and n – 10 from the control group (n – 4 from the viral RS subgroup and n – 6 from the post-viral RS subgroup). The reason was a protocol violation. These patients data were excluded from the analysis.

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).

3.2. Outcomes and estimation

Typical objective clinical symptoms of acute viral and post-viral rhinosinusitis are nasal discharge (rhinorrhea or post-nasal drip), nasal congestion/obstruction associated with mucosal oedema. Table 2 presents the severity of the principal symptoms in points, evaluated by a physician using a 4-point scale in patients with viral rhinosinusitis. When the physician assessed the symptom of nasal discharge (rhinorrhea), both groups showed comparable severity parameters during V1: 3.35 points in the treatment group and 3.34 in the control group. In the course of treatment, regression of rhinorrhea was observed in patients of both groups at V2: 3.35 to 1.89 points in the treatment group and 3.34 to 2.46 in the control group. At V3, there is a further regression of rhinorrhea in patients of both groups: 0.32 points in the treatment group and 0.49 in the control group. At V4, the severity of rhinorrhea was 0.04 points in the treatment group and 0.11 in the control group. Comparison of regression of rhinorrhea symptoms between groups shows significant differences at V2 ($p < 0.05$) and not significant differences among groups at 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 parameters at V1: 3.18 points in the treatment group and 2.96 points in the control group (Table 2). In the course of treatment, the regression of nasal congestion was observed in patients of both groups at on V2: 3.18 to 1.15 points in the treatment group and 2.96 to 1.46 in the control group. At V3, there is a further regression of nasal congestion in patients of both groups: 0.20 points in the treatment group and 0.29 in the control group. At V4, the severity of nasal congestion was 0.05 points in the treatment group and 0.08 in the control group. Significant differences at V2 ($p < 0.05$) and insignificant differences among groups at 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 parameters at V1: 2.00 points in the treatment group and 1.79 points in the control group (Table 2). In the course of treatment, regression of post-nasal drip was observed in patients of both groups at V2: 2.00 to 1.02 points in the treatment group and 1.79 to 1.51 in the control group. At 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 in the control group. At V4, the severity of post-nasal drip was 0.03 points in the treatment group and 0.00 in the control group.

Significant differences at V2 ($p < 0.05$) and insignificant differences among groups at V1, V3 and V4 ($p > 0.05$) are shown.

Table 3 presents the severity of the principal symptoms in points evaluated by a physician using a 4-point scale in patients with post-viral rhinosinusitis.

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

Comparison of regression of rhinorrhea symptoms between groups shows significant differences at V2 ($p < 0.05$) and not significant differences among groups at V1, V3 and V4 ($p > 0.05$).

When the physician assessed the symptom of nasal congestion, both groups showed comparable severity parameters at V1: 3.77 points in the treatment group and 3.78 points in the control group. In the course of treatment, the regression of nasal congestion was observed in patients of both groups at on V2: 3.77 to 1.40 points in the treatment group and 3.78 to 2.27 in the control group. At V3, there is a further regression of nasal congestion in patients of both groups: 0.07 points in the treatment group and 0.18 in the control group. At V4, the severity of nasal congestion was 0.00 points in the treatment group and 0.00 in the control group. There is a tendency to a more pronounced regression of the symptom in the treatment group Significant differences at V2 ($p < 0.05$) and insignificant differences among groups at V1, V3 and V4 ($p > 0.05$) are shown.

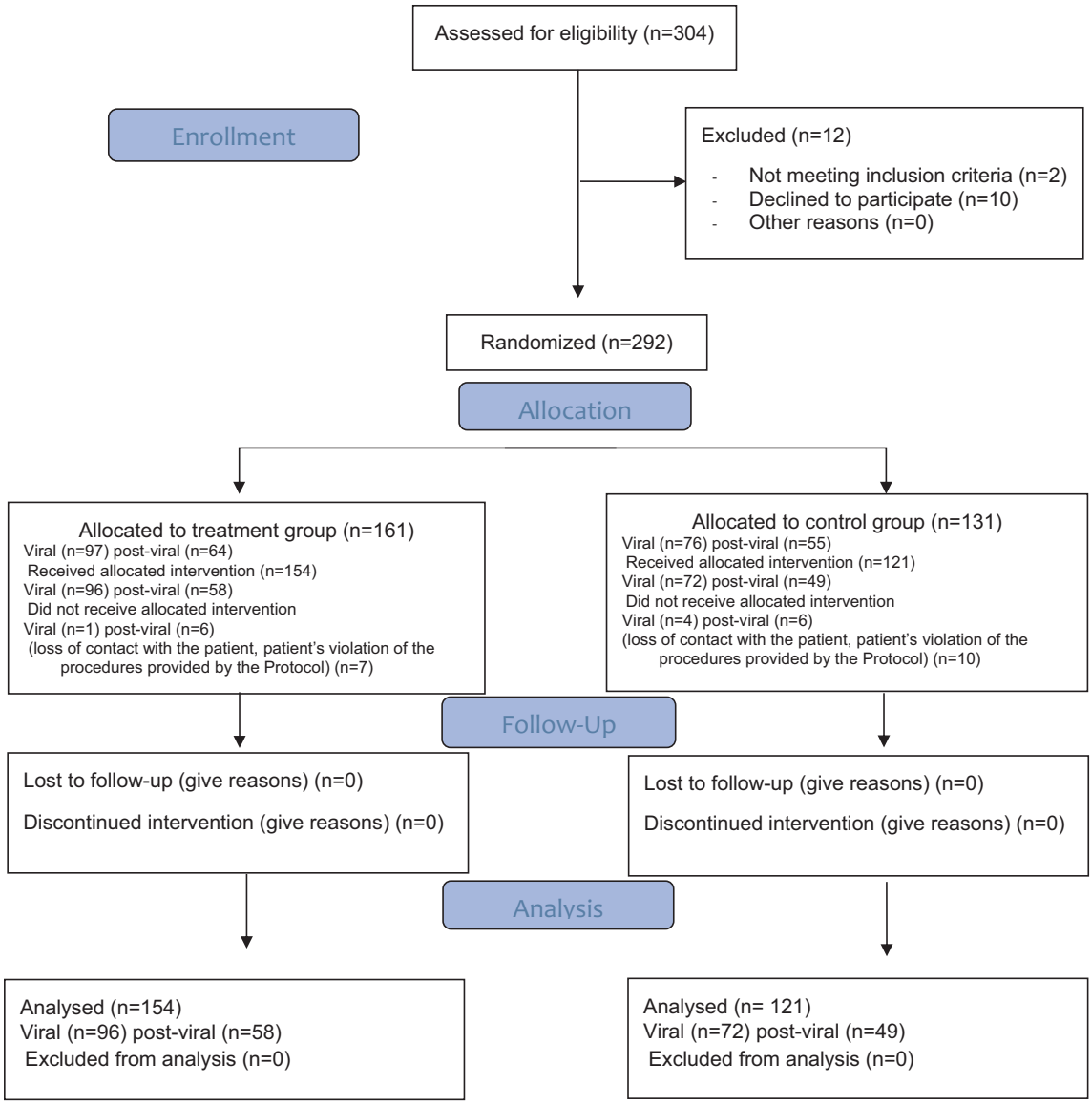

Fig. 1. Patients included in screening, randomization and excluded from the study.

Table 2
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		p-Value (two-sided)/T1-T4	Significant differences[a]
		n	Arithme-tical mean	n	Arithmetical mean		
Rhinorrhea	V 1	97	3.35	76	3.34	0.981	Non-significant
	V 2	97	1.89	76	2.46	0.000	Significant
	V 3	96	0.32	72	0.49	0.447	Non-significant
	V 4	96	0.04	72	0.11	0.421	Non-significant
Nasal congestion	V 1	97	3.18	76	2.96	0.412	Non-significant
	V 2	97	1.15	76	1.46	0.047	Significant
	V 3	96	0.20	72	0.29	0.183	Non-significant
	V 4	96	0.05	72	0.08	0.433	Non-significant
Post-nasal drip	V 1	97	2.00	76	1.79	0.369	Non-significant
	V 2	97	1.02	76	1.51	0.026	Significant
	V 3	96	0.23	72	0.19	0.260	Non-significant
	V 4	96	0.03	72	0.00	0.219	Non-significant

[a] The conclusion is drawn at the significance level of 0.05.

Table 3
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		p-Value (two-sided)/T1-T4	Significant differences*
		n	Arithme-tical mean	n	Arithme-tical mean		
Rhinorrhea	V 1	64	3.88	55	3.87	0.970	Non-significant
	V 2	63	1.49	55	2.29	0.000	Significant
	V 3	58	0.12	49	0.27	0.150	Non-significant
	V 4	58	0.00	49	0.00	1.000	Non-significant
Nasal congestion	V 1	64	3.77	55	3.78	0.834	Non-significant
	V 2	63	1.40	55	2.27	0.000	Significant
	V 3	58	0.07	49	0.18	0.209	Non-significant
	V 4	58	0.00	49	0.00	1.000	Non-significant
Post-nasal drip	V 1	64	2.86	55	2.73	0.370	Non-significant
	V 2	63	0.83	55	1.33	0.000	Significant
	V 3	58	0.00	49	0.00	1.000	Non-significant
	V 4	58	0.00	49	0.00	1.000	Non-significant

*The conclusion is drawn at the significance level of 0.05 ($P < 0.05$)

When the physician assessed the symptom of post-nasal drip both groups with post-viral RS showed comparable severity parameters at V1: 2.86 points in the treatment group and 2.73 points in the control group. In the course of treatment, regression of post-nasal drip was observed in patients of both groups at V2: 2.86 to 0.83 points in the treatment group and 2.73 to 1.33 in the control group. At 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 in the control group.

Significant differences at V2 ($p < 0.05$) and insignificant differences among groups at V1, V3 and V4 ($p > 0.05$) are shown.

Patients, either individually or with the help of parents, evaluated the main complaints on a daily basis in a diary using a ten-point visual-analogue scale. Fig. 2 presents the dynamics of self-scored symptoms of rhinorrhea and headache in patients with viral RS.

According to the self-scoring, there is a regression of rhinorrhea in patients of both groups: 5.46 to 5.22 points on Day 2 and to 4.40 points on Day 3 in patients of the treatment group. Patients in the control group had 4.96 to 4.99 points on Day 2 and up to 4.21 on Day 3. Comparison between groups shows significant differences on the second day and day 3 of treatment ($p < 0.05$). From Day 8, symptoms of rhinorrhea were practically absent in patients of both groups: 0.82 points in the treatment group and 0.97 in the control group.

Dynamics of self-scoring by “headache” symptom has been studied. Patients in the treatment group had 2.11 to 1.96 points on Day 2 and up to 1.25 on Day 3. Patients in the control group had 2.08 to 1.92 points on Day 2 and up to 1.29 on Day 3.

Comparison of rhinorrhea regression according to patient's self-scoring between groups shows significant differences on Day 4 of treatment ($p < 0.05$).

Fig. 3 presents the dynamics of self-scored symptoms of rhinorrhea and headache in patients with post-viral RS.

According to the self-scoring, there is a regression of rhinorrhea in patients of both groups: 3.88 to 3.69 points on Day 2 and to 2.89 points on Day 3 in patients of the treatment group. Patients in the control group had 3.85 to 3.73 points on Day 2 and up to 3.11 on Day 3. Symptoms of rhinorrhea were practically absent in patients of the treatment group starting from Day 9 and were 0.02 points on Day 10 in the control group. A comparison of the rhinorrhea regression shows significant differences from the day 4 to the day 8 (p. 0.05).

Dynamics of self-scoring by “headache” symptom has been studied in patients with post-viral RS. Patients in the treatment group had regression from 2.17 to 1.84 points on Day 2 and down to 1.17 on Day 3.

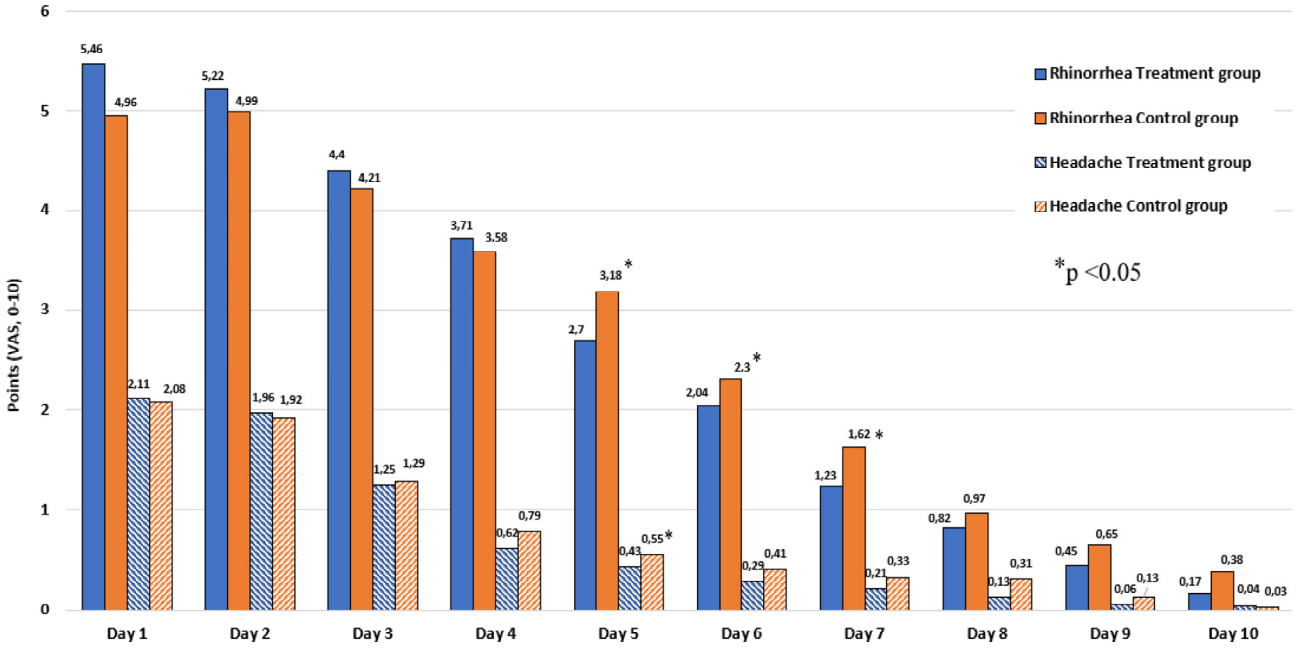

Fig. 2. Symptom self-scoring in points in patients with viral RS.

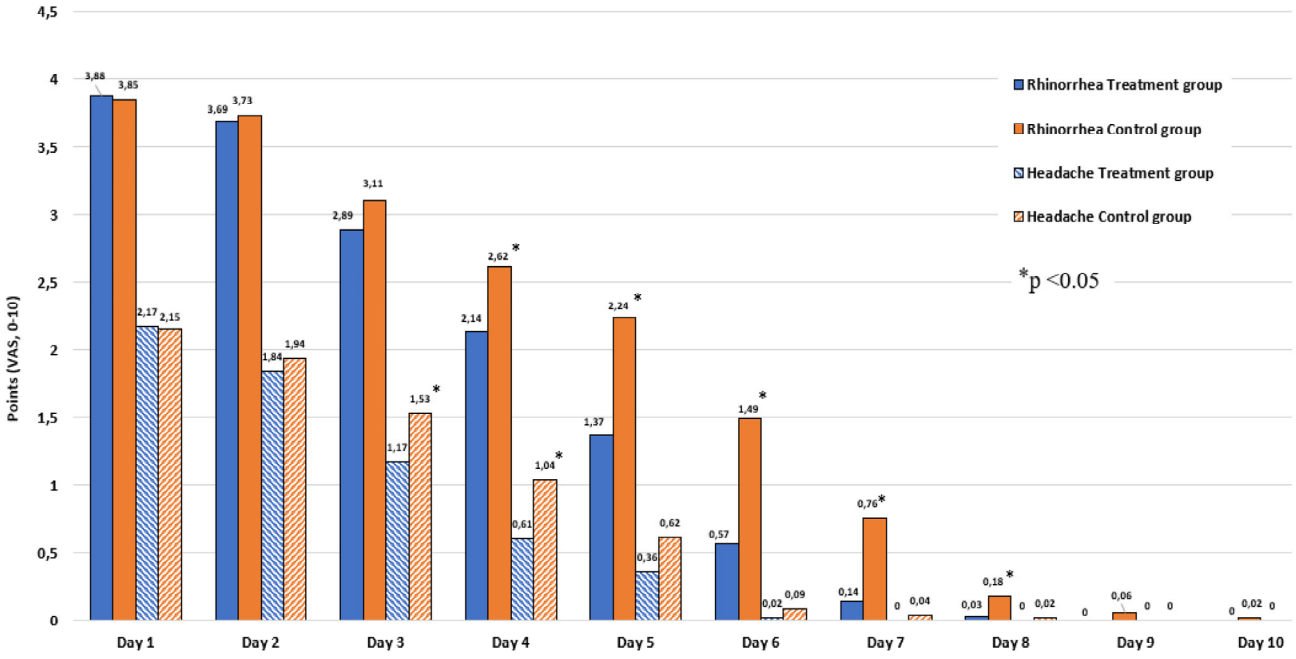

Fig. 3. Symptom self-scoring in points in patients with post-viral RS.

Table 4
Prescription of antibiotics in patients with acute RS.

Nosology	Group	n	Prescription of antibiotics	
			n	%
Acute RS total (n – 275)	Treatment	154	7	4.54%
	Control	121	10	8.26%
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%

Patients in the control group had 2.15 to 1.94 points on Day 2 and up to 1.53 on Day 3. Headache was absent in patients of the treatment group starting from Day 7 and Day 9 in the control group.

Comparison of headache regression shows significant differences from Day 3 to Day 5 of treatment ($p < 0.05$).

According to the study design at V2 (Day 5 of treatment), a comprehensive evaluation of the patient's condition was made and the decision was made on the need for antibiotic therapy. Table 4 presents data on the prescription of antibiotics in patients with acute RS.

Antibacterial therapy was prescribed to 17 (6.18%) of 275 patients with ARS: 7 (4.54%) out of 154 patients in the treatment group and 10 (8.26%) out of 121 in the control group. 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. 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. 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.

3.3. Safety and tolerability

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

4. Discussion

Acute rhinosinusitis includes viral (common cold) and post-viral/non-viral forms. The term “post-viral ARS” was chosen to indicate that the majority of ARS cases are not bacterial. Thus, not > 5% of patients with ARS require antimicrobial therapy. However, antibiotics are also prescribed for acute respiratory infections 4–9-fold more often than recommended by clinical guidelines [6]. One of the strategies to reduce the number of unnecessary prescriptions is to prescribe treatment without antibiotics and active observation within several days to decide, whether the use of antibiotic therapy is feasible.

Many specialists expressed the opinion that the presence of rhinorrhea, post-nasal drip, nasal congestion and headache in patients with acute rhinosinusitis is a driving factor in the unjustified prescription of antibiotics among doctors, as well as the desire for antibiotic therapy among patients [8].

In this study, it was demonstrated that the use of the standardized phytoextract of five medicinal plants in addition to the standard symptomatic therapy of acute rhinosinusitis has a proven therapeutic benefit in the first days of treatment.

Patients of the treatment group with acute viral rhinosinusitis demonstrated a clinically significant, adequate reduction in the severity of symptoms (rhinorrhea, nasal congestion and post-nasal drip) assessed by a physician at V2 compared to the control group ($p < 0.005$). Significant differences were noted in the patient's self-scoring of the severity of rhinorrhea using a 10-point scale on Day 2 or Day 3 of treatment, headache on Day 4 of treatment ($p < 0.005$).

Patients with acute post-viral rhinosinusitis in the treatment group with the addition of the standardized phytoextract demonstrated a clinically significant, adequate reduction in the severity of symptoms (rhinorrhea, nasal congestion and post-nasal drip) assessed by a physician at V2 using a 4-point scale ($p < 0.005$). Significant differences were noted in the patient's self-scoring of the severity of rhinorrhea using a 10-point scale from Day 4 to Day 8 of treatment, headache from Day 3 to Day 5 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 at V3, i.e. by Day 7 of treatment, 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.

These findings reflect the few literature data, which demonstrate that Sinupret® is effective for acute rhinosinusitis in adults and children [15–18]. The results obtained in these studies demonstrated that in the active treatment group, by Day 10 acute rhinosinusitis symptoms improvement occurred, which was observed in the placebo group only by Day 14. The positive effect on the clinical symptoms of ARS is confirmed by the previously obtained data showing that the standardized phytoextract enhances the activity of ciliary epithelium in vitro [10].

One of the most important symptoms of ARS in terms of the quality of patient's life is headache. In viral rhinosinusitis, headache is mainly due to the toxic effect of viruses and reactive nasal and sinus 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 Day 4 with acute viral rhinosinusitis and on Day 3 of treatment with post-viral RS ($p < 0.005$). The obtained clinical effect, especially in post-viral RS, when the oedematous-inflammatory changes of the nasal and sinus mucosa are particularly pronounced, is confirmed by previously obtained data on the anti-oedematous and anti-inflammatory properties of Sinupret in vivo [11].

Thus, an important and interesting conclusion of the study is that the use of the standardized phytoextract of five medicinal plants in patients with acute rhinosinusitis leads to a pronounced, significant regression of such important symptoms as rhinorrhea, post-nasal drip, nasal congestion and headache by V2 compared to the control ($p < 0.005$). The similar results in patients of the control group were achieved at V3. A “therapeutic benefit” from the use of phytoextract is three days with a seven-day observation period.

Many researchers have expressed the opinion that the presence of rhinorrhea 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 [8]. The proven efficacy of the standardized phytoextract regarding the indicated symptoms is an important argument for reducing the desire of patients and physicians to prescribe antibiotics due to weak symptom regression, especially in the first days of treatment.

According to the design, our study did not include patients requiring immediate prescription of antibiotic therapy. The decision on prescription of antibiotics was made after evaluation the dynamics of symptom regression at V2. In cases of weak dynamics of symptom regression or its absence, antibiotic therapy was prescribed. In fact, the prescription of antibiotic therapy is a confirmation that the patient has diagnostic criteria for acute bacterial rhinosinusitis. In our study, 17 (6.18%) out of 275 patients with ARS were prescribed with antibiotics. The obtained results correspond to the literature data, according to which bacterial RS is found in 0.5–5% of ARS cases [2,3,6].

7 out of 154 patients (4.54%) in the treatment group were prescribed with antibacterial therapy, and 10 out of 121 (8.26%) in the control group. Thus, the use of the standardized phytoextract of five medicinal plants in the strategy of preventing unreasonable antibiotic therapy in patients with acute rhinosinusitis 1.81-fold reduces its prescription.

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, antibacterial therapy was prescribed only to 6 out of 168 patients with acute viral RS (3.57%). 2 out of 96 patients (2.08%) in the treatment group were prescribed with antibacterial therapy, and 4 out of 72 (5.55%) in the control group. Thus, the use of the standardized phytoextract in patients with acute viral rhinosinusitis can 2.7-fold reduce the prescription of antibacterial drugs.

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, i.e. in post-viral RS. However, in present guidelines, the term “post-viral ARS” has been chosen to indicate that the majority of ARS cases are not bacterial. In our study, 11 (10.28%) out of 107 patients with post-viral RS were prescribed with antibiotic therapy. 5 patients out of 58 (8.62%) in the treatment group required antibiotic therapy and 6 out of 49 (12.24%) patients in the control group. Thus, the use of the standardized phytoextract in patients with acute post-viral rhinosinusitis can 1.4-fold reduce the prescription of antibacterial drugs.

An important conclusion of the study is that the use of the standardized phytoextract of five medicinal plants BNO 1012 in patients with acute rhinosinusitis almost 2-fold reduces the need for antibiotic therapy: from 8.26% to 4.54%.

However, according to literature data, unreasonable antibacterial therapy is prescribed from 54% to 77% of ARS cases [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 starting treatment without antibiotics in cases, where there are no absolute indications for their prescription. This will significantly reduce the number of unreasonable prescriptions of antibacterial drugs.

The efficacy of the standardized phytoextract described in this study generally confirms the results of earlier studies in patients with acute rhinosinusitis [15–18]. 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, who responded to treatment at V2, was significantly higher in treatment groups vs. control groups.

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 a mandatory prescription of symptomatic therapy alone using irrigation therapy and, if indicated, acetaminophen [2,19]. The effect of symptomatic therapy can be considered equivalent in groups. Consequently, all the differences between treatment results can be attributed to the clinical effects of the standardized phytoextract BNO 1012, since the group characteristics were comparable.

5. Conclusions

It was shown that in addition to standard symptomatic therapy, the use of the standardized phytoextract of five plants BNO 1012 (Sinupret®) for the treatment of acute rhinosinusitis provides a significant clinical effect in the first 3–4 days of treatment. Reliably compared with the control, the clinical symptom severity is reduced. The “therapeutic benefit” within three days reduces the need for prescription of antimicrobial drugs. The inclusion of the drug in the treatment regimen may be recommended for patients with acute rhinosinusitis as part of the strategy of the starting treatment without antibiotics in cases, where there are no absolute indications for their prescription. This will significantly reduce the number of unreasonable prescriptions of antibacterial drugs.

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

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