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A randomized, open-label, multicenter, comparative study of therapeutic efficacy, safety and tolerability of BNO 1030 extract, containing marshmallow root, chamomile flowers, horsetail herb, walnut leaves, yarrow herb, oak bark, dandelion herb in the treatment of acute non-bacterial tonsillitis in children aged 6 to 18 years

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ABSTRACT

Seventy to 95% of acute tonsillitis episodes are caused by viral infection, therefore why antibiotic therapy is not indicated in majority of cases. In such cases, acetaminophen or ibuprofen are used to alleviate the symptoms. The objective of this study was assessment of efficacy of phytoneering extract BNO 1030 (Imupret®) in patients with acute non-bacterial tonsillitis.

Methods: This randomized, open-label, multicenter, comparative study randomised 238 outpatients aged 6–18 years to receive either BNO 1030 (Imupret®) as a supplement to standard symptomatic therapy, or standard therapy. Assessment criteria were as follows: sore throat dynamics at rest and at swallowing, throat irritation associated with cough, general condition, day of withdrawal of antipyretics, the share of treatment responders, as well as assessment of "therapeutic benefit" from the use of BNO 1030.

Results: Decreased intensity of acute tonsillitis symptoms to 1 point and lower, assessed using 4-point scale starting from the day 5 of treatment ($p < 0.005$), alleviation of local symptoms and general condition starting from day 2 of the disease ($p < 0.001$), withdrawal of antipyretics starting from day 4 of treatment ($p < 0.005$), increase of the number of treatment responders to 81.6% ($p < 0.005$) versus the control were reported. "Therapeutic benefit" was 4.2 days. All patients tolerated phytotherapy well, and no adverse reactions were seen.

Conclusion: BNO 1030 (Imupret®) is a safe and effective product for treatment of acute non-bacterial tonsillitis in children aged 6–18 years, assuring therapeutic benefit when prescribed additionally to the standard symptomatic therapy.

1. Introduction

Acute tonsillitis (AT) (J03.0–J03.9) is defined as sudden onset of typical clinical symptoms, including sore throat with or without swallowing difficulty, hyperaemia, enlargement of tonsils with potential presence of plaque, enlargement of cervical lymph nodes, fever, general weakness. Such patients account for about 5% visits to a doctor, and 50% of them are aged 5 to 15 years [1]. Seventy to 95% of AT episodes are caused by viral infections. Bacterial (Streptococcal) AT develops in immunocompetent children in 15–30% of the cases, and in adults in 5–15% of the cases. Thus, in majority of AT cases, antibiotic therapy is not indicated [2,3]. Until present, no single standard parameter is available for differential diagnosis between viral and bacterial tonsillitis. Based on complex differentiation between viral and bacterial aetiology, McIsaac Scale has been suggested for patients aged 3 to 14 years, and Centor Scale has been suggested for patients over 15 years old; these scales assess the presence or the absence of several history data and clinical symptoms and are expressed as total score. The score of −1 to 3 points according to McIsaac Scale and 0 to 2 points according to Centor Scale is indicative of high probability of viral tonsillitis [1,4].

In such cases, acetaminophen or ibuprofen is successful used to

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alleviate the symptoms [1,5,6]. Nevertheless, the said symptomatic agents do not cover the whole spectrum of AT pathogenetic mechanisms, which is the main cause of recurrence, despite good immediate symptomatic effect. Based on this fact, there is a need in drug products with complex effect on the main pathogenesis links.

Main symptom of tonsillitis is sore throat that is a driving force of both unreasonable antibiotics prescription by physicians and willingness to use antibacterial therapy by patients themselves. Though, the unreasonable etiotropic therapy does not influence on this symptom dynamic. But is one of the main reasons of the global problem of antibiotic resistance [2].

Due to these data, use of phytomedicines could be interesting, as, according to the studies. Medical plant medicines ready-to-use is used in tonsillopharyngites therapy by 28% of physicians [7]. Echinacea preparations are the best studied in this respect. Nevertheless, randomized studies have not proven the efficacy of Echinacea in patients with acute tonsillitis [1]. *Pelargonium sidoides* has shown the efficacy in treatment of cold symptoms, but no data are available regarding patients with tonsillitis [8].

Sparsity of GCP-compliant studies of the efficacy of phytotherapy is obvious; nevertheless, the situation has changed after issuance of relevant recommendations [9]. A phytoneering aqueous-alcohol extract BNO 1030, comprising seven medicinal plants: marshmallow root (*Radix althaeae*), chamomile flowers (*Flores chamomillae*), horsetail herb (*Herba equiseti*), walnut leaves (*Folia jungladis*), yarrow herb (*Herba millefolii*), oak bark (*Cortex quercus*), and dandelion herb (*Herba taraxaci*), known as Imupret® (also known as Tonsilgon® N in some countries), is used in clinical practice. Imupret, unlike the traditional plant medicines, is an official medication and allowed for sale in pharmacies in Germany, Ukraine and other countries 16 of the world. In the US the drug is not available yet.

The drug product ingredients exert antiviral, antibacterial, anti-inflammatory and immunomodulatory effects [10–16], and its therapeutic indications are: “treatment of diseases of upper airways (tonsillitis, pharyngitis, laryngitis) and prevention of complications and recurrences in viral respiratory infections”. Clinical studies in children included so far the efficacy and preventive effects in children with common colds, as well as treatment of viral respiratory infections [17–20]. Still, scientific literature lacks the reports of valid (from the viewpoint of compliance with GCP standards) studies of efficacy of Imupret® in therapy of acute tonsillitis.

The objective of this study was assessment of the efficacy of phytoneering extract BNO 1030 (Imupret®) compared to patients receiving standard symptomatic therapy of AT in accordance with recommendations of national guidelines [21].

2. Materials and methods

2.1. Trial design

A randomized, open-label, exploratory, comparative, multicentre, prospective, parallel-group study was conducted in six outpatient institutions of Ukraine since June 2017 till March 2018. The study was conducted in accordance with GCP standards and the Declaration of Helsinki. Besides, before enrolment of the first patient, the study was approved by local Ethics Committee and local ethics committees at all study sites. Before inclusion to the study, parents/legal representatives of each child provided written informed consent for child's participation in the study.

2.2. Subjects

250 outpatients were selected, and 238 outpatients were randomized to the study; these patients were aged 6–18 years, and they were diagnosed with acute non-bacterial tonsillitis. The patients were divided into two groups depending on the therapy chosen: the treatment group – patients receiving BNO 1030 – standardized extract of seven medicinal plants (Imupret®) in addition to standard therapy, and the control group receiving standard symptomatic therapy. The treatment group (n = 118) included 52 (44.1%) boys and 66 (55.9%) girls (the mean age was 8.67 ± 3.219), and the control group included 62 (51.7%) boys and 58 (48.3%) girls (the mean age was 9.66 ± 3.296).

Diagnostic and differential-diagnostic criteria of acute tonsillitis conformed to DEGAM recommendations, stated in national clinical guidelines [1,21,22]. Clinical diagnosis of AT was established based on the presence of such symptoms as sore throat at rest and at swallowing, hyperaemia and swelling of tonsils with possible plaque on tonsils, cervical lymphadenitis and pyrexia. Non-bacterial tonsillitis was diagnosed provided the score was −1 to 3 points when assessed according to McIsaac Scale for patients aged 3 to 14 years, and 0 to 2 points according to Centor Scale for patients over 15 years old.

Inclusion criteria: male and female subjects aged 6 to 18 years, undergoing outpatient therapy with the diagnosis “acute non-bacterial tonsillitis”, possibility to start therapy within 72 hours since the onset of the disease symptoms, score of −1 to 3 points according to McIsaac Scale for patients aged 3 to 14 years, score of 0 to 2 points according to Centor Scale for patients over 15 years old, preparedness and ability of patient and (or) his/her parents to fulfil the requirements of the Study Protocol, and signed informed consent.

Patient withdrawal criteria from the study: decision of patient and (or) his/her parents to discontinue participation in the study and withdrawal of written informed consent; loss of contact with a patient, individual intolerability of the study drug and the reference treatment scheme; development of serious and/or unexpected adverse events/reactions in a patient during the study; considerable worsening of general condition, development of underlying disease complications, which, at physician's discretion, require patient's withdrawal from the study; violation of Protocol-provided procedures by patient; prescription of systemic antibiotic therapy.

2.2.1. Exclusion criteria

Score of 3–5 points according to McIsaac Scale, 3–4 points according to Centor Scale, presence of indications for immediate commencement of systemic antibiotic therapy, suspected infectious mononucleosis (by clinical signs), use of systemic antibacterial or antifungal agents, systemic glucocorticosteroids, cytostatics within the last 14 days; intolerability or individual hypersensitivity to any of ingredient of the drug product and reference treatment scheme.

Patients of the two groups were comparable in terms of sex, age, and clinical manifestations of the disease ($p < 0.05$).

2.3. Interventions

Since randomization, patients of the two groups were prescribed with sparing diet, elimination of irritants (physical and chemical); acetaminophen as antipyretic agent in age-specific doses (in the presence of relevant indications — pain, serious hyperthermia), benzydamine hydrochloride oral spray: 0.255 μg of benzydamine hydrochloride — 1 actuation. The dose is 4 actuations 3–4 times daily for 10 days. Patients of the treatment group were additionally prescribed with BNO 1030 (Imupret®) — oral drops in the following doses: in acute disease manifestations (first 5 days): children aged 6–11 years received 15 drops 6 times daily; children aged 12 years and over received 25 drops 6 times daily. After alleviation of acute disease manifestations (days 5 to 10): children aged 6–11 years received 15 drops 3 times daily, and children aged 12 years and over received 25 drops 6 times daily.

BNO 1030 oral drops represent standardized alcohol-aqueous extract. *Active substances*: 100 g of the drops contain 29 g of an alcohol-aqueous extract (extracting agent: ethanol 59% (V/V) produced from the following medicinal plants:

Marshmallow root (*Radix althaeae*): 0.4 g;

Chamomile flowers (*Flores chamomillae*): 0.3 g;

Horsetail herb (*Herba equiseti*): 0.5 g;
Walnut leaves (*Folia jungladis*): 0.4 g;
Yarrow herb (*Herba millefolii*): 0.4 g;
Oak bark (*Cortex quercus*): 0.2 g;
Dandelion herb (*Herba taraxaci*): 0.4 g;
Excipients: ethanol 19% (V/V), purified water.

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

The drug product is registered in Ukraine and available over the counter. Thus, its formulation, manufacturing, packaging and labelling conform to the principles of Good Manufacturing Practice and valid national requirements of Ukraine. Detailed description covering all aspects pertinent to quality and safety of BNO 1030 drops is a part of relevant characteristics of the drug product.

In Ukraine, approved therapeutic indications of the medicinal product include treatment of diseases of upper airways (tonsillitis, pharyngitis, laryngitis) and prevention of complications and recurrences in respiratory viral infections.

Medical practitioners — ENT-specialists with work experience not less than 5 years were engaged in the study.

2.4. Outcome measures

All the data were assessed by a physician at the baseline and at three subsequent visits during 10 days (Table 1).

Symptoms included to the scale of local tonsillitis manifestations were assessed at each visit: hyperaemia of posterior pharyngeal wall, hyperaemia, swelling, and plaque on tonsils, sore throat at rest and at swallowing, throat irritation associated with cough. All symptoms were assessed according to 4-point scale (0 — absent, 1 — mild, 2 — moderate, 3 — severe/pronounced). Besides, patient's general condition was assessed by physician at each visit according to 10-point visual-analogue scale. Patients in their diaries assessed their complaints such as sore throat at rest and at swallowing, throat irritation, cough, and general condition according to 10-point visual-analogue scale on a daily basis. At visit 2 (V_2), a physician assessed patient's condition and took the decision on antibacterial therapy prescription.

The primary efficacy criteria were as follows: decrease in severity of the disease symptoms assessed using a point scale at each visit versus visit 1, dynamics of assessment by physician and self-assessment by patient of general condition, dynamics of self-assessment of tonsillitis symptoms by patient. Secondary criteria were as follows: decrease in total score (the total of points for each symptom) by point scale of local tonsillitis manifestations at each visit versus visit 1, dynamics of use of antipyretics, as well as assessment of “therapeutic benefit” from the use of BNO 1030.

2.5. Sample size

The clinical study was developed to obtain reliable description of *in vivo* efficacy of active (supplementary) use of BNO 1030 versus reference standard therapy only. Depending on the data collected, several trial descriptive and statistical assessments were performed; therefore, biometric assessment of sample size is not required. Nevertheless, in order to assure sufficient sample size for analysis of the data obtained, sample size N = 250 was selected. Patients were randomised at 1:1 ratio.

2.6. Randomization

Clinical part of the randomized study was open-label, without blinding procedure. The subjects were randomly allocated to one of the two possible treatment arms in accordance with basic randomization list. Randomization was performed using the software [StatSoft — random number generator]. Randomization was performed for each patient signing the informed consent.

2.7. 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 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 independent 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

Table 1
Schedule of assessments.

V1		V2		V3					V4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Study group 1									
Imupret (acute dosage phase)					Imupret (subacute dosage phase)				
Reference treatment									
Study group 2									
Reference treatment									

V1: day 1, screening, randomization, prescription of treatment.
V2: after 36–48 h, status evaluation, possible prescription of antibiotics.
V3: day 5 ± 1, evaluation of treatment efficacy.
V4: day 10 ± 1, evaluation of treatment efficacy.

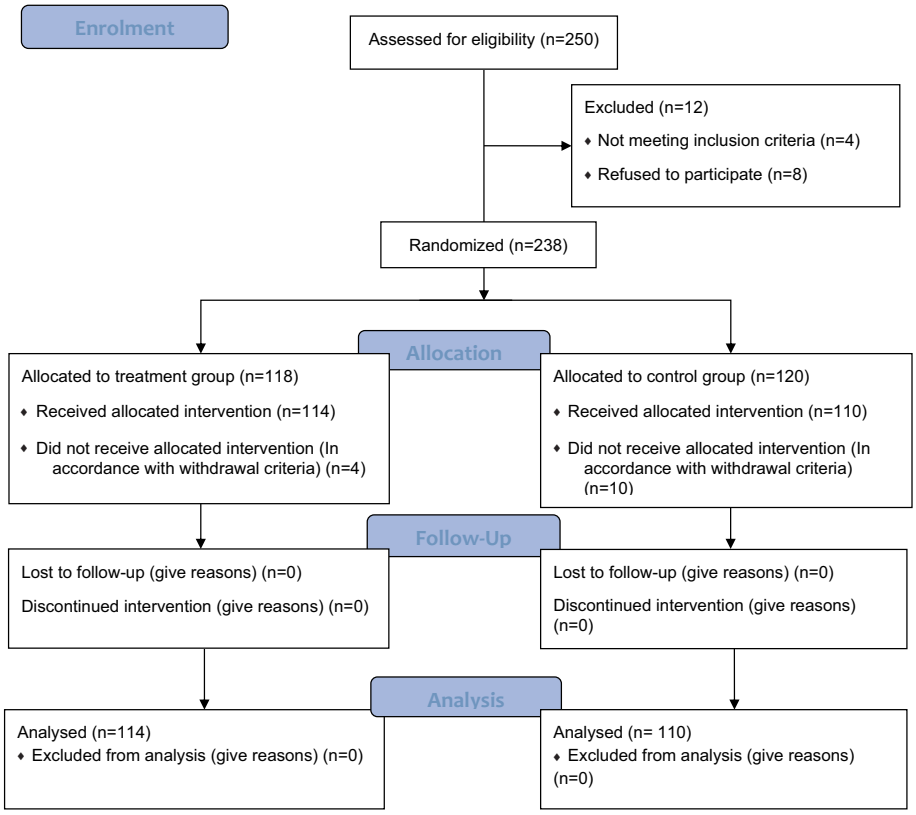

Fig. 1. Patients included to screening, randomization, and withdrawn from the study.

3. Results

3.1. Study sample

Two hundred and fifty patients aged 6–18 years were selected for participation in the study (Fig. 1)

Twelve (4.8%) out of 250 patients were excluded from the study. The reasons were non-compliance with study inclusion criteria: age beyond the age-specific criteria (n = 4) and unwillingness of patient and (or) his/her parents to fulfil the protocol requirements (n = 8). The remaining 238 patients were randomized either to control group (n = 120), or to the treatment group (n = 118). At day 2, 14 patients (11.7%) were withdrawn from the study. The cause was the presence of study withdrawal criteria (prescription of systemic antibiotic therapy): (n = 10) from the control group and (n = 4) from the treatment group. Thus, from June 2017 till March 2018, 224 (94.1%) out of 238 randomized patients (n = 114 in the treatment group) and (n = 110 in the control group) completed the study in full and were analysed.

Table 2 shows distribution of patients of both groups in terms of sex: in the treatment group, 52 (45.6%) out of 114 patients were boys, and 62 (54.4%) were girls; in the control group, 54 (49.1%) out of 110 patients were boys, and 56 (50.9%) were girls.

In general, there were somewhat more girls than boys (52.6% vs 47.3%) among the study subjects. Table 3 shows distribution of patients of both groups by age: the mean age of patients was 9.16 years: 8.67 ± 3.219 in the treatment group and 9.66 ± 3.296 in the control group.

Table 2
Distribution of patients by sex.

Parameter	Group	Statistical parameters		
		n	Boys	Girls
Sex	Treatment	114	52 (45.6%)	62 (54.4%)
	Control	110	54 (49.1%)	56 (50.9%)
In total		224	106 (47.3%)	118 (52.6%)

Table 3
Distribution of patients by age.

Parameter	Group	Statistical parameters			
		n	M ± SD	p-Value	Homogeneity of groups*
Age, years	Treatment	114	8.67 ± 3.219	0.071	Homogeneous
	Control	110	9.66 ± 3.296		

* The conclusion is made at the level of significance 0.05.

In general, there were no significant differences between baseline (day 1) demographic characteristics of patients of the treatment and control group ($p > 0.05$).

Table 4 shows comparative characteristics of the treatment and control group by 4-point assessment of severity of symptoms included to the scale of local tonsillitis manifestations.

No significant differences in terms of baseline (day 1) local tonsillitis manifestations: hyperaemia of posterior pharyngeal wall, hyperaemia, swelling, and plaque of tonsils, sore throat at rest and at swallowing, throat irritation associated with cough, were seen between patients of the treatment and control group ($p > 0.05$).

Table 5 shows comparative characteristics of the treatment and control group by 10-point assessment by physician and self-assessment by patient of general condition, and self-assessment of severity of tonsillitis symptoms by patient.

No significant differences in baseline (day 1) assessment of general condition by physician and self-assessment by patient, as well as self-assessment of severity of tonsillitis symptoms by patient: sore throat at rest and at swallowing, throat irritation associated with cough, were seen between patients of the treatment and control group ($p > 0.05$).

Table 4
Analysis of the groups according to the local symptom severity at the baseline.

Parameter (0–4 points)	Group	Statistical parameters			
		n	M ± SD	p-Value	Homogeneity of the groups*
Hyperaemia of the posterior wall	Treatment	114	2.88 ± 0.926	p = 0.719	Homogeneous
	Control	110	2.85 ± 0.877		
Hyperaemia of the tonsils	Treatment	114	2.81 ± 1.033	p = 0.497	Homogeneous
	Control	110	2.74 ± 0.957		
Swelling, plaque	Treatment	114	2.51 ± 1.044	p = 0.537	Homogeneous
	Control	110	2.59 ± 0.948		
Pain (swallowing)	Treatment	114	2.25 ± 0.776	p = 0.352	Homogeneous
	Control	110	2.18 ± 0.618		
Pain (rest)	Treatment	114	1.97 ± 0.733	p = 0.083	Homogeneous
	Control	110	1.93 ± 0.570		
Throat irritation	Treatment	114	1.60 ± 0.741	p = 0.169	Homogeneous
	Control	110	1.70 ± 0.616		

* The conclusion is drawn at the significance level of 0.05.

3.2. Outcomes and estimation

The main clinical manifestation most essential for a patient with acute tonsillitis is sore throat. Table 6 shows the assessment of dynamics of the symptom “sore throat at rest and at swallowing” in patients of both groups.

During therapy, regression of the symptom “sore throat at swallowing” was seen in patients of both groups: from 2.25 ± 0.776 points to 1.01 ± 0.910 (−55%) at day 5 and to 0.30 ± 0.544 (−88%) at day 10 in patients of the treatment group and from 2.18 ± 0.618 points to 1.31 ± 0.994 (−40%) at day 5 and to 0.54 ± 0.709 (−75%) at day 10 in patients of the control group. Hence, the additional Imupret use in standard therapy facilitates ‘swallowing sore throat symptom’ regress to 55% in comparison to 40% while standard therapy by 5th day. Comparison of regression parameters of “sore throat at swallowing” symptom between groups shows reliable differences at days 5 and 10 of treatment ($p < 0.05$).

When comparing the dynamics of symptom “sore throat at rest”, regression of this symptom was also seen in patients of both groups: from 1.97 ± 0.733 points to 0.91 ± 0.877 (−53.8%) at day 5 and to 0.19 ± 0.391 points (−90%) at day 10 in the treatment group. In the control group, it was decreased from 1.93 ± 0.570 points to 1.07 ± 0.877 (−44%) at day 5 and to 0.38 ± 0.597 (−80.3%) at day 10. Comparison of regression parameters of “sore throat at rest” symptom between groups shows significant differences at days 5 and 10 of treatment ($p < 0.05$).

Patients assessed their complaints in a dairy according to ten-point visual-analogue scale on a daily basis. Table 7 shows assessment of dynamics of the symptom “sore throat at rest and at swallowing” in patients of both groups.

In accordance with self-assessment, regression of the symptom “sore throat at swallowing” is seen in patients of both groups: from 5.90 ± 2.236 to 4.93 ± 2.371 points (−16.4%) at day 2 and to 1.33 ± 1.751 points (−77.5%) at day 10 in patients of the treatment group. In patients of the control group, it regressed from 5.51 ± 2.021 points to 4.90 ± 2.368 (−11.1%) at day 2 and to 2.40 ± 1.765 (−56.4%) at day 10.

Similar self-assessment dynamics was seen by the symptom “sore throat at rest”. In patients of the treatment group, the symptom regressed from 4.89 ± 2.179 points to 3.97 ± 2.350 (−18.8%) points at day 2 and to 0.88 ± 1.573 (−82.0%) at day 10. In patients of the control group, it regressed from 4.50 ± 1.922 points to 3.98 ± 2.055 (−11.6%) at day 2 and to 1.93 ± 1.834 (−57.1%) at day 10. Comparison of regression parameters of “sore throat at swallowing” symptom in accordance with patient's self-assessment between groups shows significant differences from day 2 to day 10 of treatment ($p < 0.05$)

It is well known that the presence of such symptom as throat irritation associated with cough is one of differential signs of viral (non-bacterial) tonsillitis. Patients of both groups performed self-assessment of severity of this symptom during therapy (Table 7). Regression of this symptom was seen in patients of the treatment group from 3.89 ± 2.175 to 3.32 ± 1.966 points (−14.7%) at day 2, to 1.74 ± 1.800 (−55.3%) at day 5, and to 0.80 ± 1.600 points (−79.4%) at day 10. In patients of the control group, it regressed from 4.02 ± 1.756 to 3.61 ± 1.767 points (−10.2%) at day 2, to 2.40 ± 1.872 (−40.3%) at day 5, and to 1.67 ± 1.710 points (−58.5%) at day 10. Comparison of regression dynamics of the symptom “throat irritation associated with cough” in patients of both groups shows significant difference at day 5 of treatment ($p < 0.05$). Beginning from day 6, no significant differences in regression rate of this symptom were observed ($p > 0.05$). Thus, the treatment group

Table 5
Analysis of the groups according to assessment values.

Parameter (0–10 points)	Group	Statistical parameters			
		n	M ± SD	p-Value	Homogeneity of the groups*
Physician's assessment of general condition	Treatment	114	6.36 ± 1.902	p = 0.053	Homogeneous
	Control	110	5.68 ± 1.961		
Patient's self-assessment, VAS	Treatment	114	6.30 ± 1.882	p = 0.069	Homogeneous
	Control	110	5.94 ± 1,616		
Pain at swallowing (self-assessment, VAS)	Treatment	114	5.90 ± 2.236	p = 0.089	Homogeneous
	Control	110	5.51 ± 2.021		
Pain at rest (self-assessment, VAS)	Treatment	114	4.89 ± 2.179	p = 0.120	Homogeneous
	Control	110	4.50 ± 1.922		
Throat irritation (self-assessment, VAS)	Treatment	114	3.89 ± 1.175	p = 0.498	Homogeneous
	Control	110	4.02 ± 1.756		

* The conclusion is drawn at the significance level of 0.05.

Table 6
Group-dependent dynamics of "sore throat" symptom.

Parameter	Statistical parameters							
	Visit	Treatment group (n = 114)		Control group (n = 110)		Comparison of the groups		
		M ± SD	Regression (%)	M ± SD	Regression (%)	dT	p-value	Significant differences*
Pain (swallowing)	Day 1	2.25 ± 0.776	–	2.18 ± 0.618	–	–	–	–
	Day 5	1.01 ± 0.910	−55	1.31 ± 0.994	−40	dT_5	p = 0.001	Significant
	Day 10	0.30 ± 0.544	−88	0.54 ± 0.709	−75	dT_{10}	p = 0.003	Significant
Pain (rest)	Day 1	1.97 ± 0.733	–	1.93 ± 0.570	–	–	–	–
	Day 5	0.91 ± 0.877	−53.8	1.07 ± 0.877	−44	dT_5	p = 0.002	Significant
	Day 10	0.19 ± 0.391	−90	0.38 ± 0.597	−80.3	dT_{10}	p = 0.000	Significant

* The conclusion is drawn at the significance level of 0.05.

shows more rapid regression of throat irritation associated with cough.

Acute tonsillitis is a disease always associated with worsening of general condition. We carried out assessment of dynamics of this parameter according to the results of physician's assessment and patient's self-assessment using 10-point scale (Table 8).

As can be seen from the table, assessment of general condition by physician in the treatment group showed the improvement of this parameter from 6.36 ± 1.902 points to 3.09 ± 2.463 (−51.4%) at day 5 and to 1.04 ± 1.553 points (−83.6%) at day 10. In the control group, improvement of general condition was seen from 5.68 ± 1.961 points to 3.29 ± 2.526 (−42.1%) points at day 5 and to 1.52 ± 1.724 points (−73.2%) at day 10 of treatment. Comparison of dynamics parameters of improvement of patient's general condition according to physician's assessment has shown significant difference between groups at day 5 and 10 of treatment ($p < 0.05$).

Similar parameters were seen in patient's self-assessment of his/her condition: from 6.30 ± 1.882 points at day 1 to 1.66 ± 1.860 (−73.7%) at day 10 in the treatment group and from 5.94 ± 1.616 points at day 1 to 2.72 ± 1.565 (−54.2%) at day 10 in the control group. Comparison of self-assessment parameters shows significant difference ($p < 0.05$) in parameters between groups, beginning from the day 2 and till day 10 of treatment.

We carried out comparison between groups in number of treatment responders versus non-responders (decrease in total score according to the scale of main tonsillitis manifestations to 4 and lower) (Table 9).

At day 10, 93 out of 114 patients of the treatment group responded to therapy, and 21 did not respond (81.6% versus 18.4%); among 110 patients of the control group, 72 were responders, and 38 were non-

Table 7
Dynamics of tonsillitis symptoms according to patients' self-assessment.

Parameter	Visit	Statistical parameters						
		Treatment group (n = 114)		Control group (n = 110)		Comparison of the groups		
		M ± SD	Regression (%)	M ± SD	Regression (%)	dT	p-Value	Significant differences*
Pain at swallowing (self-assessment, 0–10 points, VAS)	Day 1	5.90 ± 2.236	–	5.51 ± 2.021	–	–	–	Sign
	Day 2	4.93 ± 2.371	−16.4	4.90 ± 2.368	−11.1	dT_2	p < 0.001	Sign
	Day 3	4.05 ± 2.449	−31.4	4.29 ± 2.574	−22.1	dT_3	p < 0.001	Sign
	Day 4	3.12 ± 2.509	−47.1	3.59 ± 2.571	−34.8	dT_4	p < 0.001	Sign
	Day 5	2.56 ± 2.386	−56.6	3.33 ± 2.548	−39.6	dT_5	p < 0.001	Sign
	Day 6	2.21 ± 2.246	−62.5	3.08 ± 2.321	−44.1	dT_6	p < 0.001	Sign
	Day 7	2.54 ± 2.119	−56.9	3.03 ± 2.139	−45.0	dT_7	p < 0.001	Sign
	Day 8	2.02 ± 1.775	−65.8	2.62 ± 1.930	−52.5	dT_8	p < 0.001	Sign
	Day 9	1.69 ± 1.754	−71.4	2.56 ± 1.826	−53.5	dT_9	p < 0.001	Sign
	Day 10	1.33 ± 1.751	−77.5	2.40 ± 1.765	−56.4	dT_{10}	p < 0.001	Sign
Pain at rest (self-assessment, 0–10 points, VAS)	Day 1	4.89 ± 2.179	–	4.50 ± 1.922	–	–	–	Sign
	Day 2	3.97 ± 2.350	−18.8	3.98 ± 2.055	−11.6	dT_2	p < 0.001	Sign
	Day 3	3.14 ± 2.384	−35.8	3.45 ± 2.280	−23.3	dT_3	p < 0.001	Sign
	Day 4	2.46 ± 2.276	−49.7	2.83 ± 2.210	−37.1	dT_4	p < 0.001	Sign
	Day 5	2.06 ± 2.161	−57.9	2.54 ± 2.223	−43.6	dT_5	p < 0.001	Sign
	Day 6	1.82 ± 2.118	−62.8	2.34 ± 2.139	−48.0	dT_6	p < 0.001	Sign
	Day 7	1.96 ± 1.943	−59.9	2.29 ± 1.973	−49.1	dT_7	p < 0.001	Sign
	Day 8	1.70 ± 1.720	−65.2	2.12 ± 1.864	−52.9	dT_8	p < 0.001	Sign
	Day 9	1.26 ± 1.573	−74.2	1.99 ± 1.816	−55.8	dT_9	p < 0.001	Sign
	Day 10	0.88 ± 1.573	−82.0	1.93 ± 1.834	−57.1	dT_{10}	p < 0.001	Sign
Throat irritation (self-assessment 0–10 points, VAS)	Day 1	3.89 ± 2.175	–	4.02 ± 1.756	–	–	–	Sign
	Day 2	3.32 ± 1.966	−14.7	3.61 ± 1.767	−10.2	dT_2	p < 0.001	Sign
	Day 3	2.65 ± 1.942	−31.9	3.18 ± 1.784	−20.9	dT_3	p < 0.001	Sign
	Day 4	2.13 ± 1.887	−45.2	2.65 ± 1.843	−34.1	dT_4	p < 0.001	Sign
	Day 5	1.74 ± 1.800	−55.3	2.40 ± 1.872	−40.3	dT_5	p < 0.001	Sign
	Day 6	1.54 ± 1.816	−60.4	2.16 ± 1.837	−46.3	dT_6	p = 0.054	Non-sign
	Day 7	1.55 ± 1.667	−60.2	2.14 ± 1.723	−46.8	dT_7	p = 0.064	Non-sign
	Day 8	1.28 ± 1.595	−67.1	1.89 ± 1.686	−53.0	dT_8	p = 0.089	Non-sign
	Day 9	1.00 ± 1.570	−74.3	1.71 ± 1.637	−57.5	dT_9	p = 0.148	Non-sign
	Day 10	0.80 ± 1.600	−79.4	1.67 ± 1.710	−58.5	dT_{10}	p = 0.211	Non-sign

* The conclusion is drawn at the significance level of 0.05.

Table 8
Group-dependent dynamics of general condition.

Parameter (0–10 points, VAS)	Visit	Statistical parameters						
		Treatment group (n = 114)		Control group (n = 110)		Comparison of the groups		
		M ± SD	Regression (%)	M ± SD	Regression (%)	dT	p-Value	Significant differences*
Physician's assessment of general condition of patients	Day 1	6.36 ± 1.902		5.68 ± 1.961		–	–	–
	Day 5	3.09 ± 2.463	−51.4	3.29 ± 2.526	−42.1	dT_5	$p < 0.001$	Sign
	Day 10	1.04 ± 1.553	−83.6	1.52 ± 1.724	−73.2	dT_{10}	$p < 0.001$	Sign
Patient's self-assessment of general condition	Day 1	6.30 ± 1.882	–	5.94 ± 1.616	–	–	–	Sign
	Day 2	5.24 ± 2.123	−16.8	5.29 ± 1.868	−10.9	dT_2	$p < 0.001$	Sign
	Day 3	4.40 ± 2.222	−30.2	4.76 ± 2.199	−19.9	dT_3	$p < 0.001$	Sign
	Day 4	3.60 ± 2.386	−42.9	3.97 ± 2.324	−33.2	dT_4	$p < 0.001$	Sign
	Day 5	3.02 ± 2.494	−52.1	3.65 ± 2.367	−38.6	dT_5	$p < 0.001$	Sign
	Day 6	2.55 ± 2.421	−59.5	3.40 ± 2.222	−42.8	dT_6	$p < 0.001$	Sign
	Day 7	2.64 ± 2.091	−54.9	3.39 ± 1.943	−42.9	dT_7	$p < 0.001$	Sign
	Day 8	2.59 ± 2.101	−58.9	3.13 ± 1.760	−47.3	dT_8	$p < 0.001$	Sign
	Day 9	1.98 ± 1.862	−68.6	2.88 ± 1.671	−51.5	dT_9	$p < 0.001$	Sign
	Day 10	1.66 ± 1.860	−73.7	2.72 ± 1.565	−54.2	dT_{10}	$p < 0.001$	Sign

* The conclusion is drawn at the significance level of 0.05.

responders (65.4% vs 34.6%). At day 10, responder parameters between groups were significantly different ($p < 0.05$).

Improvement of local symptoms and general condition resulted in decreased rate of the use of antipyretic agents. We carried out assessment of dynamics of the use of NSAIDs (Table 10). Day of the last dosage of this drug product was taken into account.

Significant difference is seen in the rate of need in use of antipyretics between patients of the treatment and control group, starting from treatment day 4 ($p < 0.05$).

We carried out assessment in days of "therapeutic benefit" from the use of BNO 1030 in patients with acute tonsillitis. It was based on comparison of the parameters of general condition dynamics (expressed as score) (Fig. 2).

As can be seen from Fig. 2, at study completion (day 10), patients of the control group assessed their general condition as equal to 2.72 points according to 10-point scale. Similar self-assessment was reported in patients of the treatment group by the end of the fifth day of therapy. Thus, "therapeutic benefit" in treatment of patients of the treatment group comprises 4.2 days versus treatment results of patients of the control group.

3.3. Safety and tolerability

Evaluation of tolerability assessment results has shown that therapy was tolerated well or very well in all cases. No adverse events were registered in any of the patients during treatment process.

4. Discussion

Patients with inflammatory diseases of tonsils frequently use phytotherapeutic drug products. Nevertheless, latest recommendations based on proven efficacy of acute tonsillitis therapy published in press include only symptomatic agent for relief of symptoms [1,5,6]. Systemic (acetaminophen or ibuprofen) and topical (benzydamine) nonsteroidal anti-inflammatory drugs are successfully used for this purpose. Due to this fact, there is a long-standing need in conduct of valid (from the viewpoint of compliance with GCP standards) studies of efficacy of phytotherapeutic drug products, in particular, BNO 1030, in treatment of acute tonsillitis.

This study has demonstrated that the use of phytotherapeutic drug product containing an aqueous-alcoholic extract, BNO 1030, as a supplement to standard symptomatic therapy has proven therapeutic effect. Patients in BNO 1030 group have demonstrated significant decrease in severity of the disease symptoms to 1 point and lower, assessed by a physician by 4-point scale, at days 5 and 10 of treatment. Reliable differences in dynamics of self-assessment of tonsillitis symptoms by patients have been noticed from day 2 throughout day 10 of treatment.

Our results reflect the data presented in literature [18,20]. Results of these studies showed that BNO 1030 (Tonsilgon® N, Imupret®) is effective in treatment of acute respiratory viral infection and recurrent tonsillitis in paediatric patients. Our results are also confirmed by data obtained in a German observation study, which have demonstrated efficacy and safety of the medicinal product in more than 1100 children with recurrent acute infections of upper airways [19].

Acute tonsillitis is a disease always associated with pronounced

Table 9
Analysis of % of responders.

Parameter	Group	Category	Visit					
			Day 1		Day 5		Day 10	
			n	%	n	%	n	%
Average score (4 and lower — responder/more than 4 points — non-responder)	Treatment group (n = 114)	Responder	0	0.0	40	35.1	93	81,6
		Non-responder	114	100.0	74	64.9	21	18.4
	Control group (n = 110)	Responder	0	0.0	28	25.6	72	65.4
		Non-responder	110	100.0	82	74.5	38	34.6
% of responders			– $p = 0.245$		$\chi^2 = 1.849$ $p = 0.174$		$\chi^2 = 4.422$ $p = 0.036$*	

* Significant differences.

Table 10
Group-dependent dynamics of the use of antipyretic agents.

Group	Day									
	1	2	3	4	5	6	7	8	9	10
Treatment group	87	79	56	18	11	1	2	0	0	0
(n = 114)	76.3%	69.2%	49.1%	15.7%	9.6%	0.8%	1.7%	0.0%	0.0%	0.0%
Control group	88	78	60	38	31	12	3	1	0	0
(n = 110)	80.0%	70.9%	54.5%	34.5%	28.1%	10.9%	2.7%	0.9%	0.0%	0.0%
p-Value	0.945	0.867	0.793	0.005	0.002	0.0048	0.665	1.000	1.000	1.000
Conclusion*	−	−	−	+	+	+	−	−	−	−

* (−) There are no significant differences between the groups in terms of the use of NSAIDs. (+) There are significant differences between the groups in terms of the use of NSAIDs.

general disorder. This is due to the fact that palatine tonsils are among the main constituents of the immune system, and their inflammation is associated with pronounced systemic effects. The study has shown reliably superior dynamics of improvement in general condition of patients of the treatment group according to assessment by physician and self-assessment by patient. This clinical effect confirms previously reported data on *in vitro* and *in vivo* immunological efficacy of BNO 1030 [26–28].

The important and interesting conclusion of the study conducted is that, due to pronounced regression of such symptoms as sore throat and throat irritation, as well as improvement of general condition, patients in BNO 1030 group used less antipyretics in total (acetaminophen). Many investigators pass an opinion that sore throat in patients with acute tonsillitis is a driving force of both unjustified prescription of antibiotics by physicians and willingness to use antibacterial therapy of patients themselves, which is one of the main causes of the global problem of antibiotic resistance [2,23,24]. One of strategies for reduction of the use of antibiotics in adults and children with uncomplicated acute respiratory infections is delayed prescription of antibiotics [25]. More rapid regression of pain syndrome in patients receiving Imupret shown in our study is an important reason for decrease of patients' and physicians' commitment to the use of antibiotics. In our study, prescription of antibiotics was a study withdrawal criterion. For this reason, 14 patients were withdrawn from the study at visit V_2: 10 from the control group and 4 from the treatment group. These data are not significant, nevertheless, they demonstrate the trend to reduced prescription of antibiotics in the group using BNO 1030.

BNO 1030 efficacy shown in the current study generally confirms the results of earlier studies in patients with acute viral infections [18–20]. Nevertheless, its strong point is the diagnosis of acute tonsillitis (J03) established in accordance with accepted criteria. A group of randomized patients' homogeneous in terms of diagnosis and clinical manifestations, allowed to draw justified conclusions on assessment of overall treatment result. The number of treatment responders was significantly higher in the treatment group versus the control group. “Therapeutic benefit” in treatment of patients of the treatment group is 4.2 days, which reflects significant superiority in the number of treatment responders. This allows decreasing the number of days of children's absence at school or preschool institutions.

The design provided for comparative study, which did not allow to carry out “placebo” control. Nevertheless, comparison was made against therapy performed in accordance with clinical recommendations, which provide for mandatory prescription of symptomatic therapy only using systemic and topical NSAIDs [1,21]. Due to this, all differences in treatment results can be attributed to clinical effects of BNO 1030.

5. Conclusion

Supplemental use of a phytoneering medicinal product BNO 1030 (Imupret®) for treatment of acute tonsillitis has been shown to promote considerable decrease of tonsillitis clinical symptoms, improved assessment of patients' general condition and their quality of life, decrease of the rate of use of antipyretics and overall treatment duration without any adverse events. Inclusion of this medicinal product into treatment scheme can be recommended to patients with acute non-bacterial tonsillitis.

Prospects for further studies consist in investigation of anti-relapse efficacy of the drug product in patients with recurrent tonsillitis.

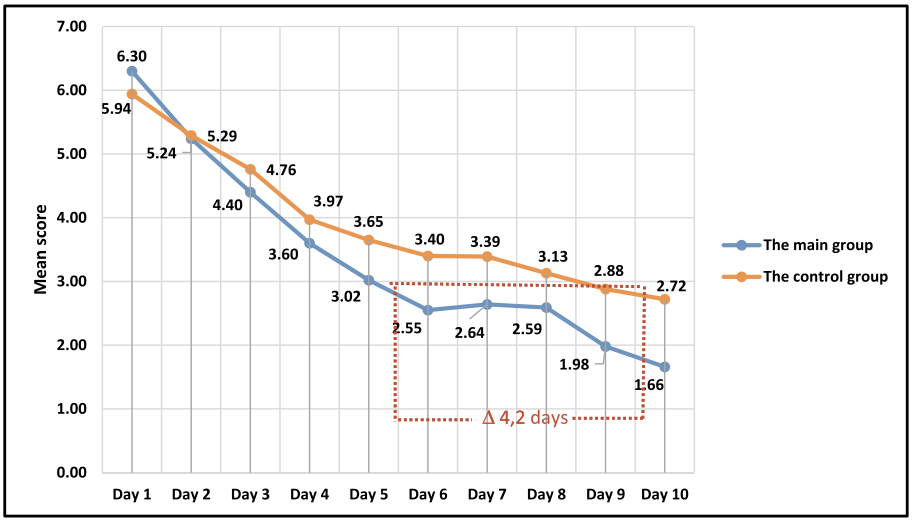

Fig. 2. Assessment of “therapeutic benefit” from the use of BNO 1030.

Registration

This trial was registered in German Clinical Trials Register retrospectively on June 27, 2018.

Trial Acronym: ATi-1.

DRKS-ID: DRKS00015020.

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