

Efficacy of Mometasone Furoate Nasal Spray in Delayed Antibiotic Prescriptions for Acute Rhinosinusitis: A Multicenter, Randomized, Open-Label, Comparative, Prospective, Parallel Group Study

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Abstract

While their clinical presentation is similar, post-viral rhinosinusitis does not indicate the possible development of bacterial rhinosinusitis which occurs in only 0.5% to 5% of all cases of ARS. However, unreasonable antibacterial therapy is prescribed in 54% to 77% of cases. The perspective is to use delayed antibacterial therapy management. The purpose of the study was to investigate the efficacy of mometasone furoate nasal spray within the delayed prescription approach. **Methods:** A multicenter, randomized, open-label, comparative, prospective, parallel group study enrolled a total of 156 patients with ARS aged 18 to 60 years, of them 155 patients completed the study. The patients were randomized into the main group of Mometasone Furoate (Flix) Nasal Spray or into the control group of amoxicillin clavulanate tablets while both groups were administered a standard ARS therapy. **Findings:** The use of MF nasal spray within the delayed antibiotics prescription approach has a significantly higher efficacy compared to the immediate antibiotics prescription in the first days of treatment ($p < 0.05$). Antibacterial therapy was prescribed to 42.3% of patients in the main group compared to 100.0% of patients in the control group ($p < 0.05$). It was shown that there were statistically significant differences in the dynamics of changes in the total symptom score between the patients administered antibiotics and the antibiotic-naive patients. **Conclusion:**

The use of MF within the delayed antibiotics prescription approach reliably improves the pattern of symptoms over time at the disease onset and significantly reduces the need for NSAIDs administration and antibiotics prescription frequency.

Keywords

Rhinosinusitis, Mometasone Furoate, Delayed Antibiotic

1. Introduction

Acute rhinosinusitis (ARS) is classified as an acute respiratory infection and is one of the most frequent diseases for which antibiotics are prescribed unreasonably. In a year, 6 to 15% of the population is infected which leads to a significant social burden in terms of impaired quality of life in ARS patients, the need for medical assistance, and decreased labour productivity. ARS is of great economic importance. In Europe, the costs per episode of the disease are more than 1,000 euros per year while in the USA, the costs reach \$1,091 per year, of which \$210 are spent on antibiotics [1] [2].

The concept of rhinosinusitis has become widely used since 2005 after it was proved that the inflammatory process develops simultaneously in the nasal cavity and paranasal sinuses [3]. According to the popular belief, the concept of ARS includes acute viral (AVRS), post-viral (APVRS), and bacterial rhinosinusitis (ABRS) [1]. AVRS, or the common cold, is a viral disease and occurs very often, with two to five episodes per person per year [4] while APVRS is less common. A recent study revealed an incidence rate of 18.8 episodes per 1000 inhabitants per year [5]. The terms “viral”, and “postviral” (alternative term “nonviral” used in the US) were chosen to indicate that most cases of ARS are caused by non-bacterial agents. Only about 0.5% to 5% of ARS cases could be characterised as ABRS and only in these cases patients require antibiotic therapy [1] [6]. The most difficult issue is the differential diagnosis of post-viral and bacterial ARS since these forms are very similar in their clinical manifestations and the current standards of differential diagnosis so far provide for the use of clinical symptoms. ABRS is diagnosed when 3 or more of the following five criteria are present: deterioration of symptoms after the initial improvement, hyperthermia $> 38^{\circ}\text{C}$, pronounced local tenderness and nasal discharge (mainly purulent) as well as increased CRP/ESR [1]. The use of only clinical symptoms is related to the fact that there is no standard parameter that allows to objectify the diagnostic process.

The use of only clinical diagnostic criteria leads to frequent ABRS overdiagnosing which in turn leads to the unnecessary prescription of antibiotics. However, post-viral rhinosinusitis does not indicate the possible development of bacterial form so the use of antibiotics does not give any advantage in the ABRS prevention and the recommended CRP/ESR tests did not lead to decreased prescription of antibiotics which is believed to be excessive [2] [7]. According to the literature

data, unreasonable antibacterial therapy is prescribed in 54% to 77% of ARS cases [8] [9]. In Great Britain, during 88% of consultations due to ARS, the patients were prescribed antibiotics which experts recognised as appropriate in only 11% of cases. The same situation was observed in the Netherlands where 34% of physicians unreasonably prescribed antibiotics in APVRS patients. In addition to the global problem of antimicrobial resistance which caused approximately 1.27 million deaths worldwide in 2019, unreasonable antibiotic prescribing could be harmful to a particular patient [10]. Currently, a whole group of diseases caused by antibiotics has been identified [11].

One of the strategies to reduce the unreasonable prescription of antibiotics in uncomplicated acute respiratory infections is the delayed prescription of antibiotic agents. The essence of this management is as follows. A specialist assumes that the immediate antibiotics prescription is not necessary expecting that the symptoms will eliminate without their administration, and that their prescription is still possible if the patient's condition does not meet the criteria of favourable changes [12]. The delayed antibiotics prescription shows a practically similar level of patient satisfaction with the treatment compared to the antibiotics prescription at the first visit (86% vs. 91%) and made it possible to reduce the frequency of antibacterial therapy cases up to 31% given that the number of complications has not increased [13].

The main condition for implementation of the delayed antibiotics prescription strategy is choosing the treatment with proven effectiveness to ensure favourable changes. Based on the above, there is a need to use drug substances for systemic and local therapy with a complex effect that has an evidence base of effectiveness, in particular in APVRS. According to the recommendations, pharmacological therapy with 1^b evidence level includes phytoextract BNO 1016 and, therapeutic irrigation with an isotonic seawater solution [1] [14] [15]. These agents have demonstrated effectiveness when used as part of the delayed antibacterial therapy strategy in patients with ARS [16] [17]. A number of studies have been conducted on the use of topical corticosteroids, in particular, mometasone furoate (MF) nasal spray, in ARS patients. The available data do not confirm the effectiveness of the topical corticosteroids used in viral RS [1] [3]. In patients with postviral RS, MF Nasal Spray 200 µg twice daily resulted in significantly higher improvement in the total points as well as in the headache, nasal congestion, and facial pain scores compared with placebo while the incidence of treatment-induced adverse events was also similar compared with placebo [18]-[20]. According to clinical recommendations, MF is recommended in cases "when the ARS symptoms reducing in adults is considered necessary" [1] [21].

In light of this, the use of MF as part of the delayed antibiotics prescription strategy in ARS could be promising since the driving force of their unreasonable prescription both by physicians and demanded by patients is an excessive precaution in case of some symptoms of APVRS, in particular in moderate to severe nasal congestion, headache, and mucous and purulent nasal discharge [14] [17]. The

action of MF is not aimed at specific pathogenic agents. Rather, its high efficiency is based on a multi-target approach affecting the main pathogenetic mechanisms that underlie the indicated clinical manifestations and contribute to the unreasonable prescription of antibacterial therapy. However, in the literature, there are only a few data comparative studies investigating the efficacy of MF against amoxicillin in the treatment of APVRS. It was shown that MF administration at a dose of 200 µg twice a day results in significantly improved symptoms compared to amoxicillin and placebo without causing the relapse or bacterial infection; at that, the treatment costs were also significantly reduced [22]-[24]. At the same time, no multicentre studies valid from the point of view of compliance with GCP standards of the MF use as part of the delayed antibiotic prescription strategy were carried out. Confirmation of the high efficacy of this medicinal product would serve as a justification for the implementation of the delayed antibiotic prescription strategy in the real clinical settings and for reducing the harm from their unjustified prescription.

This study was aimed at investigating the efficacy of mometasone furoate nasal spray (Flix) as part of the delayed strategy versus immediate antibiotic administration in moderate to severe acute postviral rhinosinusitis.

2. Materials and Methods

2.1. Trial Design

A multicenter, randomised, open-label, comparative, prospective parallel-group study was conducted in five outpatient institutions in Ukraine from September to December 2023. The study was conducted in accordance with GCP standards and the Declaration of Helsinki.

Registration: Ethics Committee of Lviv Medical University, Protocol No. 171 as of 19 September 2023.

The study was approved by the ethics committee at all study sites. A written consent to participate in the study was obtained from each patient.

2.2. Subjects

164 subjects were selected, of which 156 outpatient subjects of them aged 18 to 60 years old were randomised and diagnosed with moderate to severe or severe APVRS to participate in the study. Diagnostic and differential diagnostic criteria were evaluated while treatment was prescribed according to the recommendations presented in European and national clinical guidelines [1] [21]. The clinical diagnosis of APVRS was established on the basis of one or more major symptoms: nasal congestion/obstruction or nasal discharge (anterior rhinorrhoea or postnasal drip) and/or facial pain/pressure and/or cough/decreased sense of smell lasting > 10 days, or the disease course worsening after Day 5 and lasting less than 12 weeks.

Inclusion criteria:

- symptoms persisting for more than 10 days since the disease onset or health

state worsening after Day 5 and lasting less than 12 weeks,

- severity of at least two symptoms scored 2 to 3 points by 4-point Major Symptoms Severity score (MSS): 0 = no symptom, 1 = mild symptom, 2 = moderate symptom, 3 = severe/critical symptom,
- total points of 6 to 10 on MSS scale,
- self-assessment more than 8 points on VAS scale,
- potential of applying the delayed antibiotic prescription,
- lack of non-inclusion criteria.

Non-inclusion criteria:

- diagnosis of viral/allergic rhinosinusitis,
- known drug intolerance,
- more than 14 days from the disease onset,
- previous treatment with other study drugs prior to assessment of a patient's eligibility to participate in the study,
- indications for immediate antibiotics prescription or hospitalisation (total points by MSS scale > 10),
- immunodeficiency disorders,
- chronic pathology and anatomical abnormalities of the ostio-meatal complex that could affect the treatment outcomes.

Withdrawal criteria:

- subject's decision to terminate participation in the study and withdrawal of written informed consent,
- lost to follow-up,
- individual intolerance of the study drug or the reference treatment regimen,
- development of serious and/or unexpected side effects/adverse events during the study,
- development of the underlying disease complications that, according to the physician, require the subject's withdrawal from the study,
- violation of the procedures provided for by the Protocol by the subject.

A total of 78 subjects (n = 78) were randomised to the main group: patients receiving irrigation therapy with isotonic sea water 1 to 2 instillations in each nostril 3 to 4 times a day + BNO 1016 (Sinupret Extract, tablets) 3 times a day + MF Nasal Spray (Flix[®]) 2 instillations in each nostril twice a day.

A total of 78 subjects (n = 78) were randomised to the control group: patients receiving irrigation therapy with isotonic sea water 1 to 2 instillations in each nostril 3 to 4 times a day + BNO 1016 (Sinupret Extract, tablets) 3 times a day + amoxicillin clavulanate 1000 mg, 1 tab. twice a day.

The subjects were prescribed symptomatic analgesic therapy (Ibuprofen, single dose of up to 400 mg max. 3 times a day) or antipyretics (paracetamol, single dose of up to 500 mg 3 to 4 times a day) as indicated.

The main group (n = 78) included 26 (33.3%) men and 52 (66.7%) women while the control group (n = 78) included 24 (30.8%) men and 54 (69.2%) women.

The subjects of both groups were comparable by gender, age, and clinical

presentation of the disease ($p < 0.05$).

2.3. Interventions

Since randomisation, all the subjects received the treatment prescribed by the national clinical recommendations for the ARS therapy: irrigation therapy with isotonic sea water 1 to 2 instillations in each nostril 3 to 4 times a day + BNO 1016 (Sinupret Extract, tablet) 1 tablet 3 times a day per os. The control group additionally received amoxicillin clavulanate tablets 1,000 mg twice a day while the main group received MF nasal spray (Flix) 2 instillations (100 µg) in each nostril twice a day (400 mg in total) without antibiotic.

Flix is a nasal spray, a suspension in a polyethylene vial with a dosing pump. 1 dose contains 51.8 µg of mometasone furoate monohydrate equivalent to 50 µg of mometasone furoate.

Name and address of the manufacturer: ABDI IBRAHIM Ilac Sanayi ve Ticaret A.S. Orrhan Gazi Mahallesi, Tunc Caddesi No. 3, Esenyurt, Istanbul, Türkiye.

The medicinal product is registered in Ukraine. Therefore, the composition, manufacture, packaging, and labelling of the medicinal product comply with the principles of Good Manufacturing Practice and current national requirements of Ukraine. A detailed description covering all aspects of Flix® quality and safety is a part of the relevant product specifications. Indications for use approved in Ukraine are listed below: as a therapeutic aid within the antibiotics treatment in acute episodes of sinusitis in adults (including the elderly) and children aged over 12 years old, for treatment of the acute rhinosinusitis symptoms without signs of severe bacterial infection in adults and children aged over 12 years old.

Practicing E.N.T. specialists with at least 5 years of experience were involved in the study.

2.4. Outcome Measures

All data were evaluated at the beginning of the study and during 10 days (**Table 1**).

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 + Flix® 2 instillations in each nostril twice a day | | | | | | | | | | | |
| Control group | | | | | | | | | | | |
| Reference treatment + amoxicillin clavulanate tablets 1000 mg twice a day | | | | | | | | | | | |

V1 day 0 Screening, randomisation, prescription of treatment

V2 day 3 ± 1 Status evaluation, possible prescription of antibiotics

V3 day 7 ± 1 Evaluation of treatment efficacy, including possible prescription of antibiotics

V4 day 10 ± 1 Evaluation of treatment efficacy, end of treatment

Symptom assessment was performed both by physicians and patients. During each visit, the physicians assessed the major symptoms by MSS scale: (0 to 3 points for each symptom): anterior rhinorrhoea, nasal congestion, postnasal drip, facial pain, and headache. After the symptom severity assessment, the total points were determined.

Also, self-assessment of the severity of the symptom was carried out daily by patients in a diary: complaints (anterior rhinorrhoea, nasal congestion, postnasal drip, facial pain, and headache) were evaluated in points using a 10-point visual analogue scale; the total points were also calculated. In addition, the subjects monitored the need to use additional treatment, in particular, nonsteroidal anti-inflammatory agents.

At Visit 2 and 3 (V₂ - V₃), the physician evaluated the subjects' condition according to the assessment and self-assessment criteria; together with the patient, a decision was made regarding the need to prescribe antibacterial therapy. The follow-up duration for 1 subject was 10 ± day.

Main efficiency criterion: decreased severity of symptoms assessed by the physician in points according to MSS scale at each visit compared to V₁, favourable progression of self-assessment scores by VAS, favourable progression in NSAIDs intake, frequency of antibiotic prescription cases.

2.5. Sample Size

The clinical study was designed in order to obtain a reliable description of the effectiveness of active *in vivo* use of mometasone furoate nasal spray (Flix) at a total dose of 400 µg within the delayed antibacterial agents prescription strategy in comparison with their immediate prescription. Depending on the data, several trial descriptive and statistical estimates were made, thus, a biometric assessment of the sample size is not required. However, to ensure a sufficient sample size for the resulting data analyses, a sample size of n = 156 was selected. The subjects were randomised at a ratio of 1:1.

2.6. Randomisation

The clinical part of the randomised trial is open-label, without a blinding procedure. Subjects with ARS symptoms were randomised to one of two possible treatment groups according to the basic randomisation list. Randomisation was performed using the software [StatSoft, Random Number Generator]. Randomisation was performed for each subject who signed the informed consent.

2.7. Statistical Methods

In order to analyse 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 in-dependent samples. Otherwise (if the data distribution was different from normal), a 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 of the Flix[®] therapy efficacy significance on the reduction of the antibiotics intake rate was carried out by the method of forecast based on regression analysis using a neural network. At that, the probability that the analysed (dependent) variable will become significant at the given values of the factors (a linear combination of factors is modelled) was assessed. In this case, the regression was considered as the neural network special case.

The analysis was performed in software environment IBM SPSS 22.0.

3. Results

3.1. Study Sample

A total of 164 outpatient subjects aged 18 to 60 years old were screened, of them 156 subjects were randomised to participate in the study (**Figure 1**).

Out of 164 enrolled patients, 8 (4.9%) subjects were not included in the study due to non-compliance with the inclusion criteria, namely, diagnostic criteria for viral RS (*n* = 6) and patient's refusal to comply with protocol requirements (*n* = 2). The remaining 156 patients were randomised to either the main group: *n* = 78, or to the control group: *n* = 78. Of 78 randomised patients in the control group, one (*n* = 1) subject refused to take antibiotic treatment and, therefore, was withdrawn. The remaining 155 patients (99.4%) underwent the necessary procedures according to the study protocol and were included in the outcomes analysis.

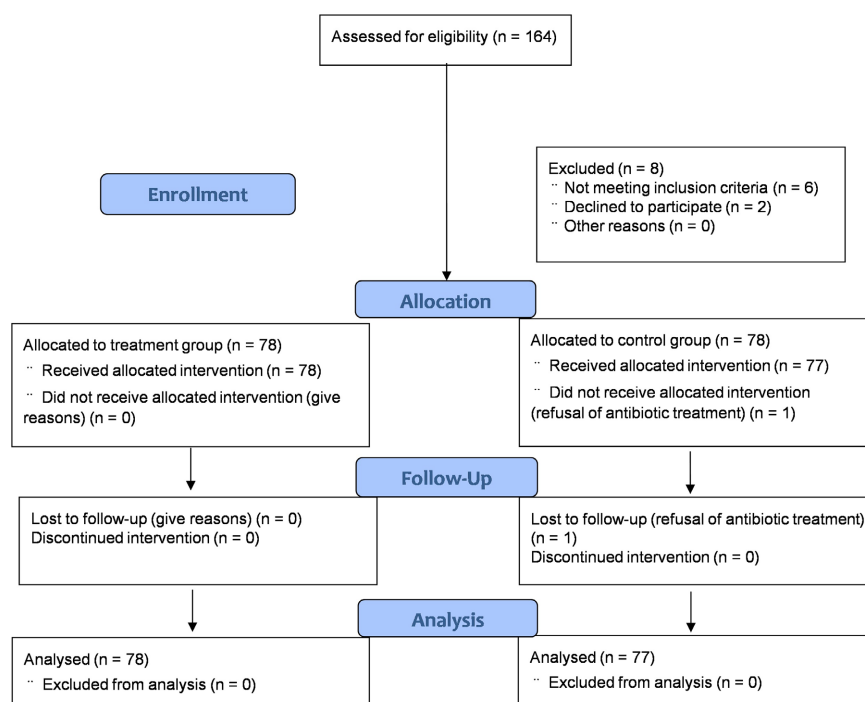


Figure 1. Patients included in screening and randomisation.

The distribution of subjects of both groups by gender is shown in **Table 2**: the main group (n = 78) included 26 (33.3%) men and 52 (66.7%) women while the control group (n = 77) included 23 (29.8%) men and 54 (70.2%) women.

Table 2. Patients distribution by gender.

| Group | Men | | Women | | Total | |
|------------------|-----|------|-------|------|-------|-------|
| | n | % | n | % | n | % |
| Main | 26 | 33.3 | 52 | 66.7 | 78 | 100.0 |
| Control | 23 | 29.8 | 54 | 70.2 | 77 | 100.0 |
| $\chi^2 = 0,085$ | | | | | | |
| $p = 0,771$ | | | | | | |

In general, by gender, the groups were statistically homogeneous.

The distribution of subjects of both groups by age is shown in **Table 3**: the average age of patients was 32.8 ± 9.98 years in the main group and 34.6 ± 11.05 years in the control group. By age, the groups were statistically homogeneous.

Table 3. Patients distribution by age.

| Parameter | Group | Statistical indicators | | | |
|-------------|---------|------------------------|------------------|---------|------------------------|
| | | n | M ± SD | p-value | Homogeneity of groups* |
| Age (years) | Main | 78 | 32.8 ± 9.98 | 0.414 | Homogeneous |
| | Control | 77 | 34.6 ± 11.05 | | |

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

In general, there were no significant differences in demographic characteristics between subjects in the main group and the control group at baseline (Day 1).

3.2. Outcomes and Estimation

Typical clinical manifestations of APVRS are divided into major symptoms such as nasal congestion/obstruction and/or nasal discharge (anterior rhinorrhoea or postnasal drip) and minor symptoms such as facial pain/pressure lasting > 10 days or health state worsening after Day 5. A comparative characteristic of the symptom's severity in subjects of the main and control groups prior to treatment scored 0 to 3 points by the physician are shown in **Table 4**.

Table 4. Comparative analysis by symptoms severity assessed by physician prior to treatment.

| Parameter (0 to 3 points) | Group | Statistical indicators | | | |
|------------------------------|-----------|------------------------|-------------|---------|----------------------------|
| | | n | M ± SD | p-value | Homogeneity of the groups* |
| Anterior rhinorrhoea | Treatment | 78 | 2.17 ± 0.93 | 0.084 | homogeneous |
| | Control | 77 | 2.35 ± 0.79 | | |
| Nasal congestion | Treatment | 78 | 2.55 ± 0.77 | 0.136 | homogeneous |
| | Control | 77 | 2.36 ± 0.71 | | |
| Postnasal drip | Treatment | 78 | 1.85 ± 0.87 | 0.812 | homogeneous |
| | Control | 77 | 1.88 ± 0.87 | | |
| Facial pain | Treatment | 78 | 1.01 ± 1.00 | 0.202 | homogeneous |
| | Control | 77 | 1.18 ± 0.94 | | |
| Headache | Treatment | 78 | 1.50 ± 0.91 | 0.046* | not homogeneous |
| | Control | 77 | 1.87 ± 0.94 | | |
| Total points | Treatment | 78 | 9.12 ± 2.82 | 0.054 | homogeneous |
| | Control | 77 | 9.66 ± 2.41 | | |

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

No significant differences in the ARS major symptoms severity such as anterior rhinorrhoea, nasal congestion, postnasal drip, facial pain between subjects of the main and control groups at baseline (V1) were observed ($p > 0.05$). There were slight differences between the groups in the assessment of headache, however, the difference was almost at the decision limit (p -value = 0.046 bordering with the specified significance level of 0.05).

According to the criteria, the study included patients with moderate to severe or severe APVRS with a total points assessed by the physician by MSS scale scored 6 to 10 points. As shown in the given table, the groups were comparable ($p > 0.05$) by the total severity points.

The progression of the major symptom's severity and the degree of their regression on the treatment background scored 0 to 3 points by the physician in patients of the main and control groups are shown in **Table 5**.

Table 5. Comparative analysis of the symptoms regression assessed by physician.

| Parameter (0 to 3 points) | Visit | Statistical indicators | | | | The comparison of the groups | |
|------------------------------|-------|-----------------------------|-------------------|---------------------------|-------------------|---------------------------------|---------|
| | | Treatment group (n = 78) | | Control group (n = 77) | | | |
| | | M±SD | Regression (%) | M±SD | Regression (%) | dTi | p-value |
| Anterior rhinorrhoea | V1 | 2.17 ± 0.93 | - | 2.35 ± 0.79 | - | - | - |
| | V2 | 1.91 ± 0.72 | -12.0 | 2.16 ± 0.80 | -8.1 | dT ₂ | 0.380 |
| | V3 | 0.74 ± 0.71 | -65.9 | 0.99 ± 0.73 | -57.9 | dT ₃ | 0.430 |
| | V4 | 0.03 ± 0.16 | -98.6 | 0.14 ± 0.39 | -94.0 | dT ₄ | 0.467 |
| Postnasal drip | V1 | 1.85 ± 0.87 | - | 1.88 ± 0.87 | - | - | - |
| | V2 | 1.50 ± 0.72 | -18.9 | 1.79 ± 0.95 | -4.8 | dT ₂ | 0.041* |
| | V3 | 0.56 ± 0.66 | -69.7 | 0.87 ± 0.73 | -53.7 | dT ₃ | 0.164 |
| | V4 | 0.12 ± 0.36 | -93.5 | 0.23 ± 0.46 | -87.8 | dT ₄ | 0.582 |
| Nasal congestion | V1 | 2.55 ± 0.77 | - | 2.36 ± 0.71 | - | - | - |
| | V2 | 2.01 ± 0.61 | -21.2 | 2.05 ± 0.83 | -13.1 | dT ₂ | 0.020* |
| | V3 | 0.96 ± 0.65 | -62.4 | 1.21 ± 0.66 | -48.7 | dT ₃ | 0.002* |
| | V4 | 0.12 ± 0.36 | -95.3 | 0.30 ± 0.56 | -87.3 | dT ₄ | 0.013* |
| Facial pain | V1 | 1.01 ± 1.00 | - | 1.18 ± 0.94 | - | - | - |
| | V2 | 0.54 ± 0.75 | -46.5 | 0.66 ± 0.88 | -44.1 | dT ₂ | 0.682 |
| | V3 | 0.13 ± 0.44 | -87.1 | 0.13 ± 0.47 | -89.0 | dT ₃ | 0.217 |
| | V4 | 0.00 ± 0.00 | -100.0 | 0.00 ± 0.00 | -100.0 | dT ₄ | 0.202 |
| Headache | V1 | 1.50 ± 0.91 | - | 1.87 ± 0.94 | - | - | - |
| | V2 | 0.88 ± 0.85 | -41.3 | 1.56 ± 2.45 | -16.6 | dT ₂ | 0.017* |
| | V3 | 0.17 ± 0.61 | -88.7 | 0.34 ± 0.79 | -81.8 | dT ₃ | 0.264 |
| | V4 | 0.01 ± 0.11 | -99.3 | 0.01 ± 0.11 | -99.5 | dT ₄ | 0.534 |
| Total points | V1 | 9.12 ± 2.82 | - | 9.66 ± 2.41 | - | - | - |
| | V2 | 6.81 ± 2.56 | -25.3 | 7.94 ± 3.22 | -17.8 | dT ₂ | 0.060 |
| | V3 | 2.54 ± 2.30 | -72.1 | 3.48 ± 2.23 | -64.0 | dT ₃ | 0.300 |
| | V4 | 0.27 ± 0.71 | -97.0 | 0.69 ± 1.15 | -92.9 | dT ₄ | 0.537 |

* Statistically significant differences between groups are observed. (the conclusion is drawn at the significance level of 0.05).

According to the physician's assessment of anterior rhinorrhoea, both groups showed comparable severity parameters at V1 as well as comparable severity and regression parameters at V2, V3, and V4 ($p > 0.05$).

The postnasal drip severity was comparable at V1. At V2, a significant difference in the symptom severity was observed between the subjects of the main group (1.50 ± 0.72) and the control group (1.79 ± 0.95). The symptom regression observed was -18.9% in the main group versus -4.8% in the control group ($p < 0.05$). At V3 and V4, both groups showed comparable severity and regression parameters of the symptom ($p > 0.05$) (Table 5).

The nasal congestion severity was comparable between groups at V1 ($p > 0.05$). At all subsequent visits, a significant difference in the symptoms severity and regression parameters was observed between the subjects of the main and control groups as follows. 2.01 ± 0.61 in the main group at V2 versus 2.05 ± 0.83 in the control group; symptom regression -21.2% and -13.1% , respectively ($p < 0.05$).

At V3, the symptom intensity was 0.96 ± 0.65 points, regression -62.4% in the main group versus 1.21 ± 0.66 points, regression -48.7% in the control group ($p < 0.05$). At V4, a significant difference in symptom intensity was also observed between the patients of the main and control groups: 0.12 ± 0.36 points (-95.3%) versus 0.30 ± 0.56 points (-87.3%), respectively ($p < 0.05$) (Table 5).

The severity of the facial pain in points in both groups showed comparable parameters at V1 (1.01 in the treatment group vs 0.018 in the control). When analysing the intensity of facial pain and its regression during the treatment, comparable parameters were observed at V2, V3, and V4 (regression in the treatment and control group at V2 by 46.5% and 44.1% ; at V3 by 88.7% and 81.8% ; at V4 by 100% and 100% respectively). The difference between the groups at all control points was not significant ($p > 0.05$).

Upon the assessment of the headache by the physician, both groups showed comparable severity parameters at V1. At V2, the severity parameters of the symptom in the main group were 0.88 ± 0.85 points versus 1.56 ± 2.45 points in the control group (symptom regression -41.3% and -16.6% , respectively), the difference between the groups was significant ($p < 0.05$). At V3 and V4, the severity of the symptom and its regression were comparable between the groups; the difference between the groups was not significant ($p > 0.05$).

At V1, the total points value was comparable between the groups and amounted to 9.12 ± 2.82 points in the main group and 9.66 ± 2.41 in the control group ($p > 0.05$). No significant difference indicated that the disease course in the patients of both groups was moderate to severe. At V2, V3, and V4, the total points value and their progression were comparable between the groups ($p > 0.05$) (Table 5).

The comparative characteristics of the main and control groups in terms of the symptoms severity according to patient self-assessment by VAS scored 0 to 10 points before treatment are shown in Table 6.

Table 6. Comparative analysis of symptoms severity by patient self-assessment score prior to treatment.

| Parameter (0 to 10 points) | Group | Statistical indicators | | | |
|-------------------------------|-----------|------------------------|------------------|---------|----------------------------|
| | | n | M \pm SD | p-value | Homogeneity of the groups* |
| Anterior rhinorrhoea | Treatment | 78 | 5.37 ± 2.40 | 0.211 | homogeneous |
| | Control | 77 | 6.64 ± 2.33 | | |
| Nasal congestion | Treatment | 78 | 6.33 ± 2.04 | 0.479 | homogeneous |
| | Control | 77 | 6.57 ± 2.13 | | |
| Postnasal drip | Treatment | 78 | 4.72 ± 2.41 | 0.118 | homogeneous |
| | Control | 77 | 5.36 ± 2.54 | | |
| Facial pain | Treatment | 78 | 2.45 ± 2.31 | 0.138 | homogeneous |
| | Control | 77 | 3.27 ± 2.59 | | |
| Headache | Treatment | 78 | 3.45 ± 2.12 | 0.071 | homogeneous |
| | Control | 77 | 4.82 ± 2.54 | | |
| Total points | Treatment | 78 | 22.28 ± 8.72 | 0.089 | homogeneous |
| | Control | 77 | 26.64 ± 8.61 | | |

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

As shown in **Table 6**, there was no significant difference in the assessed symptoms severity as well as in the total points upon self-assessment between the patients of the main and control groups at the starting point (V1) ($p > 0.05$). Thus, the groups were statistically homogeneous by the patient self-assessment score.

The self-assessment score progression of the major symptoms and their regression during the treatment in the patients of the main and control groups by the 10-point VAS scale are shown in **Table 7**.

Table 7. Comparative analysis of symptoms regression by patient self-assessment score.

| Parameter (self-assessment 0 - 10 scores, VAS) | Day | Statistical indicators | | | | | |
|---|------|-----------------------------|----------------|---------------------------|----------------|---------------------------------|---------|
| | | Treatment group (n = 78) | | Control group (n = 77) | | The comparison of the groups | |
| | | M ± SD | Regression (%) | M ± SD | Regression (%) | dTi | p-value |
| Anterior rhinorrhoea | D 1 | 5.37 ± 2.40 | - | 6.64 ± 2.33 | - | - | - |
| | D 2 | 5.37 ± 2.17 | 0.0 | 6.40 ± 2.30 | -3.6 | dT ₂ | 0.317 |
| | D 3 | 4.79 ± 1.92 | -10.8 | 6.00 ± 2.24 | -9.6 | dT ₃ | 0.807 |
| | D 4 | 3.86 ± 1.72 | -28.1 | 4.87 ± 2.13 | -26.7 | dT ₄ | 0.768 |
| | D 5 | 2.95 ± 1.55 | -45.1 | 4.14 ± 2.03 | -37.7 | dT ₅ | 0.818 |
| | D 6 | 2.13 ± 1.42 | -60.3 | 3.19 ± 2.02 | -52.0 | dT ₆ | 0.448 |
| | D 7 | 1.45 ± 1.42 | -73.0 | 2.50 ± 1.90 | -62.3 | dT ₇ | 0.347 |
| | D 8 | 0.64 ± 1.09 | -88.1 | 1.60 ± 1.53 | -75.9 | dT ₈ | 0.239 |
| | D 9 | 0.17 ± 0.54 | -96.8 | 0.92 ± 1.39 | -86.1 | dT ₉ | 0.099 |
| | D 10 | 0.06 ± 0.41 | -98.9 | 0.41 ± 1.37 | -93.8 | dT ₁₀ | 0.011* |
| Postnasal drip | D 1 | 4.72 ± 2.41 | - | 5.36 ± 2.54 | - | - | - |
| | D 2 | 4.33 ± 2.17 | -8.3 | 4.90 ± 2.60 | -8.6 | dT ₂ | 0.718 |
| | D 3 | 3.72 ± 2.11 | -21.2 | 4.85 ± 2.54 | -9.5 | dT ₃ | 0.048 |
| | D 4 | 2.87 ± 1.87 | -39.2 | 4.04 ± 2.47 | -24.6 | dT ₄ | 0.034* |
| | D 5 | 2.01 ± 1.43 | -57.4 | 3.47 ± 2.32 | -35.3 | dT ₅ | 0.025* |
| | D 6 | 1.33 ± 1.46 | -71.8 | 2.71 ± 1.97 | -49.4 | dT ₆ | 0.102 |
| | D 7 | 0.81 ± 1.33 | -82.8 | 2.28 ± 1.77 | -57.5 | dT ₇ | 0.071 |
| | D 8 | 0.41 ± 0.86 | -91.3 | 1.51 ± 1.58 | -71.8 | dT ₈ | 0.337 |
| | D 9 | 0.27 ± 0.73 | -94.3 | 0.99 ± 1.46 | -81.5 | dT ₉ | 0.943 |
| | D 10 | 0.23 ± 0.80 | -95.1 | 0.65 ± 1.53 | -87.9 | dT ₁₀ | 0.537 |
| Nasal congestion | D 1 | 6.33 ± 2.04 | - | 6.57 ± 2.13 | - | - | - |
| | D 2 | 5.65 ± 1.95 | -10.7 | 6.19 ± 2.17 | -5.8 | dT ₂ | 0.006* |
| | D 3 | 4.88 ± 1.77 | -22.9 | 5.58 ± 2.21 | -15.1 | dT ₃ | 0.009* |
| | D 4 | 4.17 ± 1.43 | -34.1 | 4.63 ± 2.10 | -29.5 | dT ₄ | 0.316 |
| | D 5 | 3.29 ± 1.40 | -48.0 | 4.03 ± 1.86 | -38.7 | dT ₅ | 0.142 |
| | D 6 | 2.38 ± 1.25 | -62.4 | 3.31 ± 1.72 | -49.6 | dT ₆ | 0.088 |
| | D 7 | 1.79 ± 1.32 | -71.7 | 2.76 ± 1.65 | -58.0 | dT ₇ | 0.128 |
| | D 8 | 0.97 ± 1.16 | -84.7 | 1.81 ± 1.48 | -72.5 | dT ₈ | 0.210 |
| | D 9 | 0.51 ± 0.98 | -91.9 | 1.24 ± 1.59 | -81.1 | dT ₉ | 0.312 |
| | D 10 | 0.27 ± 0.85 | -95.7 | 0.67 ± 1.62 | -89.8 | dT ₁₀ | 0.949 |
| Facial pain | D 1 | 2.45 ± 2.31 | - | 3.27 ± 2.59 | - | - | - |
| | D 2 | 1.87 ± 1.98 | -23.7 | 2.69 ± 2.60 | -17.7 | dT ₂ | 0.766 |
| | D 3 | 1.24 ± 1.82 | -49.4 | 2.00 ± 2.37 | -38.8 | dT ₃ | 0.755 |
| | D 4 | 0.59 ± 1.38 | -75.9 | 1.33 ± 1.90 | -59.3 | dT ₄ | 0.806 |

Continued

| | | | | | | | |
|--------------|------|--------------|--------|--------------|-------|------------------|--------|
| | D 5 | 0.29 ± 0.82 | -88.2 | 0.81 ± 1.64 | -75.2 | dT ₅ | 0.273 |
| | D 6 | 0.24 ± 0.96 | -90.2 | 0.47 ± 1.29 | -85.6 | dT ₆ | 0.067 |
| | D 7 | 0.17 ± 0.84 | -93.1 | 0.45 ± 1.50 | -86.2 | dT ₇ | 0.085 |
| | D 8 | 0.06 ± 0.47 | -97.6 | 0.23 ± 0.99 | -93.0 | dT ₈ | 0.052 |
| | D 9 | 0.00 ± 0.00 | -100.0 | 0.15 ± 1.03 | -95.4 | dT ₉ | 0.043* |
| | D 10 | 0.00 ± 0.00 | -100.0 | 0.13 ± 1.13 | -96.0 | dT ₁₀ | 0.038* |
| Headache | D 1 | 3.45 ± 2.12 | - | 4.82 ± 2.54 | - | - | - |
| | D 2 | 2.59 ± 1.98 | -24.9 | 4.10 ± 2.51 | -14.9 | dT ₂ | 0.238 |
| | D 3 | 1.96 ± 1.92 | -43.2 | 3.53 ± 2.56 | -26.8 | dT ₃ | 0.445 |
| | D 4 | 0.81 ± 1.46 | -76.5 | 2.54 ± 2.33 | -47.3 | dT ₄ | 0.221 |
| | D 5 | 0.44 ± 0.97 | -87.2 | 1.67 ± 2.04 | -65.4 | dT ₅ | 0.666 |
| | D 6 | 0.36 ± 1.02 | -89.6 | 1.15 ± 1.64 | -76.1 | dT ₆ | 0.101 |
| | D 7 | 0.27 ± 1.24 | -92.2 | 0.81 ± 1.76 | -83.2 | dT ₇ | 0.015* |
| | D 8 | 0.12 ± 0.91 | -96.5 | 0.41 ± 1.17 | -91.5 | dT ₈ | 0.002* |
| | D 9 | 0.04 ± 0.25 | -98.8 | 0.22 ± 1.06 | -95.4 | dT ₉ | 0.001* |
| | D 10 | 0.01 ± 0.11 | -99.7 | 0.19 ± 1.17 | -96.1 | dT ₁₀ | 0.001* |
| Total points | D 1 | 22.28 ± 8.72 | - | 26.64 ± 8.61 | - | - | - |
| | D 2 | 19.82 ± 7.91 | -11.0 | 24.13 ± 9.27 | -9.4 | dT ₂ | 0.182 |
| | D 3 | 16.63 ± 7.42 | -25.4 | 21.92 ± 9.20 | -17.7 | dT ₃ | 0.138 |
| | D 4 | 12.26 ± 5.94 | -45.0 | 17.17 ± 7.92 | -35.5 | dT ₄ | 0.352 |
| | D 5 | 8.85 ± 4.24 | -60.3 | 13.73 ± 6.88 | -48.5 | dT ₅ | 0.577 |
| | D 6 | 6.44 ± 4.31 | -71.1 | 10.45 ± 5.89 | -60.8 | dT ₆ | 0.737 |
| | D 7 | 4.44 ± 4.63 | -80.1 | 8.38 ± 5.92 | -68.5 | dT ₇ | 0.782 |
| | D 8 | 2.17 ± 3.09 | -90.3 | 5.09 ± 3.60 | -80.9 | dT ₈ | 0.285 |
| | D 9 | 1.00 ± 1.81 | -95.5 | 3.04 ± 2.98 | -88.6 | dT ₉ | 0.054 |
| | D 10 | 0.59 ± 1.63 | -97.4 | 1.50 ± 2.93 | -94.4 | dT ₁₀ | 0.004* |

*Statistically significant differences between groups are observed (the conclusion is drawn at the significance level of 0.05).

Upon self-assessment of anterior rhinorrhoea, both groups demonstrated comparable severity scores on Day 1 and regression scores between Day 2 and Day 9. The difference between the groups is not significant ($p > 0.05$). On Day 10, the self-assessment score of rhinorrhoea in the main group was 0.06 ± 0.41 points, the symptom regression rate compared to Day 1 was -98.9% versus 0.41 ± 1.37 , regression was -93.8% in the control group. On Day 10, the difference between groups was significant ($p < 0.05$) (Table 7).

The intensity of postnasal drip by self-assessment score was comparable between Day 1 and Day 3. A significant difference in self-assessment score was observed on Day 4: 2.87 ± 1.87 points, symptom regression -39.2% in subjects of the main group versus 4.04 ± 2.47 points, symptom regression -24.6% in the control group. Similarly, on Day 5 the severity parameter was 2.01 ± 1.43 points, the symptom regression compared to Day 1 was observed, respectively, by -57.4% in the main group versus 3.47 ± 2.32 points and regression parameter by -35.3% in the control group ($p < 0.05$). Subsequently, from Day 6 to Day 10, the difference between the groups was not significant ($p > 0.05$) in terms of the postnasal congestion severity and its regression.

Self-assessment of the nasal congestion was comparable between the groups on Day 1 ($p > 0.05$). On Day 2 and Day 3, a significant difference was observed in the self-assessment of the symptom severity and its regression, namely: on Day 2 5.65 ± 1.95 points in the main group versus 6.19 ± 2.17 in the control group, symptom regression by -10.7% and -5.8% in the main and control groups, respectively ($p < 0.05$). On Day 3 in the main group, the self-assessment of the symptom severity was 4.88 ± 1.77 points, regression by -22.9% versus 5.58 ± 2.21 points and regression by -15.1% in the control group ($p < 0.05$). Starting from Day 4 to Day 10, the self-assessment scores of nasal congestion and its regression were comparable between the groups (Table 7).

Self-assessment scores of the facial pain severity and its regression were comparable in both groups between Day 1 and Day 8. The difference between groups at all control points was not significant ($p > 0.05$). On Day 9 and Day 10, there was a significant difference in self-assessment scores of the symptom and its regression between patients. No specified symptom was observed within the specified period: regression of 100% versus -95.4% on Day 9 in the main group and -96.0% on Day 10 in the control group ($p < 0.05$).

The self-assessment scores of the headache in both groups showed comparable severity and regression parameters and no significant difference in parameters between Day 1 and Day 6 ($p > 0.05$). Starting from Day 7 and until the follow-up completion, the patients showed a significant difference in the self-assessment scores of both symptom severity and its regression: -92.2% in the main group and -83.2% on Day 7 to almost completely resolved symptoms on Day 10: 0.01 ± 0.11 points, regression -99.7% in the main group and 0.19 ± 1.17 points, regression -96.1% in the control group. The difference between groups between Day 7 and Day 10 is significant ($p < 0.05$) (Table 7).

On Day 1, the total points value was comparable in the groups and amounted to 22.28 ± 8.72 points in the main group and 26.64 ± 8.61 in the control group ($p > 0.05$). During the treatment between Day 2 and Day 9, the regression of the total self-assessment score was comparable in both groups as no statistically significant difference between the groups was observed ($p > 0.05$). Only on the last day of follow-up (Day 10), there was a significant difference in the total self-assessment score amounted to -0.59 ± 1.63 points, regression -97.4% in the main group and 1.50 ± 2.93 points, regression -94.4% in the control group ($p < 0.05$) (Table 7).

The need to use non-steroidal anti-inflammatory drugs is not a direct indicator of the disease severity and the treatment efficacy. The comparison between the groups is based on the results of NSAIDs intake using Fisher's exact test at a significance level of 0.05 (Figure 2). The day of the last dose intake was considered.

Of 78 patients in the main group, 66 (84.6%) patients recovered while the recovery rate in the control group was 58 (75.3%) out of 77 patients. The residual symptoms of ARS were observed in 12 (15.4%) patients of the main group and 19 (24.7%) patients of the control group. The difference between groups in both cases is not significant ($p = 0.165$) which indicates no significant difference in the treatment outcomes ($p > 0.05$).

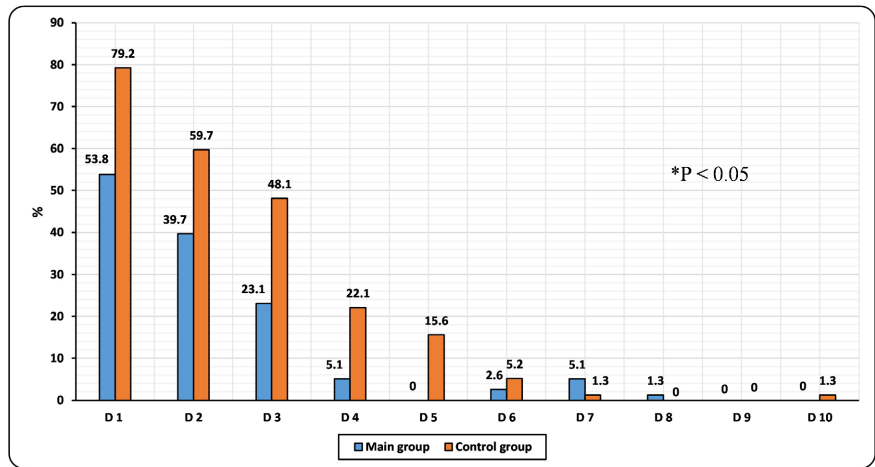


Figure 2. Progression upon NSAIDs intake in groups.

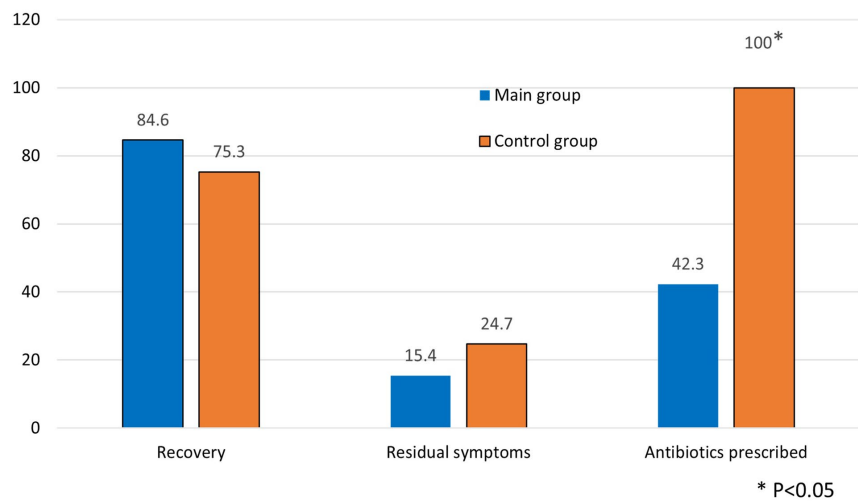


Figure 3. Comparative analysis of treatment outcomes.

According to the study design, a comprehensive assessment of the patient’s condition was carried out at follow-up V2 while in the main group, a decision was made about the need to prescribe antibacterial therapy. Antibacterials were prescribed to 33 (42.3%) out of 78 patients in the main group. In the control group, all 77 patients (100.0%) were administered antibiotics. There is a significant difference in antibiotic intake between patients of the main and control groups ($p = 0.0001, < 0.05$) (Figure 3).

As provided by the study design, the patients of the control group were prescribed antibacterial treatment according to the immediate prescription strategy on V1 for additional comparative analysis of the symptoms progression. For this purpose, the main group was divided into two subgroups: the antibiotics group and antibiotics naive group (Figure 4). The physician’s decision to prescribe antibiotics at V2 could be explained by the insufficient progression of the total points between V1 and V3. The results were compared according to the total points using the Mann–Whitney test. The significance level is set at 0.05.

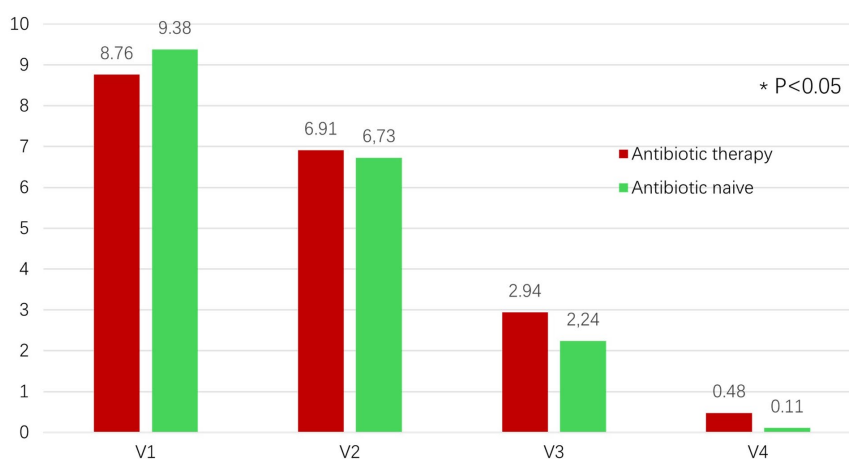


Figure 4. Comparative analysis of total points of symptoms progression in patients of main group.

As can be seen from **Figure 4**, no statistically significant differences were found between the subgroup of patients in antibiotics subgroup and antibiotics naive subgroup in the progression of the total points of the symptoms. Taking into account the absence of a significant difference between the patients in terms of the total points of the symptoms, the analysis of the symptoms progression trend depending on the antibiotic therapy prescription was carried out. Neural network modelling using artificial intelligence technologies was used for this analysis. The modelling result is the determination of the antibiotics prescription efficacy on the further progression of the total points of the symptoms and the statistic values of R^2 , MSE (mean squared error, difference between the actual and predicted values), the regression index with the deduction of the favourable progression percentage of the antibiotics use on the reduction of the total points of the symptoms assessment (**Table 8**).

Table 8. Analysis of favourable progression of antibiotics use on total points of symptoms based on the neural network modelling outcomes.

| Statistics | | | |
|------------|--------|------------------|---|
| R^2 | MSE | Regression index | Percentage of favourable progression of antibiotics use on total points |
| 0.087 | 15.831 | 0.365 | 16.24% |

The modelling outcomes showed no significant relationship between the antibiotics prescription and the subsequent total points progression of the symptoms. A very small value of R^2 and a large value of MSE were registered. In general, the effect of the antibiotics prescribing on the total points progression of the symptoms is < 16.2% in the patients prescribed with antibiotics.

3.3. Safety and Tolerability

Analysis of the tolerability results assessment when prescribing mometasone furoate nasal spray showed that the treatment was well to very well tolerated in all

patients. During the treatment, no side effects were registered in any patient.

4. Discussion

Despite the similarity of clinical manifestations, APVRS shall not be considered as a parameter of the potential ABRS development which occurs in 0.5% to 5% of all cases of ABS. That is why the prophylactic use of antibiotics in patients with non-bacterial forms of ARS does not give any advantage [2] [7]. However, unreasonable antibacterial therapy is prescribed in 54% to 77% of ARS cases [8] [9]. From the point of view of the delayed antibiotics prescription strategy, the search for the treatment options with proven effectiveness which can provide a quick favourable progression from the treatment start in patients with APVRS is relevant [12] [13]. If the initial therapy is insufficiently effective, the antibacterial agent prescription is always considered.

According to the design, the study included patients with diagnostic criteria of moderate to severe or severe ARS which, in the absence of objective diagnostic criteria, may correspond to both a postviral and a bacterial process. Therefore, the patients enrolled in the study had potential indications before the antibacterial therapy prescription which was prescribed to the patients of the control group from the first day of treatment after randomisation while the delayed antibiotics prescription strategy of the patients of the main group was used in the main group. There were no significant differences in the symptom severity parameters between the groups ($p > 0.05$).

The study demonstrated that the use of MF nasal spray as part of the delayed antibiotics prescription strategy has a comparable therapeutic efficacy compared to the immediate prescription in the terms of the symptoms assessment by the physician such as anterior rhinorrhoea, facial pain, and total points of the symptoms. The regression progression of the specified symptoms at V2, V3 and V4 were comparable ($p > 0.05$). The regression value of postnasal drip and headache at V2 was more pronounced in the main group compared to the control group ($p < 0.05$). At V3 and V4, the regression progression of these symptoms was comparable between the groups ($p > 0.05$). The assessment of the nasal congestion by the physician showed significantly better regression value in patients of the main group compared to the control group at all visits: V2, V3, and V4 ($p < 0.05$).

Similar trends were also observed in the analysis of the symptom's progression upon the health state self-assessment by the patients. On Day 1, both groups demonstrated comparable severity parameters for all assessed symptoms ($p > 0.05$). The self-assessment score of the anterior rhinorrhoea and facial pain as well as the total points of the patient's condition in both groups during the treatment showed comparable parameters between Day 2 and Day 9. The difference between the groups was not significant ($p > 0.05$). On Day 10, the difference between the groups was significant due to the main group parameters ($p < 0.05$).

The postnasal congestion regression in patients of the main group was significantly higher between Day 4 and Day 5 ($p < 0.05$). The self-assessment of the

headache in both groups showed comparable severity and regression parameters and no significant difference in parameters between Day 1 and Day 6 ($p > 0.05$). Between Day 7 and Day 10, the difference between the groups was significant ($p < 0.05$). The self-assessment of the nasal congestion, a significant difference was observed in the self-assessment scores of the symptom and its regression between patients of the main and control groups between Day 2 and Day 3 ($p < 0.05$). In the period between Day 4 and Day 10, the self-assessment of nasal congestion and its regression were comparable between the groups ($p > 0.05$).

Thus, significantly better regression of nasal congestion, postnasal drip, and headache was observed when using MF in patients of the main group in the first days of treatment. In terms of such symptoms as anterior rhinorrhoea and facial pain as well as considering the total points, the treatment efficacy was comparable to the antibiotics therapy effectiveness.

MF shows better clinical benefits compared to antibiotics therapy even at the final stages of treatment. There was a tendency towards faster regression of the main symptoms in the patients of the main group that became reliable already at the final stages of treatment.

It was shown that nasal congestion and discharge are among the main, or major, ARS symptoms associated with the swelling of nasal mucous membrane and ostia-meatal complex as well as with the mucus hypersecretion. In terms of using a delayed antibiotic prescription strategy, initial treatment shall be effective, especially for main (major) symptoms. In the main group, upon the symptoms assessment by the physician and the patient's self-assessment of their condition, a reliable therapeutic benefit was observed in the nasal congestion and discharge (postnasal drip) regression already in the first days of treatment when a decision on the delayed antibiotics prescription was made. The results obtained in the study reflect the data showing the proven clinical effect of the MF use for the APVRS treatment [18]-[20]. The high effectiveness of MF in the first days of treatment is based on a multi-target effect on the main pathogenetic mechanisms of mucosal swelling and mucus hypersecretion which are the basis of the indicated clinical manifestations [18]-[20] and contribute to the unreasonable antibacterial therapy prescription. In our study, these effects are enriched by the additional use of phytoextract BNO 1016 [1] [14] [15]. However, the few data showing that MF caused a significant improvement in symptoms compared to amoxicillin were of higher significance in the study outcomes assessment [22]-[24]. In this study, the proven high efficiency of the MF use within the delayed antibiotic prescription strategy is an important argument for avoiding the immediate antibiotics prescription by physicians in the first days of treatment.

Headache or facial pain are minor symptoms of ARS but the pain syndrome intensity serves as an indicator of the disease course severity. The pain syndrome significantly affects the quality of life and increases the likelihood of unreasonable antibacterial agents prescription. In such cases, it is recommended to consider the prescription of non-steroidal anti-inflammatory drugs for adequate pain control [1].

The study showed that the patients of the main and control groups had a significant difference in the need for the NSAIDs intakes between Day 1 and Day 5 of the treatment ($p < 0.05$). This allows us to conclude that a higher regression value of the pain syndrome when using MF in the first days of the treatment contributes to reducing the motivation to prescribe antibacterial therapy. This can be explained by the clinical benefits of the MF use. It is known that headache upon ARS is associated with a violation of the ostio-meatal complex function and the paranasal sinuses blockage due to inflammatory oedema of the mucous membrane. The powerful anti-inflammatory and anti-oedema effect of MF as well as the ability to accumulate in the area of the middle nasal passage contributes to the rapid regression of these impairments and improvement of symptoms both in the first and final days of treatment.

According to the study design, the decision to prescribe antibiotics to patients in the main group was made after evaluating the symptoms regress progression at V2. In such cases, antibacterial therapy was considered justified since the treatment prescribed at V1 did not show sufficient efficacy. Antibacterial therapy was prescribed to 33 (42.3%) patients out of 78 subjects of the main group. In the control group, all 77 patients (100.0%) received antibiotics according to the study design. There is a significant difference in antibiotic intake between the patients of the main and control groups ($p = 0.0001, < 0.05$).

Considering the absence of a significant difference between the groups in the total points of ARS symptoms, the trend analysis of ARS progression depending on the antibiotic therapy prescription was carried out. Since standard statistical methods did not allow to draw statistically reliable conclusions, the analysis was carried out using neural network modelling. It was shown that no statistically significant differences were found in the progression of the symptoms total points between the antibiotics group and the antibiotics naive patients. In general, the effect of the antibiotics prescribing on the total points progression of the symptoms is $< 16.2\%$ in the patients prescribed with antibiotics. The positive dynamics of symptoms under the influence of antibiotics could serve as confirmation of ABRS in no more than 16.2% of patients and, accordingly, of indications for antibiotics prescription. The results obtained reflect the data regarding the validity of antibacterial therapy according to which the unreasonable antibacterial therapy is prescribed in 54% to 77% of ARS patients [8] [9].

Therefore, it was shown that the MF use as part of the delayed antibiotics prescription therapy reliably improves the symptoms progression in the first days of the disease and significantly reduces the frequency of the antibiotics prescription in the main group compared to the control group. The antibiotics prescription frequency corresponds to the current recommendations regarding the need for antibacterial therapy in ARS patients [1] [8] [9].

Thus, an important conclusion of the conducted study is that the use of MF nasal spray in APVRS patients within the delayed antibiotics prescription strategy reduces the need to prescribe antibacterial therapy which in routine practice is

used unreasonably often. The proven high effectiveness of the treatment in terms of the pronounced symptoms regression in the first days as well as the low impact of antibiotic therapy on the symptoms progression in the final days of treatment compared to the MF use will allow for a wider implementation of the delayed antibiotics prescription strategy and significant reduction of the cases of the unreasonable antibacterial agents prescriptions at the first visit.

The study design involved a comparative trial which did not allow for a placebo control. However, the comparison was conducted between the groups treated according to clinical guidelines so its effect could be considered the same between the groups [2] [21]. In this regard, all differences in treatment outcomes could be attributed to the clinical benefits of the MF use since group characteristics were compared.

5. Conclusions

It has been shown that, in addition to standard BNO 1016 therapy in combination with irrigation therapy, the prescription of MF nasal spray (Flix[®]) for the treatment of ARS as part of the delayed antibiotics prescription strategy provides a significant clinical benefit compared to antibacterial therapy, both in the first and final days of treatment. The therapeutic effect of MF reduces the number of cases of the unreasonable antibacterial agents prescription since their justified prescription does not exceed 16%. The inclusion of the medicinal product in the treatment regimen could be recommended for ARS patients as part of the delayed antibiotic prescription strategy.

The perspective of further research is to investigate the MF efficacy in combination with antibiotics.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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