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Efficacy and Safety of Xylometazoline-Based Nasal Sprays with and Without Lysozyme in the Treatment of Acute Nasopharyngitis

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ABSTRACT

Background: Acute nasopharyngitis is a common condition usually accompanied by nasal congestion. The aim of this study was to compare efficacy and safety of a spray containing xylometazoline and lysozyme with a spray containing only xylometazoline in the treatment of acute nasopharyngitis.

Methods: A prospective, comparative, post-marketing study was performed on subjects with acute nasopharyngitis divided into xylometazoline+lysozyme or xylometazoline nasal spray groups. Data collection was performed at baseline before treatment, 30 minutes after treatment and at seven-day follow-up.

Main findings: Out of 173 included subjects, 59 were in the xylometazoline+lysozyme and 114 in the xylometazoline group. In both groups nasal patency was significantly improved 30 minutes after the therapy application ($p<0.001$). In the xylometazoline+lysozyme group, all subjects had nasal decongestion within 20 minutes and this was significantly quicker ($p=0.037$) than the xylometazoline group, where 16 subjects (14%) needed 20 to 120 minutes for nasal decongestion. All adverse events were mild and there was no significant difference in the number of adverse events between the groups.

Principal conclusions: Nasal sprays containing xylometazoline with or without lysozyme were effective and safe in the treatment of acute nasopharyngitis. The spray containing xylometazoline with lysozyme showed a faster effect with significantly shorter time to nasal decongestion. All recorded adverse events were mild and there was no difference between the groups in the number of recorded adverse events.

Key words: nasopharyngitis, nasal obstruction, lysozyme, xylometazoline, nasal sprays

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INTRODUCTION

Acute nasopharyngitis is among the most common infections of the upper respiratory tract. It is usually caused by viral infections (1) and the main symptom is nasal obstruction, estimated to be present in 80% of subjects (2). Treatment is symptomatic, with topical decongestants among the drugs of choice (2). A key ingredient in these decongestants is xylometazoline, which is effective in causing constriction of nasal blood vessels and increasing air-flow (3,4). The activity of this compound could be improved by combination with molecules of distinct mechanisms of activity (4–6). Since the reduction of nasal mucosa inflammation and edema is of special interest in acute nasopharyngitis (7), the natural compound lysozyme could have synergistic effects when combined with xylometazoline. Lysozyme is an antimicrobial protein present in healthy nasal secretions (8). The mucous blanket contains lysozyme and immunoglobulins and plays an important role in immune response (9). Although lysozyme is naturally present in nasal mucus, there are studies indicating that lysozyme levels and activity could be decreased in the common cold (10) and in other conditions such as chronic rhinosinusitis (11). The activity of lysozyme depends on the pH of nasal secretions, which is changed in acute nasopharyngitis (12). Oxymetazoline topical application decreases concentration of lysozyme in the nasal lavage, likely via vasoconstrictive effects and decreased blood flow into the submucosal nasal glands that produce lysozyme (13). No data have been found on the effects of xylometazoline on the concentration of lysozyme in the nasal lavage.

Lysozyme has a crucial role in the nasal mucosa immune response, but its concentrations could decrease with acute nasopharyngitis and nasal decongestant use. It would therefore be of great interest to include lysozyme in the treatment of the condition. The aim of the present study was to compare the efficacy and safety of a spray containing xylometazoline with lysozyme with a spray containing only xylometazoline in the treatment of acute nasopharyngitis.

MATERIALS AND METHODS

Participants

The study population included adult subjects of both sexes with symptoms of acute nasopharyngitis that did not last longer than seven days. The lead investigator allocated subjects the xylometazoline+lysozyme (1+0.5 mg/ml) spray or the xylometazoline spray (1 mg/ml). Non-inclusion criteria were cardiovascular, endocrinological and respiratory diseases, severe septal deviation or nasal polyps, previous surgery on the nasal passages or sinuses, taking medications that may affect nasal obstruction (e.g., systemic steroids, intranasal medications), recent usage of nasal decongestants, symptoms of nasopharyngitis lasting longer than seven days, pregnancy, breastfeeding and hypersensitivity to drug components. Exclusion criteria were the development of serious adverse events that require discontinuation of therapy, development of another disease that affects the course of the examination and withdrawal of informed consent by the subject.

Methods

Before any procedure started, each subject signed a written informed consent form to participate in the trial. The Helsinki Declaration from 1975 and its amendments from 1983 were followed in all procedures. The study was approved by the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (number: 08-07.5-1-8099-1/19).

The primary objective of the study was to examine the efficacy and the secondary objective was to evaluate the safety of the spray containing xylometazoline and lysozyme compared to the spray containing only xylometazoline in subjects with nasal obstruction as part of a cold (J00, acute

nasopharyngitis) under the conditions of routine medical practice. Data collection for each subject was performed during two visits (baseline and first follow-up visit seven days after baseline). At baseline, demographic data about the subject were collected, including risk factors and comorbidities. The visual analogue scale (VAS) was used to assess the subjective severity of nasal passage obstruction before therapy application and 30 minutes after application of the spray in both nostrils, to establish the patency of the nasal passages and concomitant medications. At the follow-up visit the VAS was used again to assess the severity of nasal passage obstruction. Adverse events were monitored at all-time points.

Statistical analysis

Common descriptive statistics (absolute and relative numbers) were calculated. Normal data distribution was evaluated with the Kolmogorov-Smirnov test. Levene's test for equality of variances was used to assess the similarity of variances and the t-test was used to compare body mass index (BMI) between groups. The Mann-Whitney U test was used to compare age, visual assessment of the nasal passage obstruction severity and time required for nasal decongestion. The chi-square test was used to compare gender and comorbidity existence between groups. To assess the difference in the visual assessment of nasal passages obstruction severity at three time intervals, the Friedman test was used, followed by the Wilcoxon signed rank test with Bonferroni correction of the p-value ($p<0.017$ was calculated as a statistically significant value) for comparison between the two measurement times. All tests were two-sided with $p<0.05$ accepted as statistically significant, except where the Bonferroni correction was applied. Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) program, version 23.0.

RESULTS

The study was performed in 30 healthcare centers in Bosnia and Herzegovina from September 2019 to September 2020 and included 173 subjects who received xylometazoline+lysozyme spray (59 subjects) or xylometazoline spray (114 subjects). Age ($U=2736$, $p=0.065$), gender ($\chi2(1)=0.005$, $p=1.000$) and BMI ($t(171) =-1.257$, $p=0.211$) were similar between the groups. A greater percentage of subjects in the xylometazoline group had significant organic disease ($\chi2(1)=8.751$, $p=0.002$) (Table 1).

The Mann-Whitney U test was used to evaluate the differences between the two treatment groups regarding the time needed for nasal decongestion after the first therapy application. Distributions of time were different in each group, as assessed visually. The time needed for nasal decongestion was significantly shorter in the xylometazoline+lysozyme group (mean rank=75.97) compared to the xylometazoline-only group (mean rank=92.71, $U=2712$, $p=0.037$) (Figure 1, Table 1). In the xylometazoline+lysozyme group, all subjects had nasal decongestion within 20 minutes, but in the xylometazoline-only group, 16 subjects (14%) needed 20 to 120 minutes for nasal decongestion (Table 1).

During the study, there was no difference between the groups in the severity of nasal passage obstruction. In both groups, nasal in passage obstruction was significantly different at the three measured time points (xylometazoline+lysozyme group: $\chi2(2)=103.738$, $p<0.001$; xylometazoline-only group: $\chi2(2)=151.974$, $p<0.001$). A significantly better nasal passage patency was recorded in both groups 30 minutes after therapy application compared to the period before therapy application, and at seven-day follow-up compared to both previous data collection points (for all compared time intervals $p<0.001$). None of the subjects had any deterioration in condition of the nasal passages, pharynx and oral cavity, larynx,

external ear canal or eardrum during the examination. All adverse events were mild, with two recorded in the xylometazoline+lysozyme group and five in the xylometazoline-only group. There was no significant difference in the number of adverse events between the groups (p=1,000, Fisher's exact test).

Table 1. Measured parameters before therapy, 30 minutes after and seven days after therapy

Parameter	All subjects (n=173)	Xylometazoline + lysozyme (n=59)	Xylometazoline (n=114)	p-value xylometazoline+lysozyme vs. xylometazoline
Age, years*	33 (26 — 45)	36 (29 — 47)	32 (25 — 45)	0.065
Gender M/F†	56 (32)/ 117 (68)	24 (41)/ 35 (59)	32 (28)/ 82 (72)	1.000
Body mass index (BMI)‡	24.1 (± 3.3)	24.5 (± 3.1)	23.8 (± 3.4)	0.211
Significant organic disease†	**29 (16)**	**3 (5)**	**26 (23)**	**0.002**
Cardiovascular†	5 (3)	0 (0)	5 (4)	
Respiratory†	2 (1)	0 (0)	2 (2)	
Hepatobiliary†	0 (0)	0 (0)	0 (0)	
Gastrointestinal†	11 (6)	0 (0)	11 (10)	
Another disease†	11 (6)	3 (5)	8 (7)	
Time required for complete nasal decongestion after first therapy application (minutes)*	**3.0 (1.0 — 10.0)**	**3.0 (0.6 — 5.0)**	**4.0 (1.0 — 15.0)**	**0.037**
Time ranges for complete nasal decongestion after first therapy application				**0.032**
1 minute or less†	61 (35)	19 (32)	42 (37)	
1.1 - 5.0 minutes†	52 (30)	31 (53)	21 (18)	
5.1 - 10.0 minutes†	22 (13)	6 (10)	16 (14)	
10.1 - 20.0 minutes†	22 (13)	3 (5)	19 (17)	
20.1 - 40.0 minutes†	4 (2)	0 (0)	4 (4)	
40.1 - 60.0 minutes†	6 (3)	0 (0)	6 (5)	
60.1 - 120.0 minutes†	6 (3)	0 (0)	6 (5)	
Visual assessment of nasal passage obstruction severity on a scale from 1 (smallest) to 10 (highest)				
Before therapy application*	7.0 (5.0 — 8.0)	6.0 (4.5 — 8.0)	7.0 (5.0 — 8.0)	0.111
30 minutes after therapy application*	4.0 (3.0 — 5.0)	4.0 (2.0 — 5.5)	4.0 (3.0 — 5.0)	0.745
Seven days after therapy application*	0.0 (0.0 — 1.0)	0.0 (0.0 — 2.0)	0.0 (0.0 — 1.0)	0.295

Data are presented as *median (interquartile range, IQR), †absolute number (percentage of the total number of respondents in the group) or as ‡mean (± standard deviation)

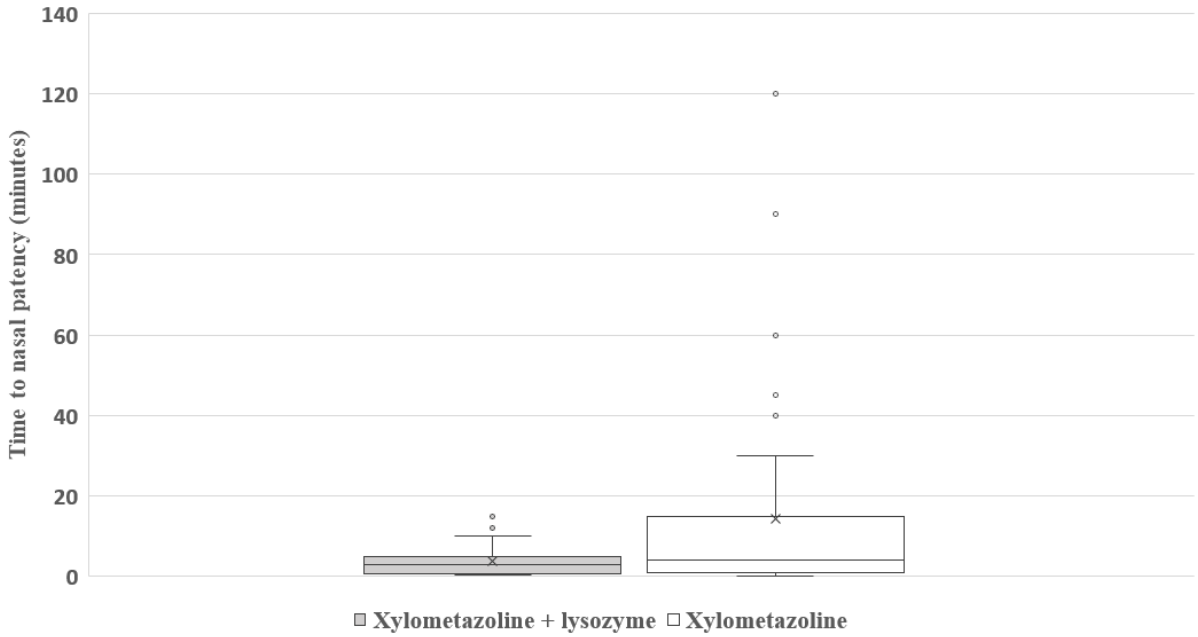

Figure 1. Time to patency of nasal passages after application of xylometazoline+lysozyme or xylometazoline-only nasal spray in both nostrils. The middle line in the box represents median, the bottom line the first quartile and the top line the third quartile. The x in the box represents the mean and the whiskers extend to the minimum and maximum values if no outliers are present, or the third quartile plus 1.5 × IQR if outliers are present. Outliers are represented by dots above whiskers.

DISCUSSION

This study showed that both nasal sprays containing xylometazoline with or without lysozyme were effective and safe in the treatment of acute nasopharyngitis. The spray containing xylometazoline and lysozyme had faster decongestant effects than the spray containing only xylometazoline. Most previous studies have evaluated the effects of xylometazoline in healthy subjects (5,14). Several studies show results regarding the time to decongestion after application of xylometazoline 0.1% spray in subjects with common cold or coryza. While Hamilton reported decongestion from 10 minutes to five hours after application of xylometazoline 0.1% nasal spray in subjects with coryza (15), Eccles et al. showed that median peak relief in nasal obstruction occurred after 30 minutes in both xylometazoline 0.1% and placebo groups of subjects with common cold (3). Faster decongestion in the group receiving xylometazoline and lysozyme could be due to effects of lysozyme on nasal cilia movement. Previous work has shown that hen egg white lysozyme hydrochloride accelerates ciliary beats and is involved in removing overlying mucus in vitro (16). Xylometazoline could also decrease mucociliary transport time and increase nasal airflow resistance in certain subjects (17).

In both examined groups, visual assessment of nasal passage obstruction showed improvements at both time points measured. The efficacy of xylometazoline spray (3,5) and xylometazoline with lysozyme spray (18) has previously been demonstrated. Both therapies were safe and there were only mild adverse events recorded. No difference was seen in the number of reported adverse events between the groups. Xylometazoline (3,5,19,20) and lysozyme (21) are compounds with confirmed safety profiles and have long been used in the therapeutic and the food industries.

The group of subjects receiving only xylometazoline had more comorbidities. This is probably because the medical doctors involved in the study were more likely to include only xylometazoline therapy to these

subjects. However, this approach should be changed considering that lysozyme is a natural compound found in nasal secretions (8). The spray containing xylometazoline and lysozyme has proven efficacy and safety and has been registered as an over-the-counter (OTC) medicine in Bosnia and Herzegovina for more than four years (18). Lysozyme is considered a natural, alternative antibiotic with synergistic effects when combined with other antimicrobial compounds (22). One hundred years since the discovery of lysozyme in nasal secretions, importance of this enzyme is yet to be fully recognized and utilized in therapy (23).

The limitations of this study were open labeling and the physicians' decision to allocate subjects to specific treatment groups. Randomized, blinded studies should be performed to confirm findings.

CONCLUSIONS

Nasal sprays containing xylometazoline with or without lysozyme are effective and safe in the treatment of acute nasopharyngitis. The spray containing xylometazoline with lysozyme showed a faster effect with significantly shorter time to nasal decongestion. All recorded adverse events were mild and there was no difference between the groups in the number of recorded adverse events.

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CONFLICT OF INTEREST
Aziz Šukalo, Meliha Mehić, Amna Tanović Avdić, and Una Glamočlija disclose the following relationships – employees of Bosnalijek d.d., a pharmaceutical company producing lysozyme- and xylometazoline-based medicines. Bosnalijek d.d. had a role in the design of the study; in the collection, analyses and interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

AUTHORS' CONTRIBUTIONS
Conception and design: AS, AŠ, MM, JDžJ, ATA, LK, ST, MTČ, and UG; Acquisition, analysis and interpretation of data: ZPi, ZPu, SI, ĐH, AS, AŠ, MM, JDžJ, ATA, , LK, ST, and UG; Drafting the article: MM, JDžJ, ATA, and UG; Critical revision for important intellectual content: ZPi, ZPu, SI, ĐH, AS, AŠ, LK, ST; All authors approved the final version of the manuscript.

ETHICAL BACKGROUND

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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