

Comparative Study of the Efficacy of the Lysozyme, Benzydamine and Chlorhexidine Oral Spray in the Treatment of Acute Tonsillopharyngitis - Results of a Pilot Study

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Introduction

Acute tonsillopharyngitis is among the most common infections in adults, and it is the second most common reason for visiting a doctor (1). Although it is a self-limiting condition, patients usually seek help for the immediate relief of symptoms such as pain, difficulty in swallowing and the throat swelling.

Objective. Lysozyme is a natural antimicrobial and immunomodulatory enzyme, which is produced as a host response to infectious agents. The objective of this study was to compare the efficacy and safety of lysozyme-based versus benzydamine and chlorhexidine-based oral spray in patients with an acute tonsillopharyngitis associated with a common cold. **Patients and Methods.** A prospective two-arm pilot study (lysozyme/cetylpyridinium/lidocaine spray versus: benzydamine spray—arm 1; chlorhexidine/lidocaine spray—arm 2) was conducted in the primary health care unit. Efficacy was evaluated by the patient's self-assessment of pain, difficulty in swallowing and the throat swelling, by using the visual analog scale (VAS) at baseline and three follow-up visits. Safety was evaluated by the assessment of the frequency and severity of adverse effects. **Results.** Lysozyme-based spray reduced pain faster than benzydamine-based spray and slower than chlorhexidine-based spray. Lysozyme-based and chlorhexidine-based sprays similarly reduced difficulty in swallowing, but were faster than benzydamine-based spray. Similar effects on the reduction of throat swelling were seen in all treated groups. All tested products showed proper safety and were well tolerated, with no serious adverse events reported. **Conclusions.** The lysozyme-based oral spray was shown to be effective and safe in the reduction of pain, difficulty in swallowing and throat swelling in patients with acute tonsillopharyngitis associated with a common cold. Lysozyme-based oral spray (containing natural compound with advantages of influencing immune system and preventing recurrences) had similar activity to benzydamine and chlorhexidine-based oral antiseptic sprays.

Viruses are responsible for 85-95% of acute tonsillopharyngitis cases in adults. In contradiction with the European guidelines for the treatment of acute viral tonsillopharyngitis, the antibiotic treatments are still inappropriately prescribed (2). Moreover, acute tonsillopharyngitis is, along with otitis and sinusitis, the leading cause of prescribing antibiotics in the world (2). Unreason-

able prescribing of antibiotics increases the risk of bacterial resistance, a stumbling block in the modern health care system (2, 3). Being the frequent indication for prescription of antibiotics, treatment of acute tonsillopharyngitis significantly contributes to an increase of antimicrobial resistance and treatment costs (4).

In the absence of complications, such as bacterial superinfection, symptoms of acute tonsillopharyngitis can be successfully reduced using local symptomatic treatment (5). Moreover, many over-the-counter (OTC) drugs, such as lysozyme, cetylpyridinium, lidocaine, benzylamine, and chlorhexidine, are available today for the topical treatment of those patients. Oral antiseptics are characterized by direct effects on viral and inflammatory causes, enabling reduction of local pain, rapid onset of action, efficacy and an excellent safety profile in the treatment of acute tonsillopharyngitis (6). Those preparations usually come in the form of sprays, solutions for gargling and lozenges or oriblettes that are applied directly to the mouth or throat mucosa, and are frequently used in the symptomatic treatment of acute uncomplicated cases of tonsillopharyngitis (6-9).

The available data from the comparative clinical trials, mainly placebo-controlled trials, indicate the efficacy and safety of benzylamine-based and chlorhexidine-based oral antiseptics in the topical treatment of acute pharyngitis associated with common cold (7, 8, 10, 11). However, the data regarding the comparison of lysozyme-based versus benzylamine-based and chlorhexidine-based antiseptics in the form of oral spray are limited.

The objective of this pilot study was to compare the efficacy and safety of antiseptics in the form of the oral spray (lysozyme-based versus benzylamine-based spray, and lysozyme-based versus chlorhexidine-based spray) in patients with an acute tonsillopharyngitis associated with a common cold.

Patients and Methods

Study Design and Data Collection

Prospective, two-arm pilot study was conducted in patients with an acute tonsillopharyngitis associated with a common cold. Patients aged 18 years and older with symptoms of acute tonsillopharyngitis which was confirmed at the baseline visit by clinical findings and symptoms on the expanded 21-point Tonsillo-Pharyngitis Assessment (TPA) were recruited in the study in the primary health care unit. Patients were assigned to one of two study arms, i.e. one of two antiseptics. In the first study arm, patients treated with lysozyme/cetylpyridinium/lidocaine oral spray (Lysobact COMPLETE Spray, Bosnalijek JSC Sarajevo, Bosnia and Herzegovina) were compared to patients treated with benzylamine oral spray, while in the second study arm, patients treated with lysozyme/ cetylpyridinium/oral lidocaine spray were compared to patients treated with chlorhexidine/lidocaine oral spray. Concomitant therapy with analgesics, antiinflammatory and antimicrobial drugs were considered exclusion criteria.

Ethics Statement

Medicines & Medical Devices Agency of Bosnia and Herzegovina approved the study. All procedures were made by following the Helsinki Declaration from 1975 and its amendments from 1983.

Evaluation of Efficacy and Safety

Efficacy of local antiseptics was evaluated by analyzing the visual analog scale (VAS) filled out by the patient for the self-assessment of pain, difficulty in swallowing and the throat swelling. Safety was evaluated based on the frequency and severity of the adverse effects of local antiseptics.

Data Collection

The data were collected during the baseline visit and three follow-up visits, at Day 2, Day 3 and Day 5. The data collected at the baseline visit were: general aspect, TPA score (oral temperature, oropharyngeal color, size of tonsils, number of oropharyngeal exanthemas, largest size of anterior cervical lymph nodes, number of anterior cervical lymph nodes, maximum tenderness of some anterior cervical lymph nodes), VAS assessment of pain, difficulty in swallowing and the throat swelling. The data collected at each follow-up visits were: general aspect, VAS assessment of pain, difficulty in swallowing and the throat swelling and the data on the adverse effects.

Statistical Analysis

Normality of quantitative variables distribution was assessed by Kolmogorov-Smirnov test. The significance of the relationship between two categorical variables was analyzed with χ^2 test. The significance of differences between groups for non-normally distributed variables was assessed using Mann-Whitney U test. Friedmans test was used to detect differences in treatments across multiple test attempts and the difference between baseline and follow up visit was tested using Wilcoxon signed-rank test. The statistically significant level was defined as $P<0.05$. Statistical analyses were performed using SPSS 23.0 package (SPSS Inc., Chicago, IL, USA).

Results

In the first study arm, out of 36 patients included, 4 patients were excluded because of the need to include antibiotic or analgesic therapy. Finally, 15 patients were treated with lysozyme-based spray and 17 patients with benzylamine based spray. Demographic characteristics and TPA score of patients in the first study arm are presented in Table 1.

In the paired efficacy analysis (Table 2), a significant reduction in all VAS scores (pain, difficulty in swallowing, throat swelling) for both medicines (lysozyme vs benzylamine based products) (Friedman's test, $P<0.001$) was shown. Both products showed proper safety and were well tolerated, with no serious adverse events reported.

Demographic characteristics and TPA scores of patients in the second study arm are presented in Table 3. In the second study arm, out of 36 patients included, 5 patients were excluded because of the need to include antibiotic or analgesic therapy. Finally, 17 patients were treated with lysozyme-based spray and 14 patients with chlorhexidine-based spray.

In the paired efficacy analysis (Table 4), a significant reduction in all VAS scores (pain, difficulty in swallowing, throat swelling) for both medicines (lysozyme vs chlorhexidine-based products) (Friedman's test, $P<0.001$) was shown. No serious adverse events were recorded, and both products were considered safe and well tolerated.

Table 1. Demographic Characteristics and Tonsillo-Pharyngitis Assessment Scores of Patients Treated with Lysozyme/Cetylpyridinium/Lidocaine Spray and Bezydamine Spray

Characteristics	Treatment		
	Lysozyme/cetylpyridinium/Lidocaine spray	Benzylamine	P
Gender, female [n (%)]	8 (53.3)	11 (64.7)	0.513*
Age, (years, median, min– max)	36 (18–93)	40 (20–75)	0.151*
TPA score median (min–max)	5 (3–10)	6 (1–11)	0.710†

*Chi square test; †Mann-Whitney U test; TPA=Tonsillo-Pharyngitis Assessment.

Table 2. Comparison of Visual Analog Scale Scores of Pain, Difficulty in Swallowing and the Throat Swelling Between Lysozyme/Cetylpyridinium/Lidocaine Spray and Benzydamine Spray at Baseline and Follow-Up Visits

VAS	Visit	Treatment			
		Lysozyme/cetylpyridinium/ lidocaine		Benzylamine	
		Median (min-max)	P*	Median (min-max)	P*
Pain	Baseline	4.0 (1-6)		2.2 (0-7)	
	Day 2	3.0 (1-4)**	<0.001	2.2 (0-5)	<0.001
	Day 3	1.0 (0-3)**		1.4 (0-4)**	
	Day 5	0.5 (0-1)**		1.0 (0-2)**	
Difficulty in swallowing	Baseline	3.2 (1-6)		2.3 (0-7)	
	Day 2	2.5 (1-5)**	<0.001	2.3 (0-5)	<0.001
	Day 3	1.0 (0-3)**		1.1 (0-3)**	
	Day 5	0.0 (0-3)**		0.6 (0-1.5)**	
Throat swelling	Baseline	4.0 (1-7)		1.9 (0-6)	
	Day 2	2.0 (0-6)**	<0.001	0.7 (0-4)**	<0.001
	Day 3	0.50 (0-3)**		0.0 (0-2)**	
	Day 5	0.0 (0-3)**		1.0 (0-1)**	

VAS=Visual analog scale; *Friedman's test; **Wilcoxon test (follow up visit vs. baseline) P<0.05.

Table 3. Demographic Characteristics and Tonsillo-Pharyngitis Assessment (TPA) Scores of Patients Treated with Lysozyme/Cetylpyridinium/Lidocaine Spray and Chlorhexidine/Lidocaine Spray

Characteristics	Treatment		P
	Lysozyme/cetylpyridinium/lidocaine spray	Chlorhexidine/lidocaine spray	
Gender, female, n (%)	12 (70.6)	5 (35.7)	0.052*
Age, years, median, (min- max)	37 (27-68)	53.5 (29-81)	0.003‡
TPA score, median (min-max)	4 (1-16)	6.5 (3-14)	0.092‡

*Chi square test; ‡Mann-Whitney U test. TPA=Tonsillo-Pharyngitis Assessment.

Table 4. Comparison of Visual Analog Scale (VAS) Scores of Pain, Difficulty in Swallowing and the Throat Swelling Between Lysozyme/Cetylpyridinium/Lidocaine Spray and Chlorhexidine/Lidocaine Spray at Baseline and at Follow-Up Visits

VAS	Visit	Treatment			
		Lysozyme/cetylpyridinium/ Lidocaine spray		Chlorhexidine/Lidocaine spray	
		Median (min-max)	P*	Median (min-max)	P*
Pain	Baseline	3.0 (0-7)		3.6 (1-6.5)	
	Day 2	3.0 (0-4.7)	<0.001	3.25 (1-5.9)**	<0.001
	Day 3	1.5 (0-3.3)**		2.0 (0-5)**	
	Day 5	0.0 (0-1.6)**		0.5 (0-2.6)**	
Difficulty in swallowing	Baseline	3.4 (0-6.7)		3.35 (1-6)	
	Day 2	2.8 (0.5-0.5)**	<0.001	3.0 (1-6)**	<0.001
	Day 3	1.3 (0-3)**		1.9 (0-5)**	
	Day 5	0.0 (0-1.6)**		0.5 (0-2.6)**	
Throat swelling	Baseline	2.0 (0-6.3)		2.5 (0-7)	
	Day 2	2.0 (0-3.5)	<0.001	2.5 (0-5.4)	<0.001
	Day 3	0.0 (0-3)**		1.25 (0-5)**	
	Day 5	0.0 (0-1.6)**		0.0 (0-2)**	

VAS=Visual analog scale; *Friedman's test; **Wilcoxon test (follow up visit vs. baseline) P<0.05.

Discussion

To our knowledge, this is the first study to compare lysozyme-based and other anti-septics in the form of oral sprays in patients with acute tonsillopharyngitis associated with a common cold. The lysozyme-based oral spray was shown to be effective and safe in the reduction of pain, difficulty in swallowing and throat swelling.

In the reduction of pain, lysozyme-based oral spray showed the faster onset of action compared to benzylamine-based spray, but delayed onset of action compared to chlorhexidine-based spray. In the reduction of difficulty in swallowing, lysozyme-based oral spray was similar to chlorhexidine-based spray but showed faster onset of action compared to benzylamine-based spray. In the reduction of throat swelling, the similar results were obtained for all treatments (lysozyme, benzylamine and chlorhexidine-based sprays).

Lysozyme, an antiseptic, is also known to have antibiotic and antiviral effects (12). Additionally, as a natural enzyme, it has an overall role in the body justifying the name - "enzyme of the future" (13). Unlike other antiseptics, in addition to its anti-inflammatory activity, lysozyme possess immunomodulatory activity. As an integral component of natural cells of the immune system, it is one of the most critical elements of the local non-specific microbial resistance of the mucosa. This is supported by the fact that the levels of immunoglobulins and lysozyme correlate (13). Also, studies demonstrated the efficacy of lysozyme-based preparations in the local treatment of pharyngitis and tonsillitis in children and adults (10, 14). According to a study with the patient reported outcomes, an oral spray containing the combination of lysozyme-chloride and cetylpyridinium-chloride could quickly, efficiently and safely solve the acute symptoms of tonsillopharyngitis associated with

common cold (9). In the treatment of a sore throat, the local symptomatic therapy aims primarily to reduce the pain (6), and the pain reduction is usually the primary outcome of clinical trials testing the efficacy of different treatments for a sore throat (15). However, besides pain reduction, the impact of additional beneficial effects such as anti-inflammatory, immunomodulatory, pro-regenerative should influence the choice of optimal therapy. Therefore, lysozyme based preparations open new perspectives in the treatment of those patients.

Benzylamine is a locally-acting non-steroidal anti-inflammatory drug with local anesthetic and analgesic properties. It is widely used in the symptomatic treatment of pain, irritation and other symptoms of inflammation of the oropharynx (8). Although benzylamine in the form of oral rinse showed the more significant reduction of pain and dysphagia compared to placebo in patients with viral pharyngitis or tonsillitis (16), in our study, in the form of the oral spray, it showed slower efficacy in reduction of difficulties in swallowing when compared to lysozyme-based spray.

In concordance with our results, chlorhexidine-based antiseptic in the form of lozenges was effective in the treatment of a sore throat in patients with upper respiratory infection (17). In the form of an oral spray, chlorhexidine-lidocaine was also as effective and safe as a product based on echinacea and sage (18). In a study that compared the efficacy of benzylamine oral spray and chlorhexidine oral spray for the treatment of streptococcal tonsillopharyngitis, both antiseptics have proven successful as an adjunct to standard antibiotic therapy (7).

Limitations of the Study

The major limitations of this study are the small sample size, no randomization and no

control arm. Larger prospective randomized placebo controlled studies are needed to confirm the obtained results.

Conclusion

The lysozyme-based oral spray was shown to be effective and safe in the reduction of pain, difficulty in swallowing and throat swelling in patients with acute tonsillopharyngitis associated with a common cold. Lysozyme-based oral spray (containing natural compound with advantages of influencing immune system and preventing recurrences) had similar activity to benzylamine and chlorhexidine-based oral antiseptic sprays.

What Is Already Known on this Topic

Bacterial resistance is one of the most significant problems in modern medicine. Although viruses are responsible for 85-95% acute tonsillopharyngitis in adults, antibiotics are often prescribed for this indication contributing to increasing of antimicrobial resistance and treatment costs. Local symptomatic treatment can be employed for reduction of symptoms of acute tonsillopharyngitis not associated with complications such as bacterial superinfection. There are many over-the-counter drugs which can be used for this purpose. Among them, lysozyme based preparations attract attention since it is a natural component of the human immunity (with activity against bacteria, fungi, and viruses and anti-inflammatory effects). There are no data comparing efficacy and safety of lysozyme-based products versus other antiseptics in patients with an acute tonsillopharyngitis associated with a common cold.

What this Study Adds:

This study confirmed that lysozyme/cetylpyridinium/lidocaine oral spray is effective and safe in patients with acute tonsillopharyngitis. Moreover, lysozyme-based oral spray (containing natural compound with advantages of influencing immune system and preventing recurrences) had similar activity to benzylamine and chlorhexidine-based oral antiseptic sprays in the reduction of pain, difficulty in swallowing and throat swelling in patients with acute tonsillopharyngitis associated with a common cold.

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