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Efficacy and Safety of Lysozyme, Cetylpyridinium and Lidocaine Fixed Combination for Treatment of Chemotherapy- and Radiotherapy-Induced Oral Mucositis: a Pilot Study

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ABSTRACT

Introduction: Beneficial effect of local administration of lysozyme in patients with recurrent aphthous stomatitis was demonstrated, but there are no published studies focused on treatment of chemotherapy or radiotherapy induced oral mucositis with lysozyme. **Aim:** The aim of this study was to compare efficacy and safety of Lysobact Complete spray (lysozyme, cetylpyridinium, and lidocaine) and compounded medication for local use in the treatment of radio- and chemo-therapy induced oral mucositis. **Patients and Methods:** This observational, phase IV study was designed as prospective cohort investigation, and conducted at two sites, Clinical Hospital Zenica and University Clinical Center Tuzla, Bosnia & Herzegovina, from August to November, 2018. The patients with oral mucositis after radio- or chemo-therapy were treated by either registered lysozyme-based or compounded medication (standardized and bicarbonate-based) for 21 days. **Results:** Both lysozyme-based (Lysobact Complete Spray) spray (lysozyme, cetylpyridinium and lidocaine) and compounded medication for local use were effective in local treatment of chemotherapy and radiotherapy-induced oral mucositis. However, lysozyme-based preparation was more effective, since signs of inflammation, number of oral ulcers and intensity of pain during eating and speaking withdrew to a greater extent than with highly variable compounded medication for local use. No adverse events were recorded in both treatment arms. **Conclusions:** Locally administered spray with fixed combination of lysozyme, cetylpyridinium and lidocaine (Lysobact Complete Spray) is very efficient and completely safe treatment of both radiotherapy and chemotherapy-induced oral mucositis.

Keywords: oral mucositis; lysozyme; radiotherapy; chemotherapy; treatment.

1. INTRODUCTION

Oral mucositis is an inflammation of oral mucosa induced by radio- or chemo-therapy, or by some other factor that causes damage of the oral mucosa (1). It characteristically develops in two phases, subepithelial one, which is characterized by hyperemia, edema and release of numerous inflammatory cytokines and autacoids, followed by epithelial phase, when parts of the epithelial lining slough, creating ulcers (2). Radiation-induced oral mucositis develops in 41.9% of patients, and is more prevalent among males (78.2%) (3), while chemotherapy induces oral mucositis in 16.7% - 40% of patients (1) (4). Oral mucositis causes severe pain and interferes with eating and speaking, severely decreasing quality of life (5).

Current recommendations for treatment of radiation-induced oral mucositis include laser therapy, normal saline and sodium bicarbonate mouth washes, and local administration of non-steroid anti-inflammatory drugs, while chlorhexidine gargles found its place in the prevention and treatment of chemotherapy-induced oral mucositis. Patients with both types of mucositis will benefit from careful use of povidone-iodine locally and antifungal drugs systemically (6). Lysozyme is ubiquitous anti-

microbial protein which is mainstay of innate immunity, and it could be found in blood, at mucosal surfaces, in liver, in tears, in saliva, in milk, in urine, and in phagocytes (7). Lysozyme causes hydrolysis of peptidoglycan within the cell wall, and is active against both bacteria and fungi, but it was scarcely used for therapeutic purposes in the past. It binds strongly to mucus glycoproteins keeping integrity of mucosal layer and promoting in the same time regeneration of epithelial cells. Lysozyme also has immunomodulatory role (degradation products of bacteria bind to pattern recognition receptors of host immune cells), contributing to the resolution of inflammation at mucosal sites; antioxydant and anti-allergy actions were also demonstrated. Several small, uncontrolled studies (8) (9) and one recent double-blind, randomized study (10) demonstrated beneficial effect of local administration of lysozyme in patients with recurrent aphthous stomatitis, but there are no published studies focused on treatment of chemotherapy or radiotherapy induced oral mucositis with lysozyme-based preparations for local administration in oral cavity.

2. AIM

The aim of this study was to compare efficacy and safety of Lysobact Complete Spray (lysozyme, cetylpyridinium, and lidocaine) and compounded medication for local use in the treatment of radio- and chemo-therapy induced oral mucositis.

3. METHODS

This observational, phase IV study was designed as prospective cohort investigation, and conducted at two sites, Clinical Hospital Zenica and University Clinical Center Tuzla, Bosnia & Herzegovina, from August to November, 2018. The study included adult (≥18 years old) patients with neoplasms, treated either by radiotherapy or by chemotherapy with one of the following protocols: 5-fluorouracil - based or capecitabine/taxanes/ anthracyclines /cisplatin – based. The patients allergic to study drugs or egg's white and pregnant or lactating women were not included in the study, while the exclusion criteria were: main disease progression, serious adverse reactions to radiotherapy, chemotherapy or study medication, and very severe form of oral mucositis, with deep ulcers, pain requiring systemic analgesia and/ or complete inability to speak and eat both hard and soft food. The study was approved by Drug Agency of Bosnia and Herzegovina. The patients were enrolled in the study at their first presentation to an oncologist with complaints of symptoms raising suspicion to oral mucositis. After signing the informed consent, the study patients were examined by their attending oncologists, and pain that they feel during eating hard food, eating soft food or speaking was measured by visual analogue scales (from 0 to 10). The same procedure was repeated after 7, 14 and 21 days from the enrollment. On the first study visit the patients were prescribed either Lysobact Complete Spray (lysozyme hydrochloride 20 mg/ml + cetylpyridinium 1.5 mg/ml + lidocaine 0.5 mg/ml, Bosnalijek, Sarajevo, Bosnia & Herzegovina) or compounded medication (standardized bicarbonate-based preparations) from community pharmacies within the region, according to preferences of their attending oncologists. In this way, four study groups were formed: two chemotherapy groups treated either by Lysobact or by the compounded medication, and two radiotherapy groups treated either by Lysobact or by the compounded medication. The patients were instructed to spray their mouth 5 times repeatedly with the prescribed preparation every 4 to 8 hours, for the next 21 days. The following outcomes were recorded at each of the study visits: presence of oral mucosa hypersensitivity and/ or erythema, presence and number of oral ulcers, intensity of pain during eating hard food, during eating soft food and during speaking, and adverse reactions to the study medication. Recorded values of continuous variables were summarized by measures of central tendency (mean and median) and variability (standard deviation and range), after checking for normality of the data distribution. Values of categorical variables were described by rates and percentages. Significance of difference between the study groups was tested by Student's T-test or Mann-Whitney U test (if the data were not normally distributed) for continuous variables, and by Chi-square test of Fisher's test (for rates lower than 5). The differences were considered significant if probability of zero-hypothesis was equal or less than 0.05. All calculations were performed by Microsoft Excel or SPSS software, version 18.

4. RESULTS

4.1. Patients on chemotherapy

There were 89 patients receiving chemotherapy, whose oral mucositis was treated either by Lysobact Complete Spray or by medications compounded in community pharmacies; characteristics of the study sample are shown in the Table 1.

In patients treated with Lysobact Complete Spray , local findings at 21st day compared to before the treatment were significantly improved on lips (X2=19.2; p=0.001), cheeks (X2=11.6; p=0.009), tongue (X2=12.8; p=0.005) and palate (X2=11.5; p=0.012). In patients treated with by compounded medication, local finding was not significantly improved at 21st day compared to before the treatment (lips-X2=3,3; p=0,2; cheeks-X2=6.7; p=0.35; tongue-X2=6.1 p=0.11 and palate-X2=10.2; p=0.11).

Patients treated with Lysobact Complete Spray showed significantly improved local findings compared to patients treated by compounded medication during the treatment period as observed on lips (X2=11.3; p=0.004), cheeks (X2=15.2; p=0.001), tounge (X2=27.1; p<0.001) and palate (X2=22.4; p=0.001) (Table 2).

Average number of mucosal ulcers in oral cavity at presentation (before the treatment) was similar in both study groups (2.9±2.8 vs. 3.7±2.6; p=0.15), and then decreased significantly with both types of treatments. However, the average number of mucosal ulcers was significantly lower in patients treated with Lysobact than in patients treated with compounded medication at 7th (0.9±1,2 vs 2.6±2,7; p=0.001), 14th (0.2±0.6 vs 1.6±1.6; p=0.001) and 21st (0.1±0.6 vs 0.6±0.9; p=0.011) day of the treatment of oral mucositis.

Intensity of pain when eating hard food at presentation was similar in both study groups (4.4±3.2 vs. 5.2±2.4; p=0.16), and then decreased significantly with both types

Oral mucositis treated by:		Lysobact (N=54)	Compounded medication (N=35)	p-value
Number of chemotherapy cycles		3.51±2.2	2.91±2.3	0.228
Order of current chemotherapy cycle	1. and 2. cycle	24 (44.4%)	20 (57.1%)	0.23
	3. and 4. cycle	16 (29.6%)	11 (31.5%)	
	⩾ 5. cycle	14 (26.0%)	4 (11.5%)	
Sex (M/F)		22/32 (40.7%/59.3%)	12/23 (34.3%/65.7%)	0.66
Age (years)		60.5±9.4	59.2±11.0	0.56

Table 1. Characteristics of the patients treated by chemotherapy.

	Lysobact (N=54)				Compounded medication (N=35)				p - value
The check-up time	Before the treatment	7th day	14th day	21st day	Before the treatment	7th day	14th day	21st day	
Lips									
Normal finding (%)	57.4	61.1	84.9	96.1	48.6	48.6	64.7	81.3	0.004
Hypersensitivity/erythema (%)	25.9	33.3	11.3	0	48.6	51.4	35.3	18.8	
Erythema/ulcers (%)	7.4	5.6	3.8	3.9	2.9	0	0	0	
Ulcers (%)	9.3	0	0	0	0	0	0	0	
Cheeks									
Normal finding (%)	33.3	55.6	86.8	94,1	14.3	20.0	55.9	71.9	0.001
Hypersensitivity/erythema (%)	31.5	38.9	9.4	0	48.6	68.6	41.2	25.0	
Erythema/ulcers (%)	14.8	3.7	3.8	5,9	28.6	8.6	2.9	3.1	
Ulcers (%)	20.4	1.9	0	0	8.6	2.9	0	0	
Tongue									
Normal finding (%)	40.7	64.8	79.2	96,0	31.4	34.3	52.9	56.3	0.001
Hypersensitivity/erythema (%)	38.9	31.5	17	0	31.4	65.7	47.1	43.8	
Erythema/ulcers (%)	7.4	1.9	3.8	4,0	31.4	0	0	0	
Ulcers (%)	13.0	1.9	0	0	5.7	0	0	0	
Palate									
Normal finding (%)	38.9	55.6	77.4	92,2	20.0	88.6	50	50.0	0.001
Hypersensitivity/erythema (%)	20.4	31.5	17.0	3,9	40.0	60.0	44.1	46.9	
Erythema/ulcers (%)	22.2	11.1	5.7	3,9	28.6	5.7	5.9	3.1	
Ulcers (%)	18.5	1.9	0	0	11.4	5.7	0	0	

Table 2. Local status of oral mucosa in patients receiving chemotherapy and treated by Lysobact Complete Spray or compounded medication

of treatments. However, the average intensity of pain was significantly lower in patients treated with Lysobact than in patients treated with compounded medication at 7th (2.0±2.0 vs 3.3±2.6; p=0.010), 14th (0.5±0.97 vs 1.9±2.0; p=0.001) and 21st (0.2±0.7 vs 1.1±1.1; p=0.001) day of the treatment of oral mucositis.

Intensity of pain when eating soft food at presentation was similar in both study groups (2.0±2.7 vs. 2.9±2.4; p=0.14), and then decreased significantly with both types of treatments. However, the average intensity of pain was significantly lower in patients treated with Lysobact than in patients treated with compounded medication at 7th (0.6±1.3 vs 1.8±1.8; p=0.001), 14th (0.2±0.7 vs 1.0±1.2; p=0.001) and 21st (0.0±0.3 vs 0.3±0.7; p=0.053) day of the treatment of oral mucositis.

Intensity of pain when speaking at presentation was similar in both study groups (0.7±2.1 vs. 1.5±2.3; p=0.10), and then decreased significantly with both types of treatments until the 14th day of treatment, only to remain at the same level until the 21st day. The average intensity of pain when speaking was not significantly different in patients treated with Lysobact and in patients treated with compounded medication at 7th (0.5±1.5 vs 0.6±1.3; p=0.700), 14th (0.0±0.3 vs 0.2±0.7; p=0.100) and 21st (0.0±0.0 vs 0.1±0.3; p=0.330) day of the treatment of oral mucositis.

In both chemotherapy groups no adverse events related to the study medication were recorded.

4.2. Patients on radiotherapy

There were 100 patients on radiotherapy, whose oral mucositis was treated either by Lysobact Complete Spray or by medications compounded in community pharmacies; characteristics of the study sample are shown in the Table 3.

In patients treated with Lysobact Complete Spray , local findings at 21st day compared to before the treatment were significantly improved on cheeks (X2=17.8; p=0.0007) and palate (X2=18.2; p=0.006), while no significant im-

Oral mucositis treated by:	Lysobact Complete Spray (N=50)	Compounded medication (N=50)	p-value
Sex (M/F)	38/16 (77.6%/22.4%)	43 (86.0%)	0.31
Age	65.4±8.9	63.5±7.4	0.26

Table 3. Characteristics of the patients on radiotherapy

	Lysobact Complete Spray (N=50)				Compounded medication (N=50)				p - value
The check-up time	Before the treatment	7th day	14th day	21st day	Before the treatment	7th day	14th day	21st day	
Lips									
Normal finding (%)	58.0	60.0	64.0	72.0	62,0	56.0	40.0	52.0	
Hypersensitivity/erythema (%)	16.0	20.0	18.0	20.0	26,0	30.0	46.0	36.0	
Erythema/ulcers (%)	14.0	14,0	18.0	6.0	10,0	10.0	10.0	10.0	0.210
Ulcers (%)	12.0	6.0	0.0	2.0	2,0	4.0	4,0	2.0	
Cheeks									
Normal finding (%)	20.0	26.0	36.0	42.0	14,0	14.0	16.0	26.0	
Hypersensitivity/erythema (%)	32.0	22.0	24.0	42.0	48,0	42.0	38.0	38.0	
Erythema/ulcers (%)	30.0	32.0	34.0	6.0	26,0	34,0	42.0	28.0	0.027
Ulcers (%)	18.0	20.0	6.0	10.0	12,0	10.0	4.0	8.0	
Tongue									
Normal finding (%)	10.0	4.0	18.0	32.0	0,0	0.0	4.0	16.0	
Hypersensitivity/erythema (%)	30.0	14.0	28.0	38.0	50,0	32.0	26.0	32.0	
Erythema/ulcers (%)	34,0	54.0	44.0	20.0	34,0	44.0	46.0	34.0	0.110
Ulcers (%)	26.0	28.0	10.0	10.0	16,0	24.0	24.0	18.0	
Palate									
Normal finding (%)	36.0	30.0	48.0	64.0	38,0	28.0	26.0	32.0	
Hypersensitivity/erythema (%)	14.0	20.0	24.0	28.0	36,0	32.0	42.0	46.0	
Erythema/ulcers (%)	28.0	32.0	20.0	6.0	12,0	24.0	20.0	16.0	0.013
Ulcers (%)	22.0	18.0	8.0	2.0	14,0	16.0	12.0	6.0	

Table 4. Local status of oral mucosa in patients on radiotherapy and treated by Lysobact Complete Spray or compounded medication.

provements were found on lips (X2=8.1; p=0.09) or tongue (X2=11.7; p=0.07).

In patients treated with by compounded medication, local finding was not significantly improved at 21st day compared to before the treatment at any examination site (lips-X2=1.7; p=0.8; cheeks-X2=7.9; p=0.25; tongue-X2=1.3 p=0.8 and palate-X2=5.2; p=0.5).

Patients treated with Lysobact Complete Spray showed significantly improved local findings compared to patients treated by compounded medication during the treatment period as observed on cheeks (X2=9.2; p=0.027), and palate (X2=10.8; p=0.013), while no significant differences in local findings on lips (X2=3.4; p=0.2), or tongue (X2=5.9; p=0.11) between patients treated with Lysobact Complete Spray compared to patients treated with compound medication was observed (Table 4).

Average number of mucosal ulcers in oral cavity at presentation (before the treatment) was higher in group of patients treated by Lysobact Complete Spray than in the group treated by compounded medication (3.6±2.4 vs 2.1±2.2; p=0.002), then increased after 7 days with both types of treatments, followed by further decrease after 14 and 21 days. The average number of mucosal ulcers was significantly higher in patients treated with Lysobact Complete Spray than in patients treated with compounded medication at 7th day of treatment (3.7±1.8 vs. 2.6±2.1 p=0,006), but at 14th (2.1±2.0vs 2.5±1.8; p=0.250) and 21st (2.2±1.9 vs 1.0±2.1; p=0.002) day number of mucosal ulcers was lower in Lysobact Complete Spray group than in compounded medication group.

Intensity of pain when eating hard food at presentation was higher in group of patients treated by Lysobact Complete Spray than in the group treated by compounded medication (5.6±2.2 vs 4.1± 2.4; p=0.001), and then decreased significantly with Lysobact Complete Spray treatment, while an increase was observed with compounded medication. The average intensity of pain was still significantly higher in patients treated with Lysobact Complete Spray than in patients treated with compounded medication at 7th day of treatment (5.52±2.5 vs 4.72±2.6; p=0.120), but then became much lower at 14th (3.9±2.4 vs 4.8±2.9; p=0.080) and 21st (2.12±2.5 vs 4.44±3.2; p=0.001) day of the treatment of oral mucositis.

Intensity of pain when eating soft food at presentation was similar in both study groups (4.1±3.1 vs. 3.3±2.0; p=0.14), and then decreased significantly with Lysobact

Complete Spray treatment, while the same happened with compounded medication, but only after transitory increase on the 7th day of treatment. The average intensity of pain was almost the same in patients treated with Lysobact Complete Spray and in patients treated with compounded medication at 7th day of treatment (4.0±3.1 vs 4.0±2.1; p=0.750), but on the 14th (2.6±2.4 vs 3.5±2.3; p=0.07) and 21st (3.0±2.0 vs 1.3±2.7; p=0.001) day it became much lower in the Lysobact group.

Intensity of pain when speaking at presentation was higher in the Lysobact Complete Spray group than in the compounded medication group (3.2±2.8 vs. 2.0±1.8; p=0.12), and then decreased significantly with Lysobact Complete Spray treatment, while the same happened with compounded medication, but only after transitory increase on the 7th day of treatment. The average intensity of pain was still higher in patients treated with Lysobact Complete Spray than in patients treated with compounded medication at 7th day of treatment (3.2±2.7 vs 2.5±2.0; p=0.130), but on the 14th (1.24±1.9 vs 2.4±2.1; p=0.005) and 21st (0.8±1.5 vs 2.04±2.3; p=0.002) day it became much lower in the Lysobact Complete Spray group.

In both radiotherapy groups no adverse events related to the study medication were recorded.

5. DISCUSSION

Our study demonstrated clear benefit of lysozyme-based (Lysobact Complete Spray) spray (lysozyme, cetylpyridinium and lidocaine) in local treatment of both chemotherapy and radiotherapy-induced oral mucositis, and its superiority over compounded medication for local use for the same purpose. Signs of inflammation, number of oral ulcers and intensity of pain during eating and speaking withdrew much more with fixed combination of lysozyme, antiseptic and local anesthetic in Lysobact Complete Spray than with compounded medication for local use.

Chemotherapy and radiotherapy-induced oral mucositis responded to the study medication with different dynamic: while in the chemotherapy groups treatment response was marked as early as on the 7th day, and then became more pronounced on the following patient visits, in the radiotherapy groups condition of the patients became worse on the 7th day of the treatment, to be followed by marked improvement after 14 and 21 days. This difference could be explained by different mechanisms and extent of tissue injury by radiotherapy and cytostatic drugs. While chemotherapy-induced oral mucositis becomes apparent as early as 7 days after introduction of the chemotherapy, onset of radiotherapy-induced oral mucositis is delayed to 14th day from beginning of the radiotherapy (11); therefore, peak of the tissue injury with radiotherapy comes later than peak of the tissue injury with chemotherapy, so the treatment response will also be delayed, as observed in our study.

Consistency of beneficial treatment effect of Lysobact Complete Spray over various outcomes was notable in patients on both chemotherapy and radiotherapy. Emergence and extent of visible pathological changes on oral mucosa were related to intensity of pain while eating and speaking, so subjective treatment outcomes were substantiated by objective findings on oral mucosa. Similar congruence of objective and subjective treatment outcomes was previously noted with some other efficient treatment methods of oral mucositis, like low-level laser therapy, which are nowadays widely recommended by treatment guidelines (12). On the other hand, it is characteristic that treatment methods with doubtful efficacy, like local administration of honey, show improvement in subjective, but not in objective treatment outcomes (13).

Excellent safety of lysozyme administered orally was already confirmed in an observational study on patients with tonsillopharyngitis, where 97% of patients tolerated oral spray with combination of lysozyme and cetylpyridinium (14). Its administration in a toothpaste for two months (with an aim to clear extrinsic stains on tooth surface) did not cause a single adverse event related to lysozyme in 70 adult participants with aphtous stomatitis (10). When used orally in patients with chronic obstructive pulmonary disease or bronchial asthma for 28 days, lysozyme did not cause any kind of adverse effect, and the patients tolerated it well (15). Results of these studies, as well as those of our study, suggest excellent safety profile of lysozyme-based products, including Lysobact Complete Spray, further recommending their use in radiotherapy and chemotherapy-induced oral mucositis.

There are a few limitations of our study, including, in the fist place, its observational design, which could not control for numerous confounding variables possibly present in the study sample. Second, although intensity of pain while eating and speaking was measured, quality of life of the patients, which has other dimensions and is one of important outcomes of oral mucositis treatment, was not followed in this study.

6. CONCLUSION

Locally administered spray with fixed combination of lysozyme, cetylpyridinium and lidocaine (Lysobact Complete Spray) is more efficient than bicarbonate-based compounded medication and completely safe treatment of both radiotherapy and chemotherapy-induced oral mucositis.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contributions:** A.R., B. K., A. A., A. MA., S. MJ. and A.L. were included in study conception and design, also in acquisition of data and statistical analysis and interpretation of data. S. MJ. drafting of the manuscript and made critical revision of the manuscript for important intellectual content. Final proof reading was made by A. R. And S. MJ.
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