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# Efficacy and safety of local lysozyme treatment in patients with oral mucositis after chemotherapy and radiotherapy

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This observational clinical study was composed of two substudies: a non-comparative one ($n$ = 166), testing only lysozyme-based compounds (LBCs), and a comparative substudy ($n$ = 275), testing both LBCs and bicarbonate-based local compounds (BBCs) on the healing of oral mucositis during radio- or chemotherapy. The density of ulcerations has decreased significantly after the treatment with lysozyme in both substudies. The density of ulcerations in the radiotherapy group was lower in patients treated with LBCs compared to patients treated with BBCs ($p < 0.001$). In the chemotherapy group, reduction of ulceration density was similar with both LBCs and BBCs. The LBCs reduced pain intensity during the intake of solid food and speech more than BBCs in both patient cohorts ($p < 0.05$). In the radiotherapy cohort, pain intensity when consuming liquid foods was reduced more with LBCs than with BBCs ($p < 0.05$). No adverse events were recorded. This study demonstrates the advantages of treating oral mucositis during radiotherapy or chemotherapy with LBCs.

*Keywords*: oral mucositis, treatment efficacy, radiotherapy, chemotherapy, topical, lysozyme

Oral mucositis is an inflammation of gastrointestinal mucosa accompanying radiotherapy or chemotherapy, most often localized to oral or oropharyngeal mucosa (1) (2). The incidence of oral mucositis depends on the type of therapy (1). It usually appears in all patients between the 7th and the 14th day after the onset of radiotherapy in head and neck cancer patients, whereas 30 to 75 % of patients on chemotherapy have oral ulcers (2) (3). Cytostatic drugs most frequently associated with oral mucositis are antimetabolites, such as 5-fluorouracil, methotrexate and purine antagonists, but this adverse effect is also encountered in patients who take anthracycline antitumor antibiotics (*e.g.* doxorubicin) or taxanes (*e.g.* paclitaxel and docetaxel) (1). It is believed that oral mucositis is a consequence of direct toxic effects of radiotherapy or chemotherapy on the epithelial lining of mucosa (1).

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Patients with oral mucositis experience strong pain and difficulties when swallowing along with impaired feeding, speech, and general functioning, since keeping oral hygiene becomes a difficult task (2–4). Diagnosis of oral mucositis is based on the patient's history and clinical examination. A number of questionnaires for the assessment of oral mucositis were developed, but one the most frequently used in the practice is the Oral Mucositis Assessment Scale (OMAS) (5). Oral mucositis is the leading cause of dose decrease or premature termination of radio- or chemotherapy (decreasing chances of survival), and is accompanied with increased utilization of analgesics and antibiotics, prolonged hospitalization and increased treatment costs (6, 7). It is also considered to be a socio-economic problem since the quality of the patient's life is severely deteriorated. The quality of life in patients with oral mucositis could be assessed by Patient-Reported Oral Mucositis Symptoms (PROMS) scale (8).

The goals of oral mucositis treatment are pain control, healing of ulcers, mucose recovery, and the prevention of secondary infection. Clinicians still do not agree about the optimal treatment protocol for oral mucositis. Currently available therapeutic options are focused on palliative measures including the control of pain, feeding support and keeping oral hygiene. The therapy mostly involves oral antiseptics, corticosteroids for local use and chamomile tea wash-ups. Additional drugs, which may be used for local treatment of oral mucositis, are oral antiseptics, antibacterial, antifungal and antiviral drugs, cytoprotective drugs, mucosa-protecting agents and drugs which stimulate regeneration of damaged mucosa (7). There are several advanced therapeutic options in the clinical development phase: cryotherapy, administration of growth factors, anti-inflammatory drugs, antioxidants and low-voltage laser therapy (9). Although the efficacy of local preparations containing lysozyme has been proved in the treatment of acute inflammatory diseases of the mouth and throat including recurrent aphthous ulcers, they were never tested on oral mucositis after radio- or chemotherapy (10). Lysozyme is present in human saliva and protects oral mucosa by killing bacteria through the hydrolysis of cell wall peptidoglycan matrix. It has also proven regenerative effects, has an immunomodulatory role and contributes to the resolution of inflammation at mucosal sites (11).

The aim of our study was to compare the efficacy and safety of oral lysozyme-based compounds and bicarbonate-based pharmaceutical compounds when used for the treatment of oral mucositis during radio- and chemotherapy.

## EXPERIMENTAL

### *Study design and patients*

Our observational study was composed of two prospective cohort substudies: in the first substudy all patients with oral mucositis after radio- or chemotherapy (179 enrolled, 166 completed the study) were treated with lysozyme-based compounds for local administration, while the other substudy was comparative: the patients with oral mucositis after radio- or chemotherapy (292 enrolled, 275 completed the study) were treated either with the lysozyme-based compounds for local use, or with bicarbonate-based pharmaceutical compounds for local administration. The study was approved by the Drug Agency of Bosnia and Herzegovina and performed in accordance with ethical principles for medical

research involving human subjects (Declaration of Helsinki). The study subjects were enrolled only after signing the informed consent for participation in the study.

The inclusion criteria were age over 18, diagnosis of any type of cancer, currently receiving one cycle of radio- or chemotherapy treatment course and diagnosis of oral mucositis. The exclusion criteria were pregnancy, premature termination of radio- or chemotherapy, incomplete follow-up, severe pain treated by systemic analgesics and severe symptoms completely precluding both solid and liquid food intake.

### *Study treatments and outcomes*

In the first, non-comparative study ($n$ = 166), the lysozyme-based compound was administered from the first day of radio- or chemotherapy; for the first 7 days. 6–8 compressed lozenges of Lysobact® (20 mg of lysozyme + 10 mg of pyridoxine, Bosnalijek d.d., Bosnia & Herzegovina, OTC preparation) were given daily, and then for the next 14 days Lysobact COMPLETE Spray® (lysozyme hydrochloride, cetylpyridinium chloride, and pyridoxine, (20 + 1.5+ 0.5) mg $mL^{-1}$, Bosnalijek d.d., OTC preparation) was administered by the patients themselves 3–6 times daily. During the final 7 days of the 28-days study period, the patients were again using 6–8 compressed lozenges of Lysobact® daily. The two dosage forms were used interchangeably in order to avoid bias from the various capability of patients to self-administer the spray properly.

Outcomes of the first substudy were measured on the 1st, 7th, 21st and 28th day. The primary outcome was the number of oral ulcers. Secondary outcomes were quality of life (assessed by the PROMS scale) and frequency of adverse events (primarily of the adverse effects listed in Summaries of the study products' characteristics, but also of any serious and unsuspected adverse event observed by the study investigators or reported to them by the study participants).

In the second, comparative substudy, there were two patient cohorts: the first cohort included chemotherapy patients ($n$ = 151) and the second radiotherapy patients ($n$ = 124). Within the cohort of chemotherapy patients 82 or 54 % were treated with local administration of lysozyme-based compounds (from the day one of radio- or chemotherapy; for the first 7 days 6-8 compressed lozenges of Lysobact® daily, and then for the next 14 days Lysobact COMPLETE Spray® 3–6 times daily), while the rest were treated by bicarbonate-based pharmaceutical compounds; patients from the radiotherapy cohort were also treated either by lysozyme-based ($n$ = 66 or 53 % for the first 7 days 6–8 compressed lozenges of Lysobact® daily, and then for the next 14 days Lysobact COMPLETE Spray® 3–6 times daily)), or by bicarbonate-based ($n$ = 58 or 47 %) pharmaceutical compounds. The bicarbonate-based pharmaceutical preparations were prepared in various community pharmacies, with variable strength and content; majority contained only sodium chloride and sodium bicarbonate, while in some hexetidine, nystatin, methylprednisolone, doxycycline, vitamin C or vitamin D were added (the most frequently used sodium bicarbonate solutions were 1–3 %, *m*/*m*).

Outcomes of the second substudy were measured on the 1st, 7th and 21st day. The primary outcome was the number of oral ulcers. The secondary outcome was the frequency of adverse events.

### *Statistics*

The data are presented as mean ± standard deviation and as median and interquartile range. Normality of the data distribution was checked by the Kolmogorov-Smirnov test. The significant differences in scale variables between two study groups were tested by Student's *t*-test and differences in scale variables for repeated measures were tested by Students paired test. The differences categorical variables were tested by Chi-square test or McNemar test for paired categorical data. All calculations were performed by Statistical Package for Social Sciences (SPSS) software, version 23.0 for Windows.

## RESULTS AND DISCUSSION

In total 166 patients were enrolled in the first, non-comparative substudy (not comparing different treatments): 92 patients were receiving chemotherapy and 74 radiotherapy. All patients were treated with lysozyme-based compounds. The average age of patients on chemotherapy was 60.5 ± 9.8 years, and of patients on radiotherapy 60.7 ± 12.3 years; the difference was not significant ($p = 0.94$). Among the patients undergoing chemotherapy, there were 48 (52.2 %) men and 44 (47.8 %) women, whereas in the radiotherapy subgroup there were 26 (35.1 %) men and 48 (64.9 %) women ($p = 0.04$).

The percentage of patients on chemotherapy with ulcerations in various parts of the oral cavity significantly decreased during the follow-up, as shown in Table I.

The percentage of patients with head or neck cancer on radiotherapy with ulcerations in various parts of the oral cavity significantly decreased during the treatment with lysozyme-based compounds. However, lysozyme treatment did not reduce the number of patients with upper and lower lip ulcerations (Table II).

Patients on both chemotherapy and radiotherapy experienced a significant improvement in the quality of life.

*Table I. Percent of patients on chemotherapy* (n = *92) with ulcerations in various parts of the oral cavity during the treatment with lysozyme-based compounds*

| The region of the oral cavity | 7 days after onset of the therapy | 21 days after onset of the therapy | 28 days after onset of the therapy | *p*-value[a] |
|---|---|---|---|---|
| Upper lip | 20 (21.7 %) | 5 (5.4 %) | 1 (1.1 %) | < 0.001 |
| Lower lip | 31 (33.7 %) | 12 (13.1 %) | 4 (4.3 %) | < 0.001 |
| Right cheek | 31 (33,7 %) | 14 (15,2 %) | 5 (5.4 %) | < 0.001 |
| Left cheek | 25 (27.2 %) | 14 (15.2 %) | 6 (6.5 %) | < 0.001 |
| Tongue (dorsal side) | 48 (52.2 %) | 32 (34.8 %) | 14 (15.2 %) | < 0.001 |
| Sublingval area | 34 (37.0 %) | 27 (29.3 %) | 5 (5.4 %) | < 0.001 |
| Soft palate | 21 (22.8 %) | 13 (14.1 %) | 7 (7.6 %) | 0.003 |
| Hard palate | 20 (21.7 %) | 9 (9.8 %) | 1 (1.1 %) | < 0.001 |

[a] Differences in ulceration occurrence between day 7 and 28 after therapy was calculated using McNemar test.

*Table II. Percent of patients on radiotherapy* (n = *74) with ulcerations in various parts of the oral cavity after treatment with lysozyme-based compounds*

| The region of the oral cavity | 7 days after onset of the therapy | 21 days after onset of the therapy | 28 days after onset of the therapy | *p*-value[a] |
|---|---|---|---|---|
| Upper lip | 13 (17.6 %) | 15 (20.3 %) | 11 (14.9 %) | 0.680 |
| Lower lip | 14 (19.0 % %) | 14 (19.0 %) | 10 (13.5 %) | 0.290 |
| Right cheek | 27 (36.5 %) | 24 (32.5 %) | 16 (21.7 %) | 0.027 |
| Left cheek | 30 (40.5 %) | 25 (338. %) | 19 (25.7 %) | 0.019 |
| Tongue (dorsal side) | 38 (51.4 %) | 35 (47.3 %) | 25 (33.8 %) | 0.015 |
| Sublingval area | 26 (35.1 %) | 20 (27.1 %) | 9 (12.2 %) | 0.001 |
| Soft palate | 24 (32.4 %) | 25 (33.8 %) | 12 (16.2 %) | 0.008 |
| Hard palate | 18 (24.3 %) | 15 (20.3 %) | 9 (12.2 %) | 0.002 |

[a] Differences in ulceration occurrence between day 7 and 28 after therapy was calculated using McNemar test.

Patients on chemotherapy had significant reductions on the pain intensity scale (PROMS is a 10-item visual analogue scale the with a maximum score of 100, which measures symptoms of oral mucositis that affect the quality of life) and scored one unit lower at each visit during the therapy with lysozyme. Pain intensity score decreased for one unit from the second to third visit (3.0 (3.0–3.0) *vs.* 2.0 (2.0–3.0); $Z = -7.08$; $p < 0.001$), and decreased an additional unit from the third to fourth visit (2.0 (2.0–3.0) *vs.* 1.0 (1.0–2.0); $Z = -6.7$; $p < 0.001$). Therefore, the mean pain intensity score decreased from 3.0 to 1.0, and the highest drop was observed between the second and fourth visit ($Z = -7.8$; $p < 0.001$). Radiotherapy patients also experienced a decrease in pain intensity score during the therapy with lysozyme-based compounds, from 2.0 (2.0–3.0) to 1.0 (1.0–2.0) ($Z = -4.7$; $p < 0.001$) between the third and fourth visit, while the decrease was not significant between the second and third visit ($Z = -1.1$; $p = 0.26$). The trend of improving the quality of life of chemotherapy patients was observed in all other domains of the PROMS scale, especially in regard to the quality of speech and intake of solid food, but without a statistical significance (results not shown for the sake of clarity and brevity). Adverse treatment effects were not observed in both subgroups of patients.

The second, comparative substudy included 275 patients, 151 of them underwent chemotherapy, and 124 received radiotherapy.

Within the radiotherapy group, 66 patients (53 %) were treated with lysozyme-based compounds, and 58 patients (47 %) were using bicarbonate-based pharmaceutical compounds. There was no significant difference in the mean age between treatment groups (63.0 ± 9.2 *vs.* 65.6 ± 10.0 years respectively, $p = 0.13$). Out of 66 patients treated with lysozyme-based compounds, 78.8 % were male and 21.2 % were female, while in the bicarbonate-based treatment group there were 65.0 % male and 35.0 % female and no significant difference in gender distribution between groups was observed ($X^2 = 2.9$; $p = 0.11$).

Within the cohort of chemotherapy patients, 82 or 54 % were treated with local administration of lysozyme-based compounds, whereas 69 (46 %) were treated with bicarbonate-

based pharmaceutical compounds. There was no significant difference in the mean age between the treatment groups (59.6 ± 12.6 *vs* 58.0 ± 10.8 years respectively; $p = 0.41$). In patients treated with lysozyme-based compounds, 37.8 % were male and 62.1 % were female, whereas in the bicarbonate-based treatment group there were 29.0 % male and 71.0 % female. There was no significant difference in the gender distribution between the two treatment groups ($X^2 = 1.3$; $p = 0.3$).

In patients receiving radiotherapy, a significant reduction in the number of oral ulcerations was observed after 21 days of the treatment with lysozyme-based therapy. Also, in the lysozyme treatment group, a significant reduction in pain intensity was observed during the study period. However, in bicarbonate treatment group no significant reduction in the number of ulcerations nor pain intensity was observed during the period of 21 days (Table III).

In patients receiving chemotherapy, a significant reduction in the number of oral ulceration and pain intensity was observed both in lysozyme and bicarbonate treatment group (Table IV).

Adverse treatment effects were not recorded in any subgroup of the study patients.

Patients with oral mucositis after radio- or chemotherapy have impaired immunity and are prone to both local and systemic infections. Oral mucositis is frequently accompanied with hyposalivation, which is an additional risk factor for the secondary bacterial infection of mucosal ulcers (6). It is known that lysozyme exerts strong antimicrobial action

*Table III. The number of ulcerations in the whole oral cavity and pain intensity in patients on radiotherapy (*n = *124) with lysozyme-* vs. *bicarbonate based treatments*

| Outcome | Treatment of oral mucositis | 7 days after the onset of therapy | 21 days after the onset of therapy | *p*-value[a] |
|---|---|---|---|---|
| Average number of oral ulcerations | Lysozyme-based therapy | 4.6 ± 3.3 | 1.6 ± 1.9[b] | < 0.001 |
| | Bicarbonate-based therapy | 4.8 ± 4.1 | 4.7 ± 3.5 | 0.080 |
| Pain intensity while eating hard food on PROMS scale | Lysozyme-based therapy | 4.0 ± 3.1 | 2.0 ± 1.7[b] | < 0.001 |
| | Bicarbonate-based therapy | 4.5 ± 3.3 | 3.6 ± 3.1 | < 0.001 |
| Pain intensity while eating soft food on PROMS scale | Lysozyme-based therapy | 2.8 ± 3.0 | 1.0 ± 1.2[b] | < 0.001 |
| | Bicarbonate-based therapy | 3.1 ± 3.3 | 2.8 ± 2.7 | < 0.010 |
| Pain intensity while speaking on PROMS scale | Lysozyme-based therapy | 2.4 ± 2.8 | 0.9 ± 1.4[b] | < 0.001 |
| | Bicarbonate-based therapy | 2.2 ± 2.6 | 2.0 ± 2.4 | < 0.010 |

[a] *p*-value presented for the difference between day 7 and day 21, tested with student paired test
[b] Significant differences between two treatment groups ($p < 0.01$) tested with students *t*-test

*Table IV. The number of ulcerations in the whole oral cavity and pain intensity in patients on chemotherapy (n = 151) with lysozyme-* vs. *bicarbonate based treatments*

| Outcome | Treatment of oral mucositis | 7 days after onset of therapy | 21 days after onset of therapy | *p*-value[a] |
|---|---|---|---|---|
| Average number of oral ulcerations | Lysozyme-based therapy | 2.3 ± 2.1 | 0.8 ± 1.6 | < 0.001 |
| | Bicarbonate-based therapy | 2.3 ± 2.0 | 0.9 ± 1.2 | < 0.001 |
| Pain intensity while eating hard food on PROMS scale | Lysozyme-based therapy | 4.4 ± 2.6 | 0.9 ± 3.1 | < 0.001 |
| | Bicarbonate-based therapy | 3.8 ± 2.5 | 1.6 ± 1.6 | < 0.001 |
| Pain intensity while eating soft food on PROMS scale | Lysozyme-based therapy | 2.1 ± 2.2 | 0.3 ± 0.7 | < 0.001 |
| | Bicarbonate-based therapy | 1.5 ± 1.8 | 0.5 ± 0.9 | < 0.010 |
| Pain intensity while speaking on PROMS scale | Lysozyme-based therapy | 1.3 ± 2.0 | 0.3 ± 0.7 | < 0.001 |
| | Bicarbonate-based therapy | 0.8 ± 1.4 | 0.2 ± 0.6 | < 0.010 |

[a] *p*-value presented for the difference between day 7 and day 21, tested with student paired test

(antibacterial, antifungal and antiviral) (12), primarily in saliva and oral cavity, since it is the most important salivary protein along with lactoferrin and salivary peroxidase (13). Lysozyme also has regenerative, anti-inflammatory and immunomodulatory roles in the human organism (13, 14).

Our study showed that local treatment of oral mucositis caused by radiotherapy with lysozyme-based compounds led to more rapid healing of oral ulcerations and more pronounced decrease of pain associated with eating and speaking compared to the use of bicarbonate-based pharmaceutical compounds. Statistical significance of the difference in efficacy between lysozyme- and bicarbonate-based preparations was not found in patients with oral mucositis after chemotherapy, but lysozyme-based compounds were clearly effective. Both lysozyme- and bicarbonate-based local preparations were well tolerated, and therapy-related adverse events were not recorded during the study.

Antimicrobial action of lysozyme is based on the hydrolysis of β-(1,4)-glycoside bond between C1 carbon of *N*-acetylmuramic acid (NAME) and C4 carbon atom of *N*-acetylglucosamine (NAG) within the peptidoglycan of the cell wall (15) (16). However, it also kills microorganisms by the non-enzymatic mechanism. Being a polycationic compound, lysozyme binds to polyanionic molecules in the cell membrane of a microorganism, teichoic and lipoteichoic acid, and this interaction activates autolysins which kill the microorganisms (15). The other proposed mechanism of action is a release of divalent cations from the membrane, leading to its instability and destruction. Certain studies confirmed that non-enzymatic mechanism of antimicrobial action is more important than enzymatic (17).

Antimicrobial action of lysozyme was primarily designed for the action against Gram-positive bacteria, with a thick cell wall, but it is also active against Gram-negative bacteria since its penetration through the outer lipid membrane and action on the cell wall has been proven. Antifungal activity of lysozyme was also observed, especially against *Candida albicans*. Although the mechanism of antifungal action is not yet clarified, it is assumed that lysozyme destructs glycoside bonds between peptidoglycan and structural proteins in the cell wall of fungi, making it unstable. A few studies have revealed a synergism between lysozyme and antifungal drugs (18).

Lysozyme is one of the most important factors of non-specific immunity in oral and pharyngeal mucosa. It causes aggregation of bacteria and, therefore, decreases their adherence to the surfaces and colonization of the oral cavity. Lysozyme also promotes adhesive and antimicrobial properties of immunoglobulin IgA, providing an optimal balance of microbial flora in the mouth. The concentration of lysozyme in the oral cavity is decreased in children who suffer from chronic tonsillitis and in patients with oral mucositis (19). Diminution of its protective role in patients on chemotherapy with oral mucositis contributes to both local infection and penetration of microorganisms from mouth to blood, which was observed in almost 50 % of patients on chemotherapy having bacteremia (20). *Candida albicans* and *Candida glabrata* from the oral cavity were also found in the blood in patients with oral mucositis (21).

In addition, lysozyme exerts anti-inflammatory activity which includes the stabilization of membranes and the prevention of over-destruction of inflammatory cells along with the release of inflammatory mediators, inhibition of destructive enzymes during inflammation and prevention of over-activation of proteolytic enzymes (22). Immunomodulatory action of lysozyme was recognized recently (11) and confirmed by observation of the correlation between lysozyme concentration in oral cavity and blood levels of immunoglobulins (12). Finally, the role of lysozyme in the regeneration of damaged mucosa was also established: it stimulates phagocytosis and helps with wound healing, regression of degenerative processes and elimination of necrotic tissue. Cells of palatal mucosa are most probably capable of producing lysozyme, which is absorbed by the oral mucosa and increases its non-specific, natural immunity (13).

Antimicrobial, anti-inflammatory, immunomodulatory and regenerative actions of lysozyme could explain beneficial effects on healing of oral ulcers in patients on the radio- or chemotherapy that were demonstrated in our study. Although our study had certain limitations, like relatively small sample size, low homogeneity of the samples in regard to stage of neoplastic disease, cytostatic regimen or radiotherapy dose, diverse bicarbonate--based therapy and lacking more extensive measurement of patients' quality of life, these results could be considered as preliminary and help with the planning of larger cohort studies and controlled clinical trials as well.

## CONCLUSIONS

In conclusion, local treatment of oral mucositis, caused by chemo- or radiotherapy, with lysozyme-based compounds is completely safe and clearly more effective than treatment with bicarbonate-based pharmaceutical compounds. Further studies are necessary to determine the optimal dose and duration of treatment with lysozyme and to investigate its effects on systemic infections rate and mortality.

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