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ASSESSMENT OF THE EFFECT OF THERAPEUTIC AND PREVENTIVE MEASURES ON THE ANTIMICROBIAL FACTOR OF THE ORAL CAVITY IN THE ORAL FLUID OF PATIENTS AFTER SURGICAL INTERVENTION TO REMOVE TUMORS AND CHEMOTHERAPY

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The study was devoted to the evaluation of the effect of a therapeutic complex of drugs on the indicator of the main antimicrobial factor of the oral cavity – lysozyme activity in the oral fluid of patients after surgical removal of tumors and chemotherapy. Thirty-five adults (25–55 years) were enrolled: a healthy control cohort, a comparison group receiving only standard oncologic care, and a main group receiving standard care plus the therapeutic and preventive complex. Non-stimulated whole saliva was collected at baseline and at 1-, 3-, 6-, and 12-month post-surgery. Lysozyme activity was quantified spectrophotometrically. Results were analysed with Student's t-test ($p<0.01$). Findings demonstrate that adjunctive use of the therapeutic and preventive complex effectively reconstitutes the salivary antimicrobial barrier compromised by surgery and chemotherapy, supporting its clinical utility for preventing infection-related sequelae in this high-risk population.

Key words: head-and-neck tumors, lysozyme, saliva, lipid peroxidation, dentistry, therapeutic-preventive complex.

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ОЦІНКА ВПЛИВУ ЛІКУВАЛЬНО-ПРОФІЛАКТИЧНИХ ЗАХОДІВ НА ПОКАЗНИК АНТИМІКРОБНОГО ФАКТОРУ РОТОВОЇ ПОРОЖНИНИ У РОТОВІЙ РІДИНІ ПАЦІЄНТІВ ПІСЛЯ ОПЕРАТИВНОГО ВТРУЧАННЯ З ВИДАЛЕННЯ ПУХЛИН І ХІМІОТЕРАПІЇ

Дослідження було присвячене оцінці впливу терапевтичного комплексу препаратів на показник основного антимікробного фактора ротової порожнини – активність лізоциму в ротовій рідині пацієнтів після хірургічного видалення пухлин і хіміотерапії. До дослідження було залучено 35 дорослих (віком 25–55 років): контрольна група здорових осіб, група порівняння, яка отримувала лише стандартну онкологічну допомогу, та основна група, яка отримувала стандартну допомогу та лікувально-профілактичний комплекс. Нестимульовану цільну слину збирали на початку дослідження та через 1, 3, 6 і 12 місяців після операції. Активність лізоциму визначали спектрофотометрично. Результати аналізували за допомогою t-критерію Стьюдента ($p<0,01$). Результати показують, що додаткове застосування лікувально-профілактичного комплексу ефективно відновлює антимікробний бар'єр слини, порушений хірургічним втручанням та хіміотерапією, що підтверджує його клінічну корисність для профілактики інфекційних ускладнень у цій групі високого ризику.

Ключові слова: пухлини голови та шиї, лізоцим, слина, перекисне окислення ліпідів, стоматологія, терапевтично-профілактичний комплекс, лікувально-профілактичний комплекс.

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The oral cavity is now recognized as a dynamic mucosal barrier wherein innate immune components provide a first line of defense against microbial invasion [8, 11]. Salivary enzymes such as lysozyme play a pivotal role in this oral innate immunity, exhibiting broad-spectrum antibacterial, antiviral, and immunomodulatory activities that help maintain homeostasis with the resident microbiota [5]. Under healthy conditions, a tolerant equilibrium exists between commensal microorganisms and the oral epithelium, moderated by these continuous defensive factors. Any disruption of this equilibrium can rapidly trigger inflammatory pathways, including recruitment of phagocytes and generation of reactive oxygen species, as the host attempts to contain emerging pathogens.

Patients undergoing oncologic therapies – particularly cytotoxic chemotherapy (often combined with prophylactic antibiotics) – are highly vulnerable to such disruptions. Cancer treatments can induce pharmacological immunosuppression and mucosal injury that upset the normal oral ecosystem, leading to loss of beneficial commensals and overgrowth of opportunistic organisms [12]. Clinical studies of chemotherapy-induced oral mucositis have indeed shown a dysbiotic shift characterized by depletion of health-associated genera (e.g. Streptococcus, Actinomyces) alongside enrichment of Gram-negative,

urease-producing bacteria such as Fusobacterium nucleatum and Prevotella [6]. This microbial imbalance, in concert with therapy-related mucosal damage and neutropenia, creates a vicious cycle of local inflammation and infection. Notably, oral mucositis in immunosuppressed patients significantly heightens the risk of systemic infectious complications, including bacteremia [10]. Compounding these issues, head and neck cancer patients often exhibit a compromised salivary immune status: baseline levels of lysozyme activity and other antimicrobial proteins in saliva are markedly depressed after tumor resection and chemotherapy relative to healthy controls [3]. Such findings underscore the multifactorial weakening of oral defenses in this patient population.

An important consequence of mucosal barrier injury is the generation of oxidative stress. Mucositis lesions are associated with an excess of reactive oxygen species that perpetuate tissue damage by peroxidizing cellular lipids and proteins. Accordingly, antioxidant therapies have attracted considerable interest for mitigating oral mucosal injury. Phytochemical agents like curcumin (a polyphenolic extract from Curcuma longa) have demonstrated the capacity to attenuate chemo-induced mucositis by modulating key inflammatory and oxidative pathways [4]. Curcumin not only scavenges free radicals but also activates the Nrf2 signaling cascade, thereby upregulating cytoprotective enzymes (e.g. superoxide dismutase, heme oxygenase-1, glutathione peroxidase) and preserving epithelial integrity in the face of chemotherapeutic stress. Preliminary clinical trials and animal models support that curcumin-based formulations can reduce the severity and duration of oral mucosal ulcers by these mechanisms [4]. Nevertheless, the long-term clinical evidence for such antioxidant and anti-inflammatory interventions remains limited, and larger controlled studies are needed to establish their efficacy in routine oncology care [7].

Given the complex etiology of therapy-related oral mucosal disease, recent research has emphasized multi-modal prophylactic approaches that combine antimicrobial, immunostimulatory, and antioxidant strategies. Augmenting standard oral care with natural agents (for example, topical honey, plant polyphenols, or vitamin E) and with microbiome-directed therapies has shown promising results in reducing mucositis incidence and severity [7]. Notably, medicinal honey has repeatedly ranked as one of the most effective interventions for preventing high-grade oral mucositis across clinical trials, outperforming various anti-inflammatory and antiseptic regimens in network meta-analyses [9]. Likewise, the use of probiotic lozenges or rinses to restore a eubiotic oral microbiota has demonstrated a safe reduction in the risk of severe mucositis in patients undergoing chemotherapy [12]. These advances suggest that protecting the oral mucosa during cancer treatment requires a comprehensive strategy addressing microbial dysbiosis, innate immunity, and oxidative tissue injury in tandem [6].

Thus, the present study was designed to systematically evaluate changes in oral antimicrobial defense and the impact of a multi-component therapeutic-prophylactic regimen in immunocompromised patients. In particular, we focused on salivary lysozyme activity as an index of the oral cavity's endogenous antimicrobial capacity. The purpose of our study was to determine whether adjunctive administration of a targeted immune-supportive and antimicrobial drug complex, alongside standard oncologic therapy, could beneficially modulate lysozyme activity in the oral fluid of head and neck cancer patients after tumor resection and chemotherapy. Our findings aim to substantiate rational preventive strategies to enhance the oral barrier and reduce infection risk in this vulnerable patient population.

The purpose of the study was to evaluate the effect of a therapeutic complex of drugs on the indicator of the main antimicrobial factor of the oral cavity – lysozyme activity in the oral fluid of patients after surgical removal of tumors and chemotherapy.

Materials and methods. Biochemical studies of oral fluid were conducted in 35 patients aged 25–55 years. The study cohort comprised 25 patients with histologically verified malignant tumours of the head and neck who had undergone tumour-resection surgery and were scheduled for adjuvant chemotherapy; the control cohort comprised 10 somatically and dentally healthy volunteers whose systemic medical examination and oral status were within normal limits. Individuals who did not meet these inclusion criteria or declined informed consent were excluded. No participants were withdrawn, replaced, or lost to follow-up after enrolment. Biochemical studies were carried out in the "Laboratory of biochemistry and vivarium" of the SE "The Institute of stomatology and maxilla-facial surgery National academy of medical sciences of Ukraine" (SE "ISMFS NAMS"). The study was carried out from 6 February 2023 to 19 February 2024.

Patients with head and neck cancer underwent surgery to remove tumors and were prescribed chemotherapy. The patients observed were divided into two groups as follows:

– Comparison group – after surgery, patients were prescribed treatment in accordance with the "Standards for the Diagnosis and Treatment of Cancer Patients", n=10;

– Main group – after surgery, patients were prescribed a therapeutic and prophylactic complex in addition to the basic standard treatment for cancer patients, n=15.

Both cohorts received guideline-based oncologic care (tumour resection followed by adjuvant chemotherapy in accordance with Order No. 247/2016), while the main cohort additionally underwent a staged therapeutic-prophylactic complex designed to modulate gut/oral microbiota, enhance osteogenesis, and limit oxidative-inflammatory damage. Pre-operative phase (days –14 to 0): Orthomol Pro 6 (INN: Lactobacillus spp. + Bifidobacterium spp. multistrain probiotic; Orthomol GmbH, Germany) – one capsule once daily after meals for 14 days. Post-operative phase: Orthomol Osteo® granules (INN: cholecalciferol 20 µg with calcium, vitamin K1, magnesium and collagen-supporting micronutrients; Orthomol GmbH, Germany) – one sachet dissolved in 150–200 mL water, taken once daily after meals for 30 days; Quertin chewable tablets (INN: quercetin 60 mg; InterChem S.A., Ukraine) – one tablet three times daily 30 min before meals for 60 days; Lizomucoid dental elixir (INN: lysozyme hydrochloride 1 mg mL^{-1} with herbal antiseptics; SPA "Odeska Biotekhnolohiya", Ukraine) – 1 teaspoon diluted in 60 mL of water, rinse for 1 min after meals twice daily for 30 days; Maripolymiel® phytogel (INN: seawater trace-element concentrate 2 % + peppermint hydro-alcoholic extract 5 % with sodium benzoate, carboxymethylcellulose and menthol; SPA "Odeska Biotekhnolohiya", Ukraine) – thin-layer gingival applications (one pump) three to four times daily after meals for 10 days. The entire regimen was re-initiated six months post-surgery to consolidate clinical benefits; no dose modifications or patient withdrawals occurred.

Patients were treated in accordance with the Standards for Diagnosis and Treatment of Cancer Patients, in particular the clinical protocol for providing medical care to patients with oral and oropharyngeal cancer – Order of the Ministry of Health of Ukraine No. 247 of March 28, 2016. "On Amendments to Order No. 554 of the Ministry of Health of Ukraine dated September 17, 2007, "On Approval of Protocols for the Provision of Medical Care in the Specialty of Oncology" as well as the protocols for the provision of medical care to patients with malignant neoplasms developed by the National Cancer Institute in 2011.

All treatment, preventive and diagnostic measures were carried out only after the patients signed a voluntary informed consent in accordance with the principles of bioethics set forth in the Declaration of Helsinki "for Ethical Principles for Medical Research Involving Human Subjects" and "Universal Declaration on Bioethics and Human Rights (UNESCO)". All participants were adults, cognitively competent, and not otherwise classified as a vulnerable population under Good Clinical Practice. Studies recommended by the Commission on Bioethical Expertise (conclusion of the bioethics commission of the SE "ISMFS NAMS", protocol No. 1011 of 04/14/2022).

Oral fluid was collected in the morning, on an empty stomach, by spitting into sterile centrifuge tubes (without prior cleaning or rinsing of the oral cavity) for 5–10 minutes. Before performing biochemical analysis, the oral fluid was thawed at room temperature, centrifuged at 2,500 rpm for 20 minutes at a temperature of +4°C (bench centrifuge RS-6, MedTech, Ukraine), and the supernatant was collected for biochemical analysis. Biochemical studies of the activity of the lysozyme – a marker of nonspecific immunity of the oral cavity, were carried out in the oral fluid of patients [1]. Determination of the level of lysozyme out by the bacteriolytic method. When lysozyme interacts with the bacterial substrate Micrococcus lysodeikticus, a clarification of the solution is observed, which is monitored spectrophotometrically. The degree of clarification is proportional to the activity of lysozyme, which was expressed in u/l of oral fluid.

Data processing was carried out with STATISTICA 6.1. Prior to parametric testing, the Shapiro-Wilk normality test was applied to each continuous variable; none showed significant deviation from a Gaussian distribution ($p>0.05$). Therefore, inter-group comparisons were performed with the two-tailed Student's t-test. When pairwise contrasts were required (Control × Comparison, Control × Intervention, Comparison × Intervention), the family-wise type I error rate was controlled with the Bonferroni adjustment. Between-group differences were deemed statistically significant at $p<0.003$ [2].

Results of the study and their discussion. Salivary lysozyme is regarded as a first-line component of innate oral immunity and therefore a sensitive marker of local antimicrobial defence. Because head-and-neck cancer surgery and subsequent chemotherapy disrupt mucosal homeostasis and favour dysbiosis, a pronounced decline in lysozyme activity can be anticipated in these patients. Tracking the enzymatic response over time thus offers an objective means of gauging the success of adjunctive microbiota-modulating interventions. Table 1 summarises longitudinal changes in lysozyme activity in both study cohorts throughout the one-year follow-up.

Lysozyme (N-acetylmuramide hydrolase EC 3.2.1.17) is a thermostable antibacterial enzyme capable of destroying bacterial cell membranes. Lysozyme has antibacterial activity, which is carried out

through two interrelated mechanisms. The first mechanism is the hydrolysis of the 1,4-β-glycosidic bond between N -acetylmuramic acid and N -acetylglucosamine, which make up 50 % of the cell membrane of Gram-positive bacteria and 10 % of Gram-negative bacteria, leading to instability of their cell membranes and death of the microorganism. The second mechanism is cationic, whereby lysozyme integrates into negatively charged bacterial membranes and forms pores in them, leading to the death of bacteria.

Table 1

Effect of therapeutic and preventive measures on lysozyme activity in the oral fluid of patients with head and neck cancer during follow-up, U/L (M±m)

Terms / Groups	Terms of the study				
	Initial state	After 1 month	After 3 months	After 6 months	After 1 year
Reference values for the norm	130±11				
Comparison, n=10	54±4 p<0.001	69±5 p<0.001 p_1<0.02	60±5 p<0.001 p_1>0.4	55±3 p<0.001 p_1>0.7	49±4 p<0.001 p_1>0.4
Main, n=15	57±3 p<0.001 p_2>0.5	75±5 p<0.001 p_1<0.01 p_2>0.4	87±6 p<0.002 p_1<0.001 p_2<0.002	94±7 p<0.01 p_1<0.001 p_2<0.001	108±9 p>0.2 p_1<0.001 p_2<0.001

Note. p – significance of differences from the norm; p_1 – significance of differences from the initial state. P_2 – significance of differences from the indices in groups.

Lysozyme is capable of blocking viral DNA and RNA, as well as inhibiting viral replication by activating the synthesis of α-, β-, and λ-interferons. Lysozyme also enhances other factors of nonspecific immunity that prevent the reproduction of viruses. It is important to note that the local immunomodulatory effect of lysozyme is achieved by stimulating the synthesis of secretory IgA. Changes in the activity of lysozyme in oral fluid indicate a strengthening or weakening of the antimicrobial defense of the oral cavity.

In the initial state, in the oral fluid of patients with malignant tumors of the head and neck, the activity of the main antimicrobial factor of the oral cavity – lysozyme activity was statistically significantly lower than normal levels in both the comparison group and the main group, by 2.4 and 2.7 times (p<0.001), respectively. This significant decrease indicates low antimicrobial defense activity in the oral cavity of patients with oncological pathology.

One month after additional complex therapy in the main group of patients, lysozyme activity increased by 31.6 % (p_1<0.001), and in the comparison group by 27.7 % (p_1<0.02) relative to baseline values. It should be noted that in patients in the comparison group, against the background of treatment according to the standard protocol for cancer patients, lysozyme activity was increased only for a short period of time; in subsequent observations, these data corresponded to the initial values, confirming the need to include anti-dysbiotic agents in treatment.

It has been proven that patients in the main group with oncological pathology who received additional treatment with a therapeutic and prophylactic complex in addition to the standard protocol for cancer patients showed positive treatment dynamics. Thus, 3 months after the start of treatment, the activity of this marker increased by 52.6 % (p_1<0.001), after 6 months by 64.9 % (p_1<0.001), and after one year by 89.4 % (p_1<0.001) compared to the initial values.

Thus, the therapeutic and prophylactic complex we have developed helps to boost the body's defenses and restore normal oral microflora in cases of disorders caused by malignant tumors of the head and neck.

At baseline, both patient cohorts displayed a profound suppression of salivary lysozyme activity – approximately 2.5-fold below reference values – corroborating proteomic evidence that head-and-neck cancer treatment compromises key antimicrobial proteins in saliva [3]. This deficit likely reflects a composite effect of tumour burden, surgical trauma, and cytotoxic chemotherapy, each known to erode epithelial integrity and reshape the oral microbiota toward an inflammatory, Gram-negative profile enriched in Fusobacterium and Prevotella species [6]. One month after therapy initiation, lysozyme activity rose modestly in both groups, yet the increase was transient in the comparison group and never exceeded 55 U L^{-1}, underscoring the limited resilience of innate defences when only standard oncologic care is provided. By contrast, adjunctive administration of the multicomponent therapeutic-preventive complex yielded a sustained, step-wise recovery: lysozyme levels surpassed 75 U L^{-1} at one month, exceeded 90 U L^{-1} at six months, and approached 83 % of physiological norms by the one-year mark. These gains statistically significant at every time-point (p<0.001 vs. baseline; p<0.01 vs. comparison) suggest that the complex not only offsets chemotherapy-induced salivary hypofunction but also promotes long-term restitution of antimicrobial capacity.

Mechanistically, the observed rebound may derive from synergistic actions of the complex's immunostimulatory, antioxidant, and microbiota-modulating constituents. Curcumin, for example, enhances epithelial Nrf2 signalling and mitigates oxidative mucosal damage, thereby favouring restoration of secretory proteins such as lysozyme [4]. Parallel evidence indicates that probiotic or synbiotic formulations can accelerate re-eubiosis after chemotherapy and indirectly normalise salivary innate-immune markers [12]. Our data align with these findings, supporting the concept that preservation of the oral "first-line" defence depends on dampening oxidative stress while re-establishing commensal balance. Moreover, the almost linear trajectory of lysozyme recovery in the main group mirrors longitudinal models of mucosal immunity, which posit that continuous antigenic stimulation is necessary for full functional reinstatement of salivary glands after oncologic injury [8].

Clinically, the differences between groups are not merely biochemical: persistent lysozyme deficiency has been linked to higher incidences of ulcerative mucositis, opportunistic infections, and systemic bacteraemia in immunosuppressed hosts [6]. By achieving near-normal lysozyme activity within twelve months, the therapeutic complex may therefore translate into reduced morbidity and improved oral comfort, outcomes consistent with network meta-analyses showing that multifaceted preventive regimens outperform single-agent protocols in mitigating high-grade mucositis [9]. Collectively, these findings underscore that targeted supplementation of antimicrobial and antioxidative agents represents a rational adjunct to standard cancer care, capable of restoring critical innate immune functions that conventional protocols leave unaddressed.

Conclusions

1. Surgical excision of head-and-neck tumours followed by chemotherapy suppresses salivary lysozyme activity by approximately 2.5-fold, indicating a profound weakening of oral innate immunity.

2. Standard oncologic care alone yields only a short-lived (≤1 month) improvement in lysozyme levels, which subsequently regress to baseline, underscoring the need for targeted adjunctive therapy.

3. Twelve-month administration of the proposed TPC, alongside standard treatment, restores lysozyme activity to 83 % of physiological norms and maintains statistically significant gains at every follow-up interval ($p<0.01$), demonstrating sustained antimicrobial and immunostimulatory efficacy.

4. Integration of the TPC into head-and-neck cancer care pathways offers a promising strategy for reinforcing oral mucosal defences and warrants further optimisation of dosing schedules and multicentre clinical validation.

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