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CLINICAL AND LABORATORY OUTCOMES OF COMPLEX THERAPY IN PATIENTS WITH CHRONIC SIALADENITIS IN THE EXACERBATION STAGE

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Chronic sialadenitis is one of the most common recurrent salivary gland diseases, complicating treatment in maxillofacial practice due to its long course and frequent exacerbations. The purpose of the study was to evaluate the clinical and laboratory effectiveness of complex therapy combining conventional treatment with local immunotherapy using autologous leukocytes stimulated by a synthetic immunomodulatory peptide. Forty-five patients were examined: the control group received standard therapy, while the main group additionally underwent three intraductal administrations of stimulated leukocytes. Complex treatment led to faster symptom regression, improved salivary parameters, normalization of the cytokine profile, and a lower recurrence rate (12 % vs. 35 %). The findings suggest that the combined therapeutic approach improves both short-term clinical recovery and long-term disease control.

Key words: chronic sialadenitis, salivary glands, immunotherapy, cytokines, sialometry.

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КЛІНІКО-ЛАБОРАТОРНІ РЕЗУЛЬТАТИ КОМПЛЕКСНОЇ ТЕРАПІЇ ХВОРИХ НА ХРОНІЧНИЙ СІАЛОАДЕНІТ У СТАДІЇ ЗАГОСТРЕННЯ

Хронічний сіаладеніт – одне з найпоширеніших рецидивуючих захворювань слинних залоз у щелепно-лицьовій практиці, лікування якого ускладнюється тривалим перебігом та частими загостреннями. Метою дослідження стала оцінка клініко-лабораторної ефективності комплексної терапії, що поєднує традиційне лікування з місцевою імунотерапією аутологічними лейкоцитами, стимульованими синтетичним імуномодулюючим пептидом. Обстежено 45 пацієнтів: контрольна група отримувала традиційне лікування, основна група додатково отримала три внутрішньопротокові введення стимульованих лейкоцитів. Комплексне лікування призвело до швидшого регресу симптомів, поліпшення показників слини, нормалізації цитокінового профілю та зниження частоти рецидивів (12 % проти 35 %).

Ключові слова: хронічний сіаладеніт, слинні залози, імунотерапія, цитокіни, сіалометрія.

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Chronic nonspecific sialadenitis (CS) is a long-standing inflammatory disease of the salivary glands, characterized by recurrent exacerbations, gradual fibrosis of the glandular parenchyma, and progressive secretory dysfunction [1–3]. It accounts for up to 40–50 % of all salivary gland pathologies and represents a significant burden in oral and maxillofacial practice [4, 5]. Despite widespread use of antibiotics, antiseptic irrigation, and physical therapy, recurrence remains frequent, and long-term remission is difficult to maintain [6].

The persistence of inflammation is closely linked with disturbances in local immunity, altered cytokine profiles, and accumulation of endotoxins [7]. Traditional therapies primarily target microbial agents but do not adequately restore immune homeostasis. Hence, immunomodulatory approaches are increasingly recognized as promising adjuncts [8–10].

Synthetic peptide immunomodulators has demonstrated immunoregulatory, anti-inflammatory,

and antioxidant properties [11]. In vitro studies confirm its capacity to enhance leukocyte activity, normalize cytokine production, and reduce oxidative stress [12]. However, its potential for local intraductal therapy in salivary gland inflammation has not been systematically evaluated.

The purpose of the study was to investigate clinical and laboratory outcomes of complex therapy including conventional treatment and local immunotherapy with Synthetic peptide immunomodulators stimulated autologous leukocytes in patients with chronic nonspecific sialadenitis during exacerbation.

Materials and methods. A prospective comparative study was conducted at the Department of Oral and Maxillofacial Surgery in Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev (ASATID) between 2014 and 2016. A total of 45 patients (19 men, 26 women; mean age 44.2±2.5 years, range 18–75) with chronic nonspecific sialadenitis during exacerbation were enrolled. To minimize potential age-related bias, patients in both groups were matched by mean age, sex distribution, disease duration, and baseline severity of inflammation. The proportion of patients younger than 30 years and older than 50 years did not differ significantly between groups ($p>0.05$). In addition, statistical analysis included correlation testing between age and the main clinical and laboratory parameters; no significant associations were found. This approach allowed us to consider age-related structural and secretory.

Inclusion criteria: confirmed diagnosis of chronic nonspecific sialadenitis, clinical signs of exacerbation, preserved duct patency, absence of prior immunotherapy.

Exclusion criteria: autoimmune disease, malignant tumors, uncontrolled metabolic disorders, pregnancy or lactation, refusal to participate.

To reduce age-related bias, both groups were comparable in mean age, disease duration, and severity of inflammation.

All patients provided written informed consent. The study protocol was approved by the Local Bioethics Committee of the Azerbaijan State Advanced Training Institute for Doctors (Protocol №4, 12.02.2014). The research followed the principles of the Declaration of Helsinki.

Treatment groups:

1. Comparison group (n = 20). Patients received conventional therapy according to national clinical practice guidelines: ceftriaxone 1 g twice daily for 7 days (Arterium, Ukraine), clemastine 1 mg daily (Sopharma, Bulgaria), duct lavage with furacilin solution 1:5000 (Darnitsa, Ukraine), enzymatic irrigation with trypsin solution (Biopharma, Ukraine), local anti-inflammatory compresses.

2. Main group (n = 25). Patients received the same treatment plus local immunotherapy. After reduction of purulent secretion, intraductal administration of autologous leukocytes stimulated with a synthetic hexapeptide immunomodulator (imunofan, 50 μg/ml, Bionox) was performed three times with 48-hour intervals.

Preparation of Imunofan-stimulated leukocytes. From each patient, 5 ml venous blood was collected into heparinized tubes. Leukocytes were isolated by centrifugation (1500 rpm, 10 min), resuspended in saline, incubated with Imunofan (0.1 ml/5 ml blood, 50 μg/ml) at 37°C for 1 h, diluted (1:3 with saline), divided into three equal doses, and stored at +4°C until use. Each dose was administered intraductally.

Clinical evaluation parameters included: swelling (graded 0–3), pain (VAS scale 0–10), xerostomia (subjective scale 0–3), salivary flow rate (sialometry), lymphadenopathy (palpation), recurrence frequency at 6 and 12 months.

Laboratory investigations: sialometry: unstimulated saliva collected by spitting method (FDI recommendations); saliva viscosity: capillary viscometer; pH: potentiometric method, cytology: smears stained by Romanowsky–Giemsa, indices of neutrophils, lymphocytes, epithelial cells; phagocytic activity (FAN-1, FAN-2); cytokines: IL-1β, IL-2, IFN-γ measured by ELISA (Vector-Best), proteins: total protein, albumin, globulins; A/G ratio, endotoxicosis markers: middle-mass molecules (MMM) (spectrophotometry at 244–304 nm).

Statistical analysis. Data analyzed with SPSS 25.0. Continuous variables presented as mean±SE. Student's t-test used for intergroup comparisons; χ^2 test for categorical data. Correlation analysis was performed between salivary proteins, sialometry, and viscosity. Significance threshold: $p<0.05$.

Results of the study and their discussion. In both groups, patients demonstrated clinical improvement over the course of therapy; however, the pace and magnitude of these improvements differed substantially. In the main group, where patients received conventional treatment combined with intraductal administration of Imunofan-stimulated autologous leukocytes, the resolution of acute symptoms occurred noticeably earlier. Pain intensity, as measured by the visual analogue scale (VAS), decreased from an initial mean of 6.8±0.5 to 1.2±0.3 within 5 days. By contrast, in the comparison group the same reduction was achieved only by day 7 (from 6.7±0.4 to 2.4±0.4). This difference was statistically significant ($p<0.05$), suggesting that the immunotherapy contributed to faster pain relief.

Swelling of the affected gland followed a similar trajectory. In the main group, swelling scores dropped from 2.7±0.2 at baseline to 0.6±0.1 by day 5, while in the comparison group the reduction was slower, from 2.6±0.2 to 1.3±0.2. Patients also reported earlier resolution of xerostomia. By the end of therapy, 52 % of the main group had no subjective dryness compared with 30 % in controls ($p<0.05$).

Lymphadenopathy, observed in 68 % of patients at baseline, resolved more quickly in the main group

(disappearing in 80 % of affected cases by day 6) compared to only 55 % resolution in controls within the same timeframe. Additionally, patients from the main group subjectively reported greater overall comfort, with improvements in chewing and speech functions, which are frequently impaired during exacerbations of chronic sialadenitis.

During follow-up, recurrence rates showed a clear distinction: only 3 patients (12 %) in the main group experienced new exacerbations within 12 months, versus 7 patients (35 %) in the comparison group. This nearly threefold reduction highlights the long-term benefits of incorporating local immunotherapy. The lower relapse rate emphasizes that the achieved therapeutic effect was not only rapid but also sustainable over time. Table 1 summarizes the principal clinical outcomes.

Table 1

Clinical dynamics in patients with chronic sialadenitis

Parameter	Comparison (n=20)	Main (n=25)	p-value
Clinical improvement	60 %	80 %	<0.05
Duration of swelling (days)	6.1±0.8	4.3±0.6	<0.05
Xerostomia remission	30 %	52 %	<0.05
Relapse in 12 months	35 %	12 %	<0.05

Salivary flow rate was significantly improved in the main group, reflecting restoration of secretory function. At baseline, both groups demonstrated hyposecretion (0.27±0.01 ml/min in main, 0.26±0.01 ml/min in controls). After treatment, the main group reached 0.43±0.01 ml/min ($p<0.05$ compared to baseline), approaching normal physiological levels. In contrast, the comparison group achieved only a modest improvement to 0.38±0.01 ml/min.

Saliva viscosity also normalized more effectively in the main group. Initial mean viscosity values were elevated (7.6±0.25 mm), consistent with impaired salivary gland function. After therapy, viscosity decreased by 21 % to 5.96±0.17 mm. In controls, viscosity improved less dramatically, from 7.5±0.24 to 6.25±0.20 mm ($p<0.05$ for intergroup comparison).

Salivary pH values shifted toward physiological norms as well. The main group demonstrated an increase from 6.3±0.09 at baseline to 6.8±0.05 post-therapy, nearly equal to healthy reference values (6.9±0.06). Controls showed a more limited improvement from 6.2±0.08 to 6.6±0.07.

The correlations between flow rate, viscosity, and pH suggest that restoration of one parameter was paralleled by improvements in the others, reinforcing the systemic effect of local immunotherapy. These objective measurements also correlated with patients' subjective reports of improved oral comfort, reduced stickiness of saliva, and easier swallowing, confirming the clinical relevance of laboratory findings. Fig. 1 illustrates the dynamics of salivary flow, viscosity, and pH.

Changes in cytokine levels provided additional confirmation of therapeutic effectiveness. At baseline, patients in both groups showed elevated pro-inflammatory cytokines and reduced interferon activity.

In the main group, IL-1β levels decreased by 20.3 %, while in controls the reduction was only 16.2 %. Similarly, IL-2 decreased by 38.8 % in the main group compared to 26.6 % in the comparison group. These reductions suggest stronger suppression of inflammatory cascades in patients receiving immunotherapy.

Importantly, IFN-γ, a cytokine critical for local immune defense, increased by 21.2 % in the main group. Controls showed only a 12 % increase. This shift reflects restoration of the Th1/Th2 balance, an essential factor in chronic sialadenitis where immune dysregulation drives disease persistence. Such immune normalization is crucial for preventing progression to irreversible glandular damage, which often complicates the disease course in patients treated only with standard protocols.

Table 2 summarizes cytokine dynamics. These findings align with clinical data showing faster remission and fewer relapses in the main group, supporting the role of immune modulation as a therapeutic mechanism.

Table 2

Cytokine concentrations before and after therapy

Cytokine	Comparison (%)	Main (%)	Effect
IL-1β	-16.2	-20.3	↓
IL-2	-26.6	-38.8	↓
IFN-γ	+12.0	+21.2	↑

Cytology. Cytological analysis of salivary smears revealed marked differences in cell composition. At baseline, smears were dominated by neutrophils (average 39.6 %), indicating ongoing acute inflammation. After therapy, neutrophil counts dropped to 24.6 % in the main group, while in controls they remained higher at 31.5 %.

Conversely, epithelial cell content increased significantly in the main group, from 14.5 % to 37.3 %, reflecting regeneration and epithelial turnover. The comparison group also showed an increase, but less pronounced (to 28.2 %).

Lymphocytes, an indicator of chronic inflammatory activity, were reduced more markedly

in the main group. Phagocytic activity indices (FAN-1 and FAN-2) increased significantly, with FAN-1 reaching 9.4±0.3 %, nearly equal to healthy reference values (9.9±0.6 %).

These cytological transformations not only confirmed the anti-inflammatory effect but also demonstrated the reparative capacity of the combined therapy, highlighting the transition from destructive processes to tissue recovery.

Protein analysis. Analysis of salivary proteins indicated normalization of biochemical balance. At baseline, both groups exhibited reduced total protein levels and altered albumin/globulin (A/G) ratios, consistent with chronic inflammation. In the main group, total protein normalized to 1.2±0.02 g/L, compared to 1.1±0.02 g/L in controls. Globulin fractions increased, but the A/G ratio improved significantly to 0.99±0.17 in the main group, approaching normal values. Controls showed only partial correction (A/G ratio 0.82±0.15).

Normalization of protein composition was also reflected in better oral mucosal health, with fewer cases of microcracks and recurrent stomatitis reported during follow-up in the main group. These shifts suggest more effective restoration of secretory and metabolic functions in the main group. Protein normalization also paralleled reductions in endotoxicosis markers, underscoring the systemic benefits of local immunotherapy.

Endotoxicosis markers. Markers of endogenous intoxication were assessed via concentrations of middle-mass molecules (MMM). At baseline, elevated absorbance values at 244–304 nm indicated significant accumulation of toxic catabolites in saliva.

After treatment, the main group demonstrated a 13 % reduction in MMM levels, particularly in the 294–304 nm fraction, which is most closely associated with protein catabolism and chronic intoxication. In contrast, controls showed only a 2.8 % decrease.

This notable difference suggests that immunotherapy accelerates detoxification processes and contributes to the resolution of chronic inflammatory activity. The reduction in MMM levels can also be interpreted as an indirect marker of improved metabolic clearance and reduced oxidative stress, factors that are strongly linked to better long-term glandular function.

Figure 2 demonstrates a significant reduction in middle-mass molecules, particularly in the 294–304 nm fraction, reflecting decreased endogenous intoxication and improved metabolic clearance in the main group.

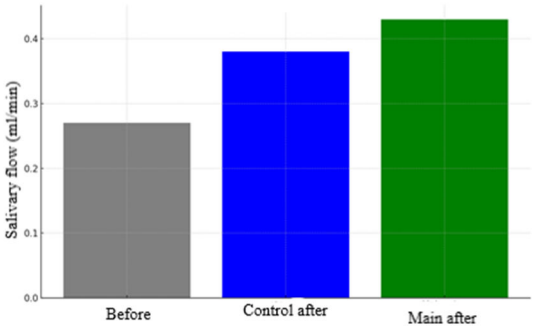

Fig. 1. Dynamics of salivary flow, viscosity, and pH.

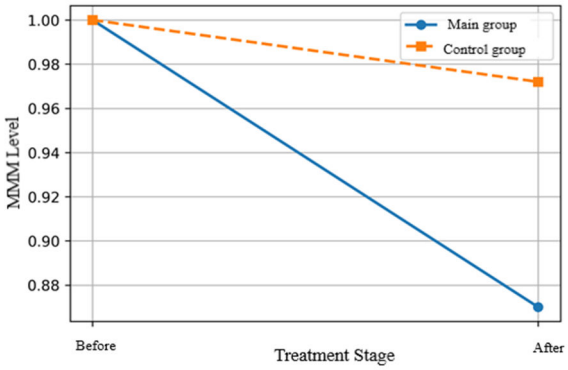

Fig. 2. Dynamics of middle-mass molecules (MMM) in saliva before and after treatment.

Overall, patients in the main group demonstrated superior outcomes across clinical, biochemical, cytological, and immunological parameters compared with those who received conventional treatment alone. Faster symptom resolution, improved salivary function, normalization of cytokine balance, and reduced endotoxicosis markers collectively resulted in better long-term remission rates.

Taken together, these findings provide convincing evidence that adding local immunotherapy with Imunofan-stimulated leukocytes enhances both short-term recovery and long-term disease control. The consistency of improvements across diverse laboratory and clinical indicators strengthens the argument that this therapeutic approach addresses the multifactorial nature of chronic sialadenitis rather than merely alleviating symptoms.

The addition of local immunotherapy with Imunofan-stimulated autologous leukocytes significantly enhanced outcomes compared to conventional therapy alone. Faster clinical remission and normalization of salivary parameters correlated with improved cytokine balance and immune function.

The observed decrease in IL-1β and IL-2 with concurrent rise in IFN-γ suggests restoration of Th1/Th2 balance and local immune defense. Similar findings have been reported in chronic inflammatory and autoimmune conditions where peptide immunomodulators improve cytokine regulation [13, 14].

Normalization of protein composition and reduction of middle-mass molecules demonstrate attenuation of endogenous intoxication, which is crucial in chronic sialadenitis pathogenesis [15].

Compared with published data, our results confirm that conventional therapy alone insufficiently restores immune homeostasis, while combined approaches provide longer remissions. Clinical relevance. The two-step protocol – (1) infection control and duct sanitation, followed by (2) immunomodulation – ensures both immediate relief and prevention of relapses.

Limitations. The study has several limitations: relatively small sample size, single-center design, absence of follow-up beyond 12 months, lack of stratification by gland type, and disease duration. Further multicenter studies with longer observation are required.

Conclusion

The results of this study demonstrate that complex therapy, which combines conventional treatment with local immunotherapy using Synthetic peptide immunomodulators -stimulated autologous leukocytes, provides clear clinical and laboratory advantages in patients with chronic nonspecific sialadenitis during exacerbation. Compared with standard therapy alone, the proposed approach accelerated the resolution of pain, swelling, xerostomia, and lymphadenopathy, while also improving salivary flow rate, viscosity, and pH. These clinical improvements were closely correlated with normalization of cytokine balance, particularly the decrease of IL-1β and IL-2 and the increase of IFN-γ, which reflects restoration of immune homeostasis and enhanced local defense mechanisms. In addition, cytological analysis confirmed a shift from neutrophil-dominated inflammation to epithelial regeneration, while biochemical studies revealed normalization of protein composition and reduction of middle-mass molecules, indicating attenuation of endogenous intoxication. Importantly, these benefits translated into a significantly lower recurrence rate over 12 months (12 % vs. 35 %), underscoring not only the short-term but also the long-term efficacy of the combined treatment protocol. Taken together, our findings suggest that a two-step therapeutic strategy – initial infection control and duct sanitation followed by targeted immunomodulation – ensures both rapid symptom relief and prolonged remission. This method may therefore be recommended as an effective adjunct to conventional therapy in oral and maxillofacial surgical practice.

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