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Clinical results of the application of perftoran for the treatment of odontogenous abcesses and phlegmons in the maxillofacial region☆

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SUMMARY. Introduction: **The study was carried out to ascertain the effects of perftoran in the treatment of facial and Dupuytren's phlegmons with simultaneous estimation of the general reaction in humans.** Material and methods: **Seventy-six patients with facial or Dupuytren's phlegmons were divided into 2 groups, one with mild and the other with a severe course of the inflammatory process. Each group was subdivided into 2 subgroups: one control group with "traditional" treatment and one study group where the traditional treatment was supplemented with perftoran. Perftoran was given to both study groups (1–3 ml/kg body weight, single intravenous injection) immediately after surgery plus further daily local wound treatment with perftoran until the end of exudation. The condition of the purulent wound and its reparative processes, the state of free-radical oxidation processes, antihypoxia and effects of perftoran were evaluated at various treatment stages (the moment of surgically opening the phlegmon, on the 1st, 3rd and 7th postoperative days).** Results: **Perftoran considerably decreased the tissue hypoxia as well as the transaminase and creatinine levels in blood serum. Perftoran helped to decrease the intoxication indices, hypoxaemia by 10–15%, to speed local wound healing by 2–5 days and to shorten the time of hospital treatment by 3–6 days on average.** Conclusions: **The many positive effects of perftoran on the clinical course of the disease and on a series of homeostatic parameters allow us to recommend that this drug to be added for treating patients having odontogenous phlegmons in the maxillofacial region. © 2008 European Association for Cranio-Maxillofacial Surgery**

Keywords: **perftoran, purulent wound, reduced systemic toxicity, perfluorocarbonic compounds**

INTRODUCTION

The treatment of inflammatory diseases in the maxillofacial region, amongst which face and neck phlegmons holding a peculiar place, constantly attracts the attention of researchers (*Platonova*, 1990, 1999; *Bridgeman* et al., 1995; *Bezuglaya* et al., 1995; *Levenets* et al., 1995; *Shargorodsky*, 1996, 2001; *Bazhanov* et al., 1997; *Durnovo*, 1998, 2003; *Agapov* et al., 2000). Among all patients admitted to maxillofacial hospitals in this country, 60–70% are currently suffering from odontogenic inflammatory diseases. The overwhelming majority of these (60–80%) have face and neck abscesses (*Durnovo*, 1998, 2003; *Shargorodsky* et al., 1998; *Agapov* and *Shulakov*, 1999; *Timofeyev*, 2002).

Development of systemic toxicity in the case of pyogenic processes results in disturbances of water-salt, protein, and carbohydrate metabolism, in failure of systemic and peripheral circulation of the cardiovascular system, in functional hepatic and renal insufficiency (*Karandashev*, 1988; *Ganina* et al., 1990; *Zabelin*, 1997). Due to systemic toxicity and microcirculation failure, oxygen delivery to tissues damaged by suppurative inflammation deteriorates which causes development of hypoxic conditions and increase of products of glycolysis in blood (*Lukyanova*, 2001). Destruction aggravates, and reparative processes in the tissues of a purulent wound slow down (*Taychenachev* et al., 1999).

The systemic character of disturbances arising with maxillofacial inflammation requires simultaneous prescription of several drugs (*Ganina* et al., 1990; *Mazepin* et al., 1990; *Flood* et al., 1990; *Ragimov*, 1992; *al Shawi*, 1995; *Zabelin*, 1997; *Dilu* and *Giyulu*, 1998). In this connection, improvement in the treatment of patients with facial and neck abcesses is required (*Bazhanov* and *Shcherbatyuk*, 1992; *Bazhanov*, 1995; *Volozhin* et al., 1995; *Platonova*, 1999; *Shargorodsky*, 2001; *Timofeyev*, 2002).

Amongst the wide range of modern blood substitutes, "Perftoran"®, a new national product (OJSC SPF "Perftoran", Puschino, Russia) (*Beloyartsev*, 1980; *Mayevsky*, 1980; *Beloyartsev* et al., 1985; *Ilgyavichute* et al., 1993; *Khrupkin* et al., 1997; *Shilov* et al., 1997; *Adamson* et al.,

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1998; *Audran* et al., 1999; *Mayevsky* et al., 1999; *Moroz* and *Krylov*, 1999; *Srednyakov* et al., 1999; *al Hallag* et al., 2000; *Moroz* et al., 2001) is used for eliminating hypovolaemia and hypoxia, for improving the rheological properties of blood as well as for stimulating reparative regeneration in various fields of medicine.

Perftoran is a submicron emulsion with gas-carrying function, containing 10 vol.% of perfluoro-organic compounds (perfluorodecalin and perfluoro-methyl-cyclo-hexyl-piperidin) and is stabilized with 4% of proxanol-268, a surfactant (*Ivanitsky* et al., 1995; *Golubev* et al., 1995, 1997a,b; *Ivanitsky* and *Vorobiev*, 1997; *Golubev*, 1998; *Ivanitsky*, 1999, 2001). The average size of the emulsion particles is of 0.03−0.15 μm, which is nearly 100 times less than that of erythrocytes. Thanks to this fact, the particles are able to penetrate into narrow, spasmodic vessels (e.g., as a result of the oedematous surrounding tissues) where erythrocytes cannot penetrate. They can enter hypoxic tissues and provide good oxygenation of tissue, including zones of hypertrophy (*Bailey* and *Ariga*, 1998; *Bartlett*, 1999; *Sofronov* et al., 1999a,b; *Shumakov* et al., 1999; *Baryshev*, 2001). Solubility of oxygen in perftoran is between 6 and 7 vol.% (at $pO_2 = 760$ mm Hg), which is 20 times higher than oxygen solubility in aqueous media and 3 times higher than that in blood plasma (*Riess*, 2001). The perfluorocarbons are chemically inert and do not undergo metabolic transformation in the organism of man or animals. The half-life of perftoran in blood is about 24 h, proxanol leaving the body completely via the kidneys within the 1st day. The time required to eliminate the perfluorocarbons from the body depends on the dose injected: when injecting perftoran in therapeutic amounts (10 ml/kg of body weight), the perfluorocarbons are completely eliminated within 8 months (*Ivanitsky*, 2001).

Perftoran is a blood substitute with a gas-carrying function, which is used as an antishock and antiischaemic drug. It shows rheological, haemodynamic, membrane-stimulating, cardioprotective, and diuretic properties. Perftoran is used in the treatment of hypovolaemia, in shock (of various origins), of craniocerebral injuries; in cases of microcirculatory and peripheral circulation disturbances; it is used locally for regional perfusion, for pulmonary lavage, for bathing of purulent wounds in abdominal and other cavities; for antiischaemic protection of donor organs. While applying perftoran, side reactions are possible such as urticaria, pruritus, skin rashes, tachycardia, hypotension, pyrexia headache, retrosternal and low back pain, dyspnoea, anaphylactoid reactions. The rate of side effects is of about 1.8% and depends on the nature of the disease, on preliminary patient selection, observation of the storage rules, defrosting technology, observation of precautions in application (*Ivanitsky* et al., 1995; *Ivanitsky* and Vorobiev, 1997).

Lately, the efficiency of perftoran in maxillofacial plastic surgery has been demonstrated. According to *Orlov* (2005), local application of the drug into a bone wound and injured soft tissues along with intravenous infusion promotes better healing. Intensification of osteogenesis is observed. Full thickness skin grafts immersed into perftoran prior to transplantation had less oedema, a decrease in metabolism and activation of glycolysis (*Orlov*, 2005). A study of *Zhartibaev* and *Ris-Uli* (2004) demonstrated successful application of perftoran for treating periodontitis in patients suffering from diabetes mellitus. Local application of perftoran added to the therapy of generalized periodontitis resulted in an earlier stabilization of periodontal indices promoted the development of reparatory processes and the recovery of the periodontal epithelial integrity, and/consequent decrease of the hypoxia in the latter.

Lately, perftoran has been used in general surgery for infections but the mechanisms of its effects on inflammatory processes are not fully known. There are no data yet on the use of perftoran in purulent maxillofacial surgery.

The aim of this study was to increase the efficiency of treatment measures for odontogenic abcesses and phlegmons by adding perftoran.

MATERIAL AND METHODS

This is a retrospective comparative study performed using data of patients treated in the Department of Maxillofacial Surgery at the Clinical Hospital No. 39, a public treatment and prophylactic establishment of Nizhny Novgorod, between 1999 and 2003. While carrying out the study, a total of 91 patients with an average age of 36.9 ± 1.9 years (range 18−63 years) were included.

The *study group* comprised 76 patients (33 women, 43 men). All these were admitted as emergencies with the diagnosis of "odontogenic abcesses/phlegmons". The progressive course of the process was observed in 13 patients (24%), and complications in the form of mediastinitis or sepsis, in 4 patients (6%). Depending on the gravity of the inflection and on the extent of inflammation all patients were divided into 2 major study groups: 43 patients with a mild course (1st group; 24 men, 19 women), and the other 33 with a severe course of the inflammatory process (2nd group; 19 men, 14, women).

In the 1st study group, the abcess was located in 1 or 2 neighbouring tissue sites and was characterized by pronounced local symptoms. The general condition of the patients on admission ranged from satisfactory to severe.

In the 2nd study group, the inflammatory process was located in 3 or more neighbouring tissue sites, had a tendency to progress and the general condition was evaluated as severe. All those abcesses/phlegmons were characterized by substantial local and systemic symptoms including fever. The disease was accompanied by pronounced signs of systemic toxicity and various organ failures. In one case, the disease was fatal.

Each major study group was subdivided into 2 study subgroups receiving the combined treatment including perftoran (31 patients), and study subgroups (for comparison) in whom only traditional treatment was carried out (45 patients). In particular, in the 1st major group, those receiving perftoran comprised 16 patients, and those without perftoran comprised 27 patients; in the 2nd major group perftoran was administered to 15 patients, and 18 patients remained without perftoran (Fig. 1).

There also was an additional *control group* comprising 15 "practically healthy" people aged 18−50 years, without any pathology in the maxillofacial region. These

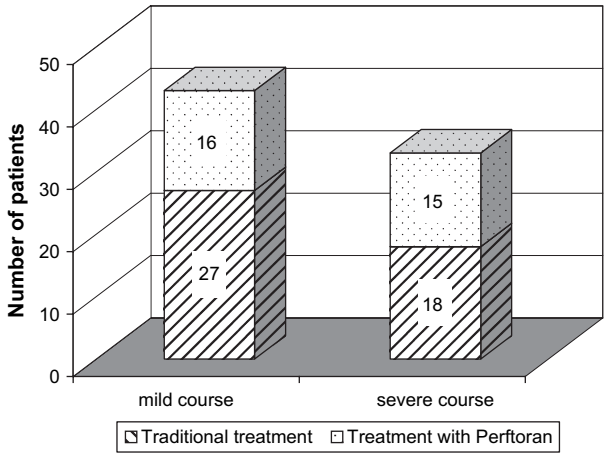

Fig. 1 – Distribution of patients into subgroups according to treatment method.

were volunteer students and patients admitted to the hospital for planned plastic operations. The values of indices obtained from these people were treated statistically and used as reference figures.

Methods of investigation

During the study, 3292 clinical, X-ray, morphological, cytological and biochemical investigations were performed. The patients were examined at the stage of surgical treatment and on the following (1st, 3rd, and 7th) postoperative days as well as at discharge. The healthy patients were examined only once.

(1) *Clinical investigation* traditionally comprised clarification of complaints and the full history (site of inflammation and duration of periodontal disease) as well as clinical symptoms (*Shulakov*, 1995). Particular attention was paid to the cause and duration of the disease, to treatment carried out before hospital admission, and to any accompanying pathology. Usual examination features recorded were: temperature, pulse rate, degree of systemic toxicity and disturbance of mastication, swallowing, respiration and speech. Local alterations in the maxillofacial and neck region included associated oedema, cutaneous hyperaemia and consistency, crepitation or fluctuance and tongue restriction. The need for emergency measures was also assessed (e.g., tracheostom). During the operation particulars of the tissue, volume and type of pus as well as the tissue planes involved were noted. Postoperatively, the duration of discharge, and signs of wound healing were also noted.

The shape and volume of in flamed tissue were calculated either as a circle according to the formula: $S = \pi R^2$, or as an ellipse according to: $S = \pi ab$, where R is the radius, a is the long semiaxis, b is the small semiaxis, $\pi = 3.14$ (*Shulakov*, 1995).

(2) For *overall assessment* and to chart the progress of the inflammation and of the patient's recovery, a combined analysis of all the general and local clinical characteristics was performed by awarding points, the number of which increased according to the gravity of the clinical setting (Tables 1–3; *Durnovo*, 1998). The data of the dynamic patient survey, with the calculation of points, were documented on the day of admission, and on the 3rd and 7th postoperative days as well as at discharge. Then a general cumulative table was compiled to give final values and total cumulative points. These data provided criteria for establishing the dynamics of the progress of the disease.

(3) Radiographic *investigation* identified the cause of the inflammatory process in the maxillofacial region.

(4a) *Histological investigations* of soft tissues were carried out with conventional methods (*Shekhter* et al., 1983, 1984; *Datsenko*, 1995; *Platonova*, 1999). Tissue samples from the inflammatory area and underlying tissues, were fixed in 10% formaldehyde, passed through alcohol of increasing concentrations and set in paraffin wax. Sections 0.6 μm thick were prepared and stained with haematoxylin–eosin and Van-Gieson (*Avtandilov* et al., 1981; *Avtandilov*, 1990; *Sapozhnikov* and *Dorosevich*, 2000).

Quantitative morphometry was the main investigation. The ratio of the number of neutrophils and of "round cells" was calculated among a group of 100 cells. Necrotic tissue areas and connective tissue areas were measured at various treatment periods. Using the immersion system of the MBI-15 microscope (objective 90 and ocular 10). The necrotic surface of the inflammatory focus was determined by the method of point calculation using an eyepiece insert. Since the method of point calculation is statistical, the specific surface of the objects was determined in mm^2 as an average value of 10 visual fields. Cellularity in the surrounding tissue was determined as well as the average value of cells from 10 visual fields. Mucicarmine was used to stain – mucus to determine cellular functional activity (*Sapozhnikov* and *Dorosevich*, 2000).

The activity at the nucleolar level was studied to obtain a proliferative activity index at the secondary healing stage of a purulent wound (*Anichkov* and *Tolybekov*, 1987; *Anichkov*, 1990; *Crocker*, 1990; *Derenzini* et al., 1990; *Derenzini* and *Trere*, 1991). For this, paraffin sections were impregnated with silver nitrate colloidal solution to reveal argyrophilic proteins associated with in the area of the nucleolus. This was carried out by fixing paraffin sections in acetic acid solution at 4°C for 30 min, washing in distilled water and staining with a solution of 1 volume of 2% gelatin, 1% aqueous solution of formic acid and 2 volumes of 50% silver nitrate solution, for 20 min in darkness at the ambient temperature. After that, silver colloid was washed out with distilled water, the sections were covered with 5% sodium thiosulphate solution, washed again with distilled water, contrast stained and dehydrated. Under oil immersion the number of silver granules was calculated in 100 selected cells. For each cell, the total number of observed visible spots (silver granule aggregation) was determined using careful focussing. Quantitative evaluation was then completed using variation statistical methods (*Avtandilov* et al., 1981; *Avtandilov*, 1990).

(4b) *Cytological investigations* were performed to evaluate the reparative process in the purulent wound. Material sampling was carried out using standard

Table 1 − Evaluation of the general condition

No.	Index	Number of points
1.	Temperature	
	Up to 37.0 °C	0
	37.1−38.0 °C	1
	38.1−39.0 °C	2
	More than 39.0 °C	3
2.	Pulse	
	Up to 80/min	0
	81−90/min	1
	90−100/min	2
	More than 100/min	3
3.	Excitation	
	Non-existent	0
	Existing	2
4.	Weakness, flabbiness	
	Non-existent	0
	Existing	2
5.	Pain	
	Non-existent	0
	Localized	1
	Spread	2
	Spread with irradiation	3
6.	Mastication disturbed	
	Non-existent/possible	0
	Existing	1
7.	Dysphagia	
	Non-existent	0
	Existing	4
8.	Dyspnoea	
	Non-existent	0
	Existing	3
9.	Dysphoria	
	Non-existent	0
	Existing	4
10.	Total number of points	

impression smears. The preparations were stained with azure-P−eosin according to Romanovsky's method. Cell composition was calculated in percentages, from 100 to 300 cells in different areas of the preparation (*Astakhova* et al., 1998; *Grigoryan* et al., 2000; *Sapozhnikov* and *Dorosevich*, 2000).

(5) *Laboratory investigation* (all patients).

(a) *Total blood count* − leucocyte count, leucocytic intoxication index (LII) (a marker of endogenous intoxication), and erythrocyte sedimentation rate (ESR, mm/h). LII was determined on admission and at treatment stages. Its calculation was based on modifications in the qualitative composition of the different blood elements according to the following formula:

$$\mathrm{LII} = \frac{(4\mathrm{My} + 3\mathrm{Y} + 2\mathrm{St} + \mathrm{Sg}) \times (\mathrm{PI} + 1)}{(\mathrm{Mon} + \mathrm{Lym}) \times (\mathrm{E} + 1)},$$

where My are myelocytes; Y, young forms; St, stab cells; Sg, segmented cells; Pl, plasma cells; Mon, monocytes; Lym, lymphocytes; and E, eosinophils.

When normal, LII is 0.5−1.5. LII represents the integral haematologic index of adaptation reactions of the

Table 2 − Evaluation of local alterations

No.	Indices	Number of points
1.	Oedema in soft tissues (number of sites)	1 site = 1 point
2.	Infiltrate in soft tissues (number of sites)	1 site = 1 point
3.	Integument: integument hyperaemia sites	1 site = 1 point
4.	Infiltrate symptoms: tension	
	Non-existent	0
	Existing	1
5.	Fluctuation	
	Non-existent	0
	Existing	1
6.	Crepitation	
	Non-existent	0
	Existing	1
7.	Wound with discharge	
	Non-existent	0
	Existing	1
8.	Maximum interincisal distance	
	0 cm	0
	1 cm	1
	2 cm	2
	3 cm	3
9.	Limited mandibular motion	
	Non-existent	0
	Existing	1
10.	In oral cavity: infiltrate (number of sites)	1 site = 1 point
11.	Symptoms in the infiltrated area: tension	
	Non-existent	0
	Existing	1
12.	Pain	
	Non-existent	0
	Existing	1
13.	Fluctuation	
	Non-existent	0
	Existing	1
14.	Wound(s) with discharge or fistula(e)	
	Non-existent	0
	Existing	1
15.	Tongue motion limited	
	Non-existent	0
	Existing	1
16.	Number of neighbouring tissue sites involved in the process	1 tissue site = 1 point
17.	Tracheostoma necessary?	
	No	0
	Yes	3
18.	Were muscles dissected next to the mandible during surgery?	
	No	0
	Yes	2
19.	Peculiarities in the tissue condition:	
	Haemorrhagic, red colour, viable	1
	Necrotic tissues, grey colour, "digested"	2
20.	Character and amount of purulent discharge	
	Non-existent	0
	Insignificant	1
	Abundant, viscous	2
	Moderate, liquid, malodorous with air bubbles	3
21.	Identification of microbes in the purulent discharge	
	Aerobic	1
	Anaerobic	2
22.	Total number of points	

Table 3 − Evaluation of the purulent wound during treatment

No.	Indices	Number of points
1.	Amount of purulent exudate	
	None	0
	Reduced	1
	Abundant	2
2.	Granulation tissue	
	Oozing wound with abundant granulation	0
	Insignificant amount (primary signs)	1
	No granulation tissue	2
3.	Sutures applied to the wound	
	Yes	0
	No	1
4.	Wound epithelization	
	Epithelialized	0
	Primary signs	1
	None	2
5.	Total number of points	

patient in response to infection. If the differential white blood count shifts to the left, LII increases, respectively.

(b) Biochemical analysis.
- linear function − ASAT, ALAT (μmol/l s) in blood serum were measured using methods approved by the International Federation on Clinical Chemistry.
- reval function − serum creatinine (μmol/l) was determined using Yaffe's colour reaction.
- *to evaluate hypoxia*, the lactate and pyruvate blood levels (mmol/l) were measured according to Hochorst.
- *lipid peroxidation (LPO) processes and the protective antioxidant activity (AOA)* were studied using biochemiluminescence (*Kuzmina* et al., 1983), and LPO molecular products: primary, diene and triene conjugates and final, Schiff bases (SBs) were assayed (*Fletcher* et al., 1973). The direction of oxidation processes in substrates was evaluated on the basis of the value of the oxidation coefficient characterizing the ratio of LPO primary products such as diene conjugates to the secondary ones, i.e, SBs (*Durnovo*, 2003). The level of LPO intensity and antioxidant protective activity was evaluated on the basis of examining blood and soft tissue homogenates from the suppurative focus in study patients.

To evaluate the AOA, the following most informative parameters were used:

(1) I_{max} (pulse/s), the maximum luminescence intensity representing the potential ability of a biological object to be oxidized by free-radicals. The values of this parameter depend on the concentration of total lipids in blood plasma.
(2) S is the total light in 30 s in the plasma, that represents the content of radicals corresponding to the break of the free-radical oxidation chain and is inversely proportional to the AOA activity.
(3) I_{max}/S (relative units) is the ratio of the maximum intensity to the cumulative chemoluminescence in 30 s. This coefficient correlates with the variation of the chemoluminescence curve of tangent inclination angle and characterizes total AOA of blood plasma.

Statistical analysis

The universal data processing software package "Statgraphics" and "Statistica" were used for calculating the arithmetic mean (M) and the error of the mean (m). Verification of the differences was performed using the Student's t-test.

Treatment methods

All patients were submitted to an identical series of procedures based on the gravity of the inflammatory process, of the endogenons "toxicity", of hypoxia, and of the hepatic and renal functions. All patients underwent surgical and conservative treatments.

The surgical treatment consisted of imaging the abcesses and/or phlegmon area(s) and extraction of the causal tooth or teeth as indicated. The extent of surgery, access and the type of anaesthesia depended on the location and extent of the inflammation and consisted of a thorough re inspection of all the affected cavities and resection of necrotic tissue. All patients were prescribed general and local treatment procedures.

Traditional treatment

Preoperative therapy was aimed at decreasing systemic toxicity and normalizing cardiohaemodynamics. This was achieved by haemodilution. Amongst the infusions were electrolyte solutions (isotonic solution of sodium chloride, Ringer-Lock's solution), 5−10% glucose solution with insulin, plasma substitutes with detoxicating effects (polyglucin, rheopolyglucin, hemodez). The mean volume of infusion solutions was 30−40 ml/kg of body weight. Patients with decompensated metabolic acidosis received injections of 4% sodium bicarbonate solution (2−3 ml/kg). The infusion comprised 5% ascorbic acid solution (5.0 ml), antihistaminic preparations (1−2% dimedrol or pipolphen solution: total 2.0 ml), and in the case of exacerbated abcess development heparin was prescribed preventively (2500 units, 9 ds). Thirty-six patients from the 2nd major group were also submitted to "forced" diuresis, to increase the detoxication. It consisted of injection of 2% lasix solution at a dose of 1.0−2.0 ml/kg first. This was repeated after opening the phlegmon or abcess until disappearance of toxic symptoms.

Antibacterial therapy was given to all patients, the selection of the drug depending on the gravity of the disease (most often, oxacillin, ampicillin, gentamycin, lincomycin, metronidazole, cephalosporins of III generation were used). Whilst identifying pathogens, antibacterial drugs were prescribed according to gravity of the inflammation and to hepatic and renal function. Suprastin, dimedrol, and tavegil were used as desensitizers.

Daily dressing changes were performed on all patients. For local treatment, antiseptic solutions (0.06% chlorhexidine, 0.03% sodium hypochlorite, 1% dioxidine

solutions), proteolytic enzymes (trypsin and chymotrypsin) were used with subsequent administration of hydrophilic ointments (levosin and levomecol). During the proliferation phase until complete healing, drugs stimulating the reparative processes (actovegin, solcoserylic jelly, oil solutions of keratoplastic drugs) were introduced daily into the wound.

Treatment with the application of perftoran
In the 2 study subgroups receiving perftoran (31 patients), a single-stage postoperative intravenous injection of perftoran was given in addition to the general infusion therapy: in the 16 patients with mild disease, 1 ml/kg of body weight; in the 15 patients with a severe course, 2—3 ml/kg of body weight. The indication to administration more intravenous perftoran was the rise of hypoxia and signs of increasing endogenous systemic toxicity. Further dosage increases together with single-dose increases for the intravenous injections lead to the development of hyperoxia as well as to activation of free-radical oxidation processes. Local treatment consisted of daily irrigation of the surgical wound with perftoran until the end of exudation (up to 5 days). The first local treatment of the wound was carried out directly in the operating room after opening the phlegmon or abcess, respectively. For the first 2—3 days (at the purulent phase), gauze tampons soaked with perftoran were introduced into the wound (to increase the local drug effect), together with performing tube drainage.

Contraindications for perftoran treatment were as follows: hemophilia, pregnancy, individual drug intolerance.

RESULTS

The patients with abcesses and/or phlegmons whose treatment included perftoran (study group) had a more mild disease course. *Clinical symptoms* of endogenous toxicity and pain were curtailed faster than in patients receiving only "traditional treatment". Already on the 1st day after starting treatment with perftoran in mild disease (1st group) and on the 3rd day in patients with severe disease (2nd group) there was improvement of their general condition and the clinical course of the inflammatory process: decrease of temperature and of pulse rate, reduction and significant decrease in intensity of pain, recovery of mental and emotional status, normalization of sleep and appetite.

Whereas in the 1st group of patients the total number of points was slightly higher than 30, on admission, in the 2nd group it was close to 60. During treatment, recovery of their general condition was recorded. But in the study subgroups (compared with the traditional therapy subgroups) a faster and more intensive decrease of the total number of points was recorded, indicating a faster decline of the symptoms under study (Fig. 2).

Regression of local clinical features (oedema, hyperaemia, size of swelling, intensity, and character of wound discharge) in the subgroups having been given perftoran (study groups) was noted after 2 days. However, using traditional therapy, the improvements were observed only by the 7th day. The study subgroups with perftoran experienced a faster reduction of purulent exudation (2 days on the average) than the comparison groups, and granulation commenced in the wound 3 days earlier on average. In the study subgroup (with perftoran) of the 1st major group, the epithelium formation commenced on day 4 (4.29 ± 0.35), whereas in traditional treatment group epithelalization commenced after 8 (8.18 ± 0.53) days. In the 2nd major group, the time of epithelium formation commenced on day 5 (5.65 ± 0.43) in the study subgroup, but only on day 8 (8.68 ± 0.69 days) in the comparison subgroup (Table 4).

The results of cytological investigations confirmed the clinical examinations: in the perftoran subgroups touch smears showed a considerable decrease in neutrophils with a simultaneous increase in the number of round cells (Table 5). Indices characterizing the commencement of wound repair nucleolar organizer activity demonstrated that these patients, independently of the severity of inflammation, showed an earlier and more intensive start of the proliferative phase.

Some objective indices of systemic toxicity (leukocyte count, LII, ESR levels, serum transaminase and creatinine) showed a more pronounced decrease in the perftoran subgroups, independent of the extent of the inflammatory process (Table 6).

On admission, the ESR increased in all patients and varied between 32 and 62 mm/h. In the healing phase, the ESR level in perftoran patients with mild disease (1st major group), decreased by 53% (from 38.45 ± 7.85 to 18.08 ± 3.63 mm/h, $p < 0.001$) and with traditional treatment, by 42% (from 42.81 ± 11.12 to 24.72 ± 5.33 mm/h, $p < 0.001$). In the 2nd major group (severe inflammation) this index decreased by 66% in the study subgroup with perftoran and by 55% in the comparison subgroup, respectively ($p < 0.001$; Table 6). But in all subgroups, there was no ESR normalization at the moment of discharge from the hospital.

The leukocyte count in peripheral blood decreased also: in the 1st major group (mild disease) at the moment of clinical healing, this index was $5.26\ (\pm 0.87) \times 10^9$/l when using perftoran, and it was $6.26\ (\pm 1.15) \times 10^9$/l with traditional treatment; in the 2nd major group it was $4.9\ (\pm 0.81) \times 10^9$/l and $6.73\ (\pm 0.97) \times 10^9$/l, respectively ($p < 0.001$; Table 6). When comparing the leukocyte indices at discharge with the data of the control group (i.e., without abcesses) it was noted that the patients with face and neck phlegmons/abcesses in the 2 study subgroups receiving perftoran showed conformity of clinical healing and of laboratory data. The patients of the 2 comparison subgroups without perftoran, the parameters showed only a tendency to recover and normalization of the laboratory data was observed at ward discharge.

On admission, LII had a statistically significantly higher level in both study groups when compared with the control (Table 6). After treatment, this decreased considerably in all patients. However, it corresponded to the values in healthy people only with the application of perftoran (Table 6).

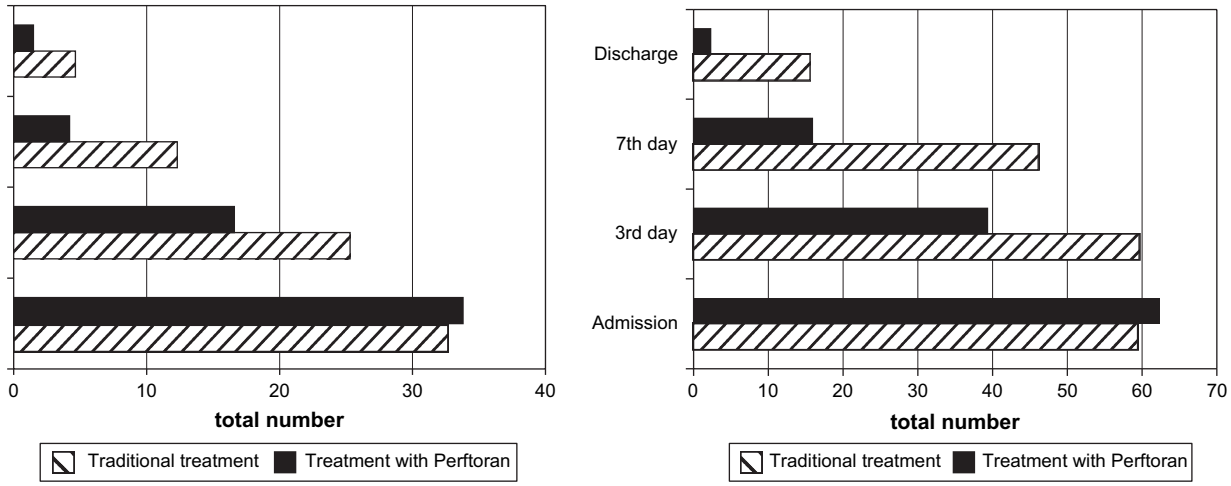

Fig. 2 – Dynamics of the clinical development in terms of "points" related to traditional treatment and treatment with perftoran in patients of the 1st (mild course) and 2nd (severe course) major groups having face and neck abscesses phlegmons.

Table 4 – Duration of pus formation and times when granulation tissue and epithelium started to appear in patients having abcesses of phlegmons in the maxillofacial region

Major groups	Subgroups	Duration of suppurative exudation (days)	Time when granulation tissue appeared (days)	Time of epithelialization appeared (days)
1 (Mild course)	Study subgroup (with use of perftoran)	2.78 ± 0.29†	3.18 ± 0.36†	4.29 ± 0.35†
	Control subgroup (traditional treatment)	5.21 ± 0.51	5.63 ± 0.18	8.18 ± 0.53
2 (Severe course)	Study subgroup (with use of perftoran)	4.79 ± 0.69†	3.92 ± 0.58†	5.65 ± 0.43†
	Control subgroup (traditional treatment)	7.85 ± 0.67	6.62 ± 038	8.68 ± 0.69

†$p < 0.05$ in comparison with the indices of the control subgroup.

The serum cytolytic enzymes and creatinine were increased at admission: the ALAT level was increased 2–3 times on average, ASAT 1.7–2 times on average, and creatinine was increased by 30% on average (Table 6) and were dependent on disease severity and extent of inflammation. After treatment with perftoran, these data were close to normal (Table 6).

On admission, all patients had increased serum levels of lactate and pyruvate as well as an increased lactate/pyruvate ratio, being evidence of tissue hypoxia (Table 6, Fig. 3). After performing traditional treatment, these indices decreased a little; however, after treatment with perftoran, all the indices approached the control level (Table 3, Fig. 3).

The patients having odontogenic abcesses/phlegmons had decreased AOA with an increase of free-radical oxidation reactions prior to drainage (Table 6, Fig. 4). In addition, in the mild disease group, AOA was lower than in the 2nd major group (severe course of the inflammatory process). Following traditional treatment, variation in the dynamics of the AOA and of the LPO was noted, which seemed to be due to the gravity of the patients' condition in different groups. Including perftoran in the treatment enabled a reduction of LPO products by normalization of the antioxidant system and to draw the AOA values closer to control levels (Table 6, Fig. 4). Such an antioxidant effect of perftoran was confirmed when studying free-radical oxidation processes in the patient's blood and tissue. At the end of treatment, the SB concentration decreased in the 1st major group from 18.23 ± 3.64 relative units/mg of total blood lipids to 3.71 ± 0.92 ($p < 0.001$) and in the tissue from 27.11 ± 5.04 relative units/mg of total lipids to 8.91 ± 2.57 ($p < 0.001$). In the 2nd major group, similar results were observed: in blood 23.89 ± 5.86 and in tissues 30.63 ± 6.33 relative units/mg of total lipids during the inflammatory process, and 3.20 ± 0.797 relative units/mg of total lipids in blood and 6.66 ± 1.295 in tissues during clinical healing ($p < 0.001$).

DISCUSSION

The positive effect of perftoran found on the regeneration processes in purulent wounds is consistent with the findings of other authors (*Pokruchin* et al., 1995; *Khrupkin* et al., 1997; *Osipov* and *Gusenkov*, 1999; *Dalgatov*, 2001). But these authors evaluated the effects of perftoran only when using it locally for purulent wounds. When treating patients with odontogenic of the maxillofacial region, the combined use of perftoran is probably the most rational. The combination of intravenous and local administration promotes adequate oxygenation of the wound and optimizes penetration of antibacterial drugs into the wound. The application of perftoran intensifies necrolysis and reparative regeneration processes by 1.5–2 times on average when compared with traditional treatment methods. It shortens wound healing by 3–5 days (mean 4.82 ± 1.17 days). In particular, the average time of purulent wound healing in the patient study subgroups was only 8.3 ± 1.1 days which is 28% less

Table 5 – Percentage of neutrophils/round cells in smears from the surface of wounds in patients having odontogenic abcesses or phlegmons

Indices	Treatment methods	Treatment phases		
		1st day	3rd day	7th day
Neutrophils, %	Traditional treatment	87.69 ± 2.18†	70.82 ± 1.28†	64.73 ± 1.48†
	Treatment with perftoran	78.26 ± 1.24†,‡	60.12 ± 2.51†,‡	37.58 ± 2.27†,‡
Round cells, %	Traditional treatment	11.23 ± 1.06†	28.12 ± 1.38†	34.12 ± 1.29†
	Treatment with perftoran	22.84 ± 2.48†,‡	37.84 ± 2.74†,‡	60.12 ± 1.85†,‡

†$p < 0.001$ in comparison with indices on admission.
‡$p < 0.001$ in comparison with traditional treatment.

Table 6 – Development of haematological indices in patients having odontogenic abcesses/phlegmons in the maxillofacial region, depending on the treatment method (the numerator being for admission and the denominator for discharge)

Indices	Control	Treatment methods			
		Traditional treatment		With the use of perftoran	
		1st Group (mild course)	2nd Group (severe course)	1st Group (mild course)	2nd Group (severe course)
ESR, mm/h	8.57 ± 1.21	42.81 ± 11.12‖ / 24.72 ± 5.33‡, ‖	53.33 ± 8.89‖ / 24.00 ± 6.32‡, ‖	38.45 ± 7.85‖ / 18.08 ± 3.63‡, ‖	49.93 ± 9.07‖ / 16.91 ± 3.81‡, ‖
Leukocytes ($n \times 10^9$/l)	5.03 ± 0.87	8.88 ± 2.22‖ / 6.26 ± 1.15‡, ‖	10.15 ± 2.85‖ / 6.73 ± 0.97‡, ‖	10.98 ± 2.78‖ / 5.26 ± 0.87‡	10.56 ± 2.28‖ / 4.90 ± 0.81‡
LII, rel. units	0.79 ± 0.11	2.69 ± 0.63‡ / 1.00 ± 0.24‡, §	3.73 ± 0.87‖ / 1.69 ± 0.43‡, ‖	2.79 ± 0.94‖ / 0.72 ± 0.17‡	4.76 ± 1.17‖ / 0.76 ± 0.15‡
ALAT, μmol/l s	0.21 ± 0.042	0.457 ± 0.089‖ / 0.418 ± 0.063‖	0.548 ± 0.095‖ / 0.391 ± 0.068‡, ‖	0.406 ± 0.068‖ / 0.202 ± 0.049‡	0.757 ± 0.122‖ / 0.249 ± 0.052‡
ASAT, μmol/l s	0.17 ± 0.027	0.33 ± 0.06‖ / 0.25 ± 0.06‡, ‖	0.35 ± 0.08‖ / 0.25 ± 0.06‡, ‖	0.26 ± 0.05‖ / 0.15 ± 0.04‡	0.49 ± 0.09‖ / 0.16 ± 0.03‡
Creatinine, μmol/l	77.27 ± 8.17	99.84 ± 8.90‖ / 85.76 ± 7.23‡, §	96.94 ± 9.38‖ / 83.44 ± 8.02‡, §	100.80 ± 15.06‖ / 76.27 ± 7.74‡	106.86 ± 16.13‖ / 81.15 ± 7.95‡
Lactate, mmol/l	0.9 ± 0.11	2.305 ± 0.456‖ / 1.919 ± 0.433†, ‖	2.573 ± 0.453‖ / 1.953 ± 0.312‡, ‖	2.35 ± 0.34‖ / 1.07 ± 0.25‡, §	2.581 ± 0.198‖ / 1.058 ± 0.214‡, §
Pyruvate, mmol/l	0.09 ± 0.02	0.17 ± 0.04‡ / 0.12 ± 0.03‡, §	0.21 ± 0.04‖ / 0.17 ± 0.04†, ‖	0.18 ± 0.04‖ / 0.09 ± 0.02‡	0.22 ± 0.04‖ / 0.12 ± 0.03‡, §
Lactate/pyruvate, rel. units	8.68 ± 1.35	14.75 ± 4.35‖ / 16.79 ± 0.03†, ‖	12.47 ± 2.31‖ / 11.86 ± 2.29‖	11.49 ± 1.74‖ / 9.38 ± 1.55†	12.19 ± 2.65‖ / 8.86 ± 1.99†
AOA, conv. units	0.190 ± 0.009	0.088 ± 0.009‖ / 0.101 ± 0.008‡, §	0.095 ± 0.009‖ / 0.089 ± 0.009‖	0.0886 ± 0.009‖ / 0.151 ± 0.022‡	0.113 ± 0.018‖ / 0.163 ± 0.029†

†$p < 0.05$ in comparison with indices on admission.
‡$p < 0.001$ in comparison with indices on admission.
§$p < 0.05$ in comparison with the control.
‖$p < 0.001$ in comparison with the control.

($p < 0.05$) than in the "traditional treatment" only subgroups (11.6 ± 1.9 days). A decrease of the area of infiltrate and of pain intensity in the study subgroups was observed as early as 1–2 days after starting the treatment. In the comparison subgroups the decrease of the infiltration area was noted on average 3–4 days after starting the treatment. Necrolysis was accelerated in the study subgroups, it was on average 2.5 days or 39% earlier than in the controls ($p < 0.05$), and the active growth of granulation tissue was accelerated on average by 3 days or 33% ($p < 0.05$).

The addition of perftoran to the combined treatment of patients having face and neck abcesses reduces, the intensity of systemic toxicity considerably more than traditional treatment. This positive effect of perftoran was supported by the decrease of leukocyte count, ESR, LII, and transaminase activity (Table 6). The normalization of serum creatinine allowed to conclude that perftoran reduced the intensity of hepatic and renal insufficiency and that it had no negative effects. These results are confirmed by the studies of Shulakov (1995), Zabelin et al. (1997), Durnovo (1998), and Gubin et al. (1998).

Administration of perftoran as described here assisted gas exchange in tissues, favouring a decrease of lactate-acidosis. In the patients receiving perftoran, on the 1st day of treatment a decrease of the lactate/pyruvate ratio was recorded. This was more prominent in the patients receiving "traditional treatment", which showed that the biochemical processes adopted more energy demanding aerobic pathways (Fig. 3). It is believed that this anti-hypoxic activity of perftoran is due to its gas-carrying function.

Various papers describing inflammatory diseases in the maxillofacial region especially the course of face and neck abcesses, its therapy and the prognosis, assign

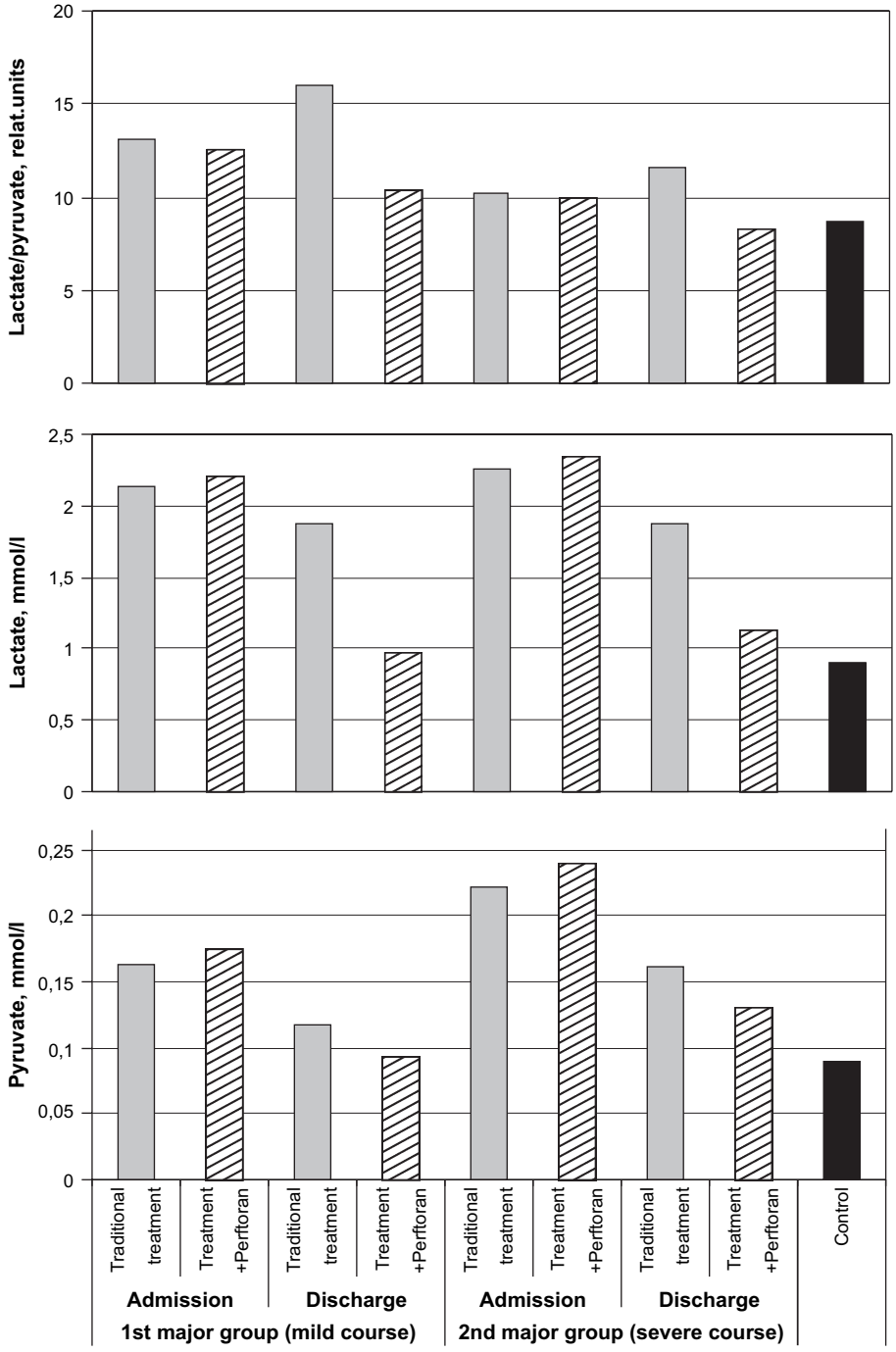

Fig. 3 – Lactate pyruvate and lactate/pyruvate ratio in the blood of 1st (mild course, $n = 43$) and 2nd (severe course, $n = 33$) major groups of patients having odontogenic abcesses or phlegmons in the face/neck in relation to traditional treatment and treatment with perftoran.

the most important part to the free-radical oxidation processes. The clinical signs of the disease were related to the level of LPO products and to the activity of the antioxidant protection system (*Ganina* et al., 1990; *Durnovo*, 2003). One of the criteria for treatment efficiency is the stabilization of the membrane lipid oxidation processes that is obtained by levelling of free-radical oxidation products due to accumulation of antioxidants. The data of the AOA dynamics obtained in this study agreement with several other studies (*Ragimov*, 1992). In the 1st major group of patients with mild disease, the AOA indices were lower when abcesses were drained than in the 2nd major group (severe disease). At the time of discharge, the activity of the antioxidant protection system of the 1st group increased for a lower final content of products of LPO. In the 2nd group, slight inhibition of the LPO processes was still observed with a background of destabilization of the antioxidant protection system. In contrast to this, no normalization of the indices of LPO or AOA occurred, during traditional treatment, and in some cases LPO indices even continued to grow in intensity whilst there was some decrease in the AOA level. This

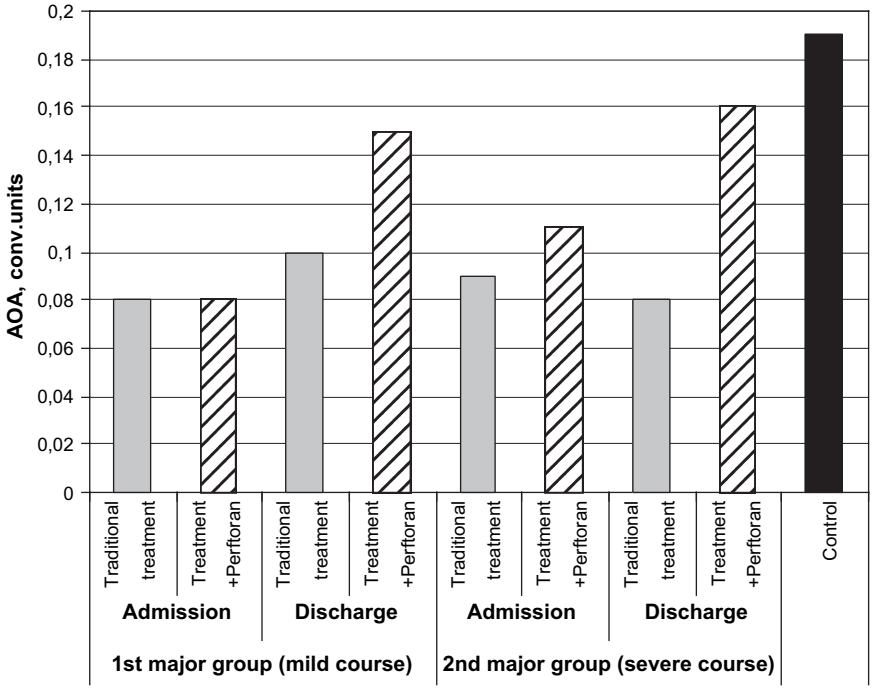

Fig. 4 – AOA levels in patients of 1st (mild course, $n = 43$) and 2nd (severe course, $n = 33$) major groups having odontogenic abcesses or phlegmons in the face/neck in relation to traditional treatment and treatment with perftoran.

represented a poor prognostic sign demonstrating the low efficiency of traditional treatment.

While using perftoran, the AOA and LPO were similar in all patients. The study groups showed a considerable increase in the antioxidant protection level (homogenates of purulent wound tissues and serum) in the media under investigation starting from the 1st 3 days after treatment commenced. The effect might be explained by activation of the enzymatic component of the antiradical protection as a result of restoration of metabolism in the wound and as a result of a decrease of lactate-acidosis. The intensification of the activity of the antioxidant protection system allows latter oxidation of free-radical and thus enabling faster clinical healing. Inhibition of the LPO processes when applying perftoran is related to the activation of oxygen-dependent membrane-contained enzymatic antioxidants. The recovery of superoxide-dismutase and catalase activity enables initiation of the antioxidant protection mechanism, which prevents cell degradation.

CONCLUSION

While correlating the results of clinical, morphological, cytological and biochemical investigations one could may conclude that the use of perftoran optimizes traditional treatment of patients with odontogenic abcesses ad phlegmons (in the maxillofacial region). The drug under investigation seems to enable faster eradication of the suppurative focus and to stimulates reparative processes, providing antihypoxic, detoxicating and antioxidant effects. These data demonstrate the high efficiency of the method presented both for treating patients with a mild and those with severe forms of the inflammatory process. It is also necessary to note that no adverse side effects occurred as a result of its use.

Perftoran should be included in the therapeutic strategy of patients having treatment for odontogenic abcesses and phlegmons in the maxillofacial region.

The method of treating patients with face and neck abcesses and phlegmons with perftoran is covered by the Russian Federation Patent No. *2003106491 of 07.03.03*.

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