

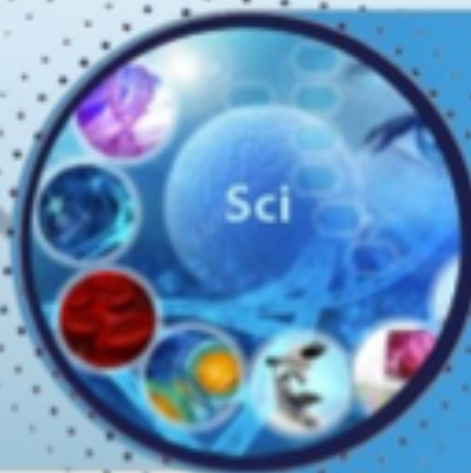


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The Role and Place of Sulfated Glycosaminoglycans in the Treatment of Phlegmon, Odontogenic Origin

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ABSTRACT

Background. The current system of prevention of complications in odontogenic phlegmons is carried out by intensifying anti-inflammatory and detoxification therapy, with the inclusion of hyaluronidase inhibitors - heparin, proteolytic enzymes, improvement of methods of local treatment of purulent in the treatment complex.

Material and methods. The study was conducted on 457 patients with phlegmon of odontogenic origin. Studies of blood biochemical parameters of the LBP protein, antibodies, and antigens to the core region of bacteria and their endotoxins were carried out. This study is based on the method of ion exchange chromatography.

Results. It was revealed that odontogenic phlegmon occurs against the background of a persistent decrease in the body's immune resistance, which ensures a long and severe course of the disease. At the same time, the use of glycosaminoglycans in odontogenic phlegmons increases the level of immunoglobulins. The complex treatment of odontogenic phlegmon creates optimal conditions for improving blood counts and immune response and reduces the risk of spreading purulent infection in patients with odontogenic phlegmon.

Conclusion. The microflora of the surgical wound in odontogenic phlegmons is associated with bacteria of the residual flora constantly present in the oral cavity. The relationship between the level of IgG bacteria associated with the core region and the LBP protein in the blood, exudation, and epithelialization of the surgical wound, reflecting the dynamics of the inflammatory process and compensatory restructuring of the body due to bacterial infection, has been established.

Keywords: sulfated glycosaminoglycans, immunoglobulins, odontogenic phlegmon, residual microflora of the oral cavity

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INTRODUCTION

It is known that the causative agents for abscesses and phlegmons of the maxillofacial region are resident mixed microflora-streptococci in symbiosis with other types of cocci, Escherichia, and other coli [1]. Severe complications of odontogenic phlegmons, such as sepsis, thrombophlebitis of the facial veins and cavernous sinus thrombosis, mediastinitis, are the main cause of mortality in acute odontogenic infection [2]. The authors' poison data confirm the high mortality of the developed phlegmon due to severe intoxication, which causes dysfunction of organs and body systems, which leads to a critical condition of the patient's body [3,4]. Therefore, the issues of prevention, prediction of the course and outcomes of complications of odontogenic phlegmon are still relevant.

Analyzing the literature data on the methods of surgical and conservative treatment of purulent-inflammatory diseases and the maxillofacial region, we did not identify publications on the effectiveness of the use of drugs based on glycosaminoglycans for the treatment of odontogenic phlegmon.

MATERIAL AND METHODS OF RESEARCH

The study of the incidence of odontogenic phlegmon according to the Department of Maxillofacial Surgery of the Tashkent State Dental Institute and the Multidisciplinary Clinic of the Tashkent Medical Academy was carried out. In total, the medical histories of 457 patients for the period 2017-2022 were studied.

Despite preventive measures, the improvement of treatment methods, the emergence of new drugs, and purulent-inflammatory diseases of the maxillofacial region with the alignment of the indicators of the dynamic series tend to increase the incidence, on average by 3.1% annually. For the period 20,17-20, 22 years, the mortality rate from this pathology varies from 3.3 to 2.1%.

The decrease in mortality is associated with the emergence of new broad-spectrum antibacterial agents and the proper organization of care in specialized hospitals. The peak incidence occurs in the February and April months of the year.

The period of admission of patients to the hospital from the onset of the disease averaged 5.2 days. Many patients (54.2%) were admitted to the department by referral from other medical institutions, 22.9% - self-referral of patients, 19.8% - delivered by ambulance, and 3.1% - transferred from other hospitals.

Our studies have shown that odontogenic phlegmon was more common in people aged 20-29 years 39 (37.5%), 30-39 years 22 (20.8%), and among men (67 people) the figure is 1.7 times higher than among women (38 people).

In older people, the course of the odontogenic purulent-inflammatory process was more severe. On the day of hospitalization, 16.7 per cent of patients were in satisfactory condition, 20.8 per cent in relatively satisfactory condition, 50 per cent in moderate condition, and 12.5 per cent in serious condition.

Most often (58.3 per 100 cases) phlegmon was localized in the submandibular region and a minority of cases (2.1 per 100 cases) in the infraorbital, which is associated with the structural feature of the lymphatic system.

At the next stage of the study, we identified the main (24 people) and control groups (29 people). In 20.8% of patients in the main and 20.7% of patients in the control groups, the inflammatory process occupied one topographic and anatomical region, in 79.2% and 79.3%, respectively, two or more. Surgical intervention with external access was performed in 44 patients, in combination with intraoral - 9. In 49 patients, odontogenic phlegmon was opened under anaesthesia, and in 4 patients under local anaesthesia with a 0.5% solution of Novocaine.

Microbiological examination of the surgical wound and biochemical analyzes of blood plasma were carried out in the central research laboratory of the Tashkent Medical Academy. Biochemical studies included new methods of laboratory studies on the day of admission, on the third and on the tenth day of treatment with the Hbt Human LBP ELISA kit for the quantitative determination in the blood plasma of the LBP protein synthesized by the liver in response to bacterial lipopolysaccharides intended for enzyme-linked immunosorbent assay based on the sandwich principle and determination of antibodies (bound Ig G) to the core region of bacteria by the Hbt EndoCab ELISA kit, designed for the quantitative determination of antibodies to the core region of endotoxin in blood plasma. The kits are manufactured by the Scottish National Blood Transfusion Service.

To assess the changes occurring in the connective tissue in patients with odontogenic phlegmon, the content of glycosaminoglycans in the blood plasma was determined. This study is based on the method of ion exchange chromatography.

Statistical processing of the results of the study was carried out using Statistica 6.0 for Windows software

packages. Preliminary analysis of the data included a homogeneity test using the Fisher test.

RESEARCH RESULTS

Microbiological examination of the surgical wound in odontogenic phlegmons showed that in 15.1% of cases, the growth of microorganisms was not detected; in 44% - streptococcus was sown; in 81.1% - crops found symbiosis of streptococcus and staphylococcus; in 7.5% - a symbiosis of streptococcus and Proteus, Escherichia coli and other gram-negative bacteria.

In the presence of an association of microorganisms, inflammatory processes with deeper and more pronounced tissue necrosis were more often noted, which significantly increased the time of cleansing and healing of the wound. The general reaction of the body was expressed by a severe general condition caused by intoxication, inhibition of the main body systems up to the development of toxic nephritis, hepatitis, and respiratory and circulatory dysfunction.

The content of LBP and Ig G associated with the core region in the blood plasma can serve as an objective indicator of the level of endotoxemia in patients with odontogenic phlegmon. Determination of their quantitative level in the blood serum with daily administration of Don's drug showed a decrease in the main group, compared with the control group. In the study group, there was a significant decrease in the concentration of LBP in the blood plasma of patients ($F = 4.47$, $p = 0.018$), although the effect of the treatment time factor was relatively weak (19.87%).

In the control group, there was also a decrease in the content of LBP, but these changes were statistically insignificant ($F = 2.10$, $p = 0.13$).

The above data determine the importance of quantifying the concentration of LBP to predict the degree of risk of development and progression of odontogenic inflammatory diseases of the maxillofacial region and show the feasibility of using sulfated glycosaminoglycans in the treatment of purulent-inflammatory diseases.

The concentration of Ig G associated with the core region in the blood changed during treatment similarly, both in the main and in the control group of patients. There is an increase in IgG by 1.5 times in the main and control group of patients with phlegmon of the maxillofacial region compared with the norm. An increase in the level of the immune response of patients of the main group to 0.19 ± 0.034 g/l by 10 days of treatment, in our opinion, is associated with the introduction of Don's drug, which is confirmed statistically.

Thus, in the control group of patients, the changes were statistically insignificant ($F=1.71$, $p=0.18$). In the main group of patients, this dynamic was statistically significant ($F=4.93$, $p=0.13$). On the 10th day, the content of bound IgG was significantly higher than on the 3rd day ($p=0.0034$). In addition to studying the levels of LBP protein and bound IgG, we assessed the changes occurring in the connective tissue in phlegmons of the maxillofacial region, we determined the state of the proteoglycan system, and their quantitative characteristics in the body's blood plasma. Serum proteoglycans are of tissue origin and are indicators of the intensity of their metabolism.

Our results indicate profound changes in the metabolism of glycosaminoglycans in odontogenic phlegmons. In the main and control groups, a significant increase in the concentration of metabolites (glycosaminoglycans) in the peripheral blood was found on average by two times compared with the norm. In the main and control groups, an increase in the content of glycosaminoglycans in plasma was observed. However, the influence of the dynamics factor (day) was statistically insignificant ($F=1.21$, $p=0.31$ for the main group and $F=0.89$, $p=0.41$ for the control group). The found violations can be associated with changes in the biosynthesis of glycosaminoglycans, and with an increase in the catabolism of glycosamine-containing complexes.

Summarizing the result, in our opinion, it can be argued that exogenously incoming glycosaminoglycans are almost completely absorbed by the body, which creates optimal conditions in the wound to optimize regeneration.

The average biochemical parameters in patients before surgery and on day 10 did not significantly differ from the norm. The change in serum bilirubin was not statistically significant ($p=0.58$).

By day 10, a statistically insignificant increase in bilirubin levels was observed in both groups ($p=0.68$ for the main group and $p=0.58$ for the control group). There was a statistically significant decrease in protein on day 10 in the study group ($p=0.036$).

In the control group, although there was a decrease in the level of total protein to 73.23 ± 4.22 , it was statistically insignificant ($p=0.079$). Plasma creatinine decreased slightly in the main and control groups but was statistically insignificant.

On the third day after surgery, there was a significant ($p<0.001$) decrease in the number of leukocytes in the main group to $7.0 \pm 0.2 \times 10^9/l$ and the control group to $9.20 \pm 0.15 \times 10^9/l$. Before surgery, these indicators were

12.90±0.3x10⁹/l and 12.80±0.2x10⁹/l respectively. Normalization of leukocyte counts in patients with odontogenic phlegmon occurred by the 10th day of treatment and was 6.5±0.2x10⁹/l in the study group and 7.7±0.2x10⁹/l in the control group. The erythrocyte sedimentation rate before surgery was 17.1±2.1x10⁹/L (p<0.05). The decrease in this number occurred gradually and by the 10th day of treatment reached 8.2±2.1x10⁹/l in the main group, in the control group - 12.2±1.0x10⁹/l, which indicates a more rapid relief of the inflammatory process in the main group (p<0.05).

An elevated level of class A and G immunoglobulins in phlegmon indicates the progression of pathological changes leading to the spread of the pathological process.

On the first day after surgery, patients had an increase in IgA, IgG, and a decrease in IgM. On the 10th day after surgery and appropriate conservative therapy, it was in the main group: IgA — 2.8±1.2 g/l; IgM - 1.2±0.6 g/l; IgG -16.97±0.42 g/l and control - respectively: IgA - 2.3±1.1 g/l; Ig M - 2.96±0.6 g/l; Ig G - 9.9±0.71 g/l.

At the next stage, we investigated the effect of DONA drug on the timing of purulent wound regeneration in patients with odontogenic phlegmon. Evaluation of the effectiveness of various methods of treatment of surgical wounds and the data of clinical trials causes certain difficulties since there is still no single approach in the methods for assessing the results of therapy. In our case, the terms exudation and epithelialization are considered as criteria for the regenerative process. By 3 days of observation, the main and control groups had no statistically significant differences in the frequency of exudation (Chi²=1.71, p=0.191).

However, on the 5th day, there was a statistically significantly higher incidence of cases of absence of exudation in the main group than in the control group (Chi²=4.78, p=0.028).

Observations of the course of wound epithelialization after treatment showed the following: on the 12th day of observation there were no statistically significant differences in the timing of wound epithelialization in patients of the main and control groups (Chi²=1.71, p=0.191).

On the 14th day of follow-up, the proportion of patients with wound epithelialization in the study group was statistically higher, while in the control group, there were more wounds in the exudation stage (Chi²=4.63, p=0.031).

Thus, because of our research, we found that the complex treatment of odontogenic phlegmon with the use of DONA drug has a more pronounced clinical ef-

fect. The foregoing allows us to recommend this drug for widespread use in the practice of a maxillofacial surgeon.

DISCUSSION

Sulfated glycosaminoglycans are unbranched polysaccharide chains composed of repeating disaccharide units, one of which is an amino saccharide, which in most cases is sulfated, and the other is uremic acid. Due to the degree of sulfation, their physicochemical properties differ. Glycosaminogs include chondroitin-4,6-sulfates, keratan sulfates, dermatan sulfates, heparin, and heparan sulfate [5].

Each tissue or organ has its own characteristic set of glycosaminoglycans. In free form, sulfated glycosaminoglycans are practically not found. By covalently binding to the protein, they form proteoglycans and determine their functions. Sulfated glycosaminoglycans are part of the intercellular substance along with collagen, elastin, and glycoprotein fibers, and are also structural components of the cell (secretory granules), cell membranes and glycocalyx [6].

Analysis of the results of various studies on the physiology and pathophysiology of sulfated glycosaminoglycans allows us to identify the following functions [7]:

Trophic - regulate the transport of water, salts, amino acids, lipids, and metabolites in non-vascular brady trophic tissues [8].

Structural - ensure the correct stacking of tropocollagen in fibrils and fibrils in collagen fibers, contributing to the specific structural organization of the tissue. They form a bond between the cell surface and the intercellular substance [9].

Regulatory - participate in physiological and pathological processes; Due to the polyanionic structure with sulfated glycosaminoglycans, they can change the conformation of various molecules, regulating the production and activity of cytokines, the maturation of leukocytes and other inflammatory cells. One of the most important regulatory properties is their ability to inhibit the action of cellular enzymes by binding to their active sites and altering their conformation, as well as contributing to the spatial distribution of cytokines and cellular enzymes in tissues [10].

Free glycosaminoglycans are synthesized when tissue is damaged and affect the earliest stages of the inflammatory process. By partially binding the decay products, the formed free oxygen radicals and, possibly, part of the mediators, they are also able to block antigenic determinants, preventing the development of immune and au-

to immune processes. All this inhibits the intensity of the subsequent cascade of inflammatory mediators and the number of macrophages in the lesion, thereby reducing the inflammatory response of the tissue to damage [11].

Thus, sulfated glycosaminoglycans are a natural component of any tissue, and depending on their qualitative and quantitative composition, they can regulate various physiological or pathological processes.

Odontogenic phlegmon occurs against the background of a persistent decrease in the body's immune resistance, which ensures a long and severe course of the disease. We have shown that the use of glycosaminoglycans in odontogenic phlegmons increases the level of immunoglobulins. This is consistent with several known data under the condition of other inflammatory processes [12-14].

The use of Don's drug in the complex treatment of odontogenic phlegmon creates optimal conditions for improving blood counts and immune response and reduces the risk of spreading purulent infection in patients with odontogenic phlegmon. A complex method of treatment with the use of Don's drug has a more pronounced therapeutic effect, due to the activation of regeneration processes in the soft tissues of the maxillofacial region.

CONCLUSION

The incidence of odontogenic phlegmon with the alignment of the indicators of the dynamic series tends to increase the incidence by an average of 3.1% annually, the mortality rate from this pathology varies from 3.3 to 2.1%. The microflora of the surgical wound in odontogenic phlegmons is associated with bacteria constantly present in the oral cavity: facultative aerobes and anaerobes, representing more than 80% of the residual flora.

The relationship between the level of IgG bacteria associated with the core region and the LBP protein in the blood, exudation, and epithelialization of the surgical wound, reflecting the dynamics of the inflammatory process and compensatory restructuring of the body due to bacterial infection, has been established.

The results of the study indicate changes in the metabolism of glycosaminoglycans in phlegmons of the maxillofacial region. In the main and control groups of patients, a significant increase in the concentration of glycosaminoglycan metabolites in the peripheral blood was found on average by two times compared with the norm.

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Conflict of interest - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability statement - The original contributions presented in the study are included in the article material, further inquiries can be directed to the corresponding authors.

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The authors agree to open the publication.

Availability of data and material - Available

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**ODONTOGEN FLEGMONALARNI DAVOLASH-
DA SULFATLANGAN GLYUKOZAMINOGLYKANLARNING O'RNI**

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АБСТРАКТ

Dolzarbliqi. Odontogen flegmonlarda asoratlarni oldini olishning hozirgi tizimi yallig'lanishga qarshi va detoksikasiya terapiyasini kuchaytirish heparin, proteolitik fermentlar, davolash kompleksida yiringli mahalliy davolash usullarini takomillashtirish orqali amalga oshiriladi.

Material va tadqiqot. Odontogen kelib chiqishi flegmona bo'lgan 457 nafar bemorda o'tkazildi. LBP oqsilining qon parametrlarining biokimyoviy parametrlari, bakteriyalarning asosiy mintaqasi va ularning endotoksinlariga antitelolar va antigenlar bo'yicha tadqiqotlar olib borildi.

Natijalar. Ma'lum bo'lishicha, odontogen flegmona organizmning immun qarshiligining doimiy pasayishi fonida sodir bo'ladi, bu esa kasallikning uzoq va og'ir kechishini ta'minlaydi. Shu bilan birga odontogen flegmonlarda glikozaminoglikanlarning qo'llanilishi immunoglobulinlar darajasini oshiradi. Odontogen flegmonni kompleks davolash uchun qon hisobini yaxshilash uchun maqbul shart-sharoitlar yaratiladi.

Xulosa. Odontogen flegmonlarda xirurgik yaraning mikroflorasi oraliqda doimo mavjud bo'lgan qoldiq floraning bakteriyalari bilan bog'liq. Asosiy mintaqaga boradigan Ig G bakteriyalari darajasi bilan qondagi LBP oqsili darajasi, jarrohlik yarasining eksudatsiyasi va epitelizatsiyasi, yallig'lanish jarayoni dinamikasini aks ettiruvchi va bakterial infeksiya tufayli organizmni kompensator qayta qurish o'rnatildi.

Tayanch iboralar: sulfatlangan glyukozaminoglikanlar, immunoglobulinlar, odontogen flegmon, qoldiq oraliq mikroflora, sepsis

**РОЛЬ И МЕСТО СУЛЬФАТИРОВАННЫХ
ГЛИКОЗАМИНОГЛИКАНОВ ПРИ ЛЕЧЕНИИ
ФЛЕГМОН, ОДОНТОГЕННОГО
ПРОИСХОЖДЕНИЯ**

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АБСТРАКТ

Актуальность. Сложившаяся к настоящему времени система профилактики осложнений при одонтогенных флегмонах осуществляется путем интенсификации противовоспалительной и дезинтоксикационной терапии, с включением в комплекс лечения ингибиторов гиалуронидазы - гепарина, протеолитических ферментов, усовершенствования способов местного лечения гнойных.

Материал и методы. Исследование проведено у 457 больных с флегмонами одонтогенного происхождения. Проводились исследования биохимических показателей крови белка LBP, антитела и антигены к core-региону бактерий и их эндотоксинов.

Результаты. Выявлено, что одонтогенные флегмоны протекают на фоне стойкого снижения иммунной резистентности организма, что обеспечивает длительное и тяжелое течение заболевания. При этом применение гликозаминогликанов при одонтогенных флегмонах увеличивает уровень иммуноглобулинов. Комплексное лечение одонтогенных флегмон создает оптимальные условия для улучшения показателей крови и иммунного ответа, снижает опасность распространения гнойной инфекции у больных с одонтогенными флегмонами.

Заключение. Микрофлора операционной раны при одонтогенных флегмонах ассоциируется с постоянно присутствующими в полости рта бактериями резидуальной флоры. Установлена взаимосвязь между уровнем связанного с core-регионом бактерий Ig G и белком LBP в крови, экссудацией и эпителизацией операционной раны, отражающая динамику воспалительного процесса и компенсаторную перестройку организма в связи с бактериальной инфекцией.

Ключевые слова: сульфатированные гликозаминогликаны, иммуноглобулины, одонтогенные флегмоны, резидуальная микрофлора полости рта, сепсис