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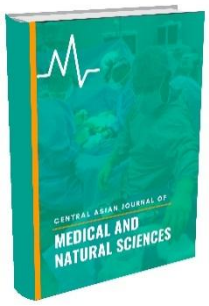

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Lymphotropic therapy for diseases of the Maxillofacial Region

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ABSTRACT: *Lymphotropic therapy is an effective and simple method of saturating the lymphatic system with medications. This review of the literature examines the pathogenetic and practical justification for the use of lymphotropic therapy in maxillofacial surgery.*

Key words: *lymph, lymphatic system, lymphotropic therapy, regional lymphotropic therapy.*

Introduction.

The search for and development of new methods of drug delivery to target organs is an urgent problem of modern medicine. One of these methods is lymphotropic therapy, which ensures the creation of sufficient and stable therapeutic concentrations of drugs in the lymphatic region of the lesion, and, consequently, in the target organ [1]. Its essence consists in the introduction of active substances into a zone containing a large number of lymphatic vessels and nodes, which allows you to achieve saturation only of a certain region of the lymphatic system that drains this area. In recent years, lymphotropic therapy has been of increasing interest in clinical practice and is widely used in the treatment of various diseases [2].

Main Part

The elements of the lymphatic system include: lymphatic capillaries, lymphatic vessels, lymph nodes, lymph trunks and lymph ducts [28].

Lymph is formed in the lymphatic capillaries by absorption from the intercellular fluid and moves only in one direction – from the "periphery" to the center. It consists of lymphoplasma, similar in composition to blood plasma, and lymphocytes, joining in the lymph nodes.

Lymphocapillaries have a blind origin in the intercellular space "like the fingers of a glove" and a lumen that exceeds the lumen of venous capillaries by 4-6 times, which allows large molecules, foreign bodies and microorganisms that do not correspond to the size of blood capillaries to penetrate

into them. Lymph vessels are formed when the lymphocapillaries merge; they have bivalve valves that provide centripetal movement of the lymph [28].

As is known, there are 3 relatively independent systems of lymph vessels: intra-organ lymph vessels, superficial extra-organ lymph vessels, and deep extra-organ vessels [28].

Lymphatic vessels are divided into regional – between the lymph nodes of individual anatomical areas, and collector, which are the central trunks and ducts. In relation to the lymph node, the lymphatic vessels are divided into bringing and carrying out. The lymphatic vessels that carry the lymph from the regional lymph nodes are collected in large lymph trunks, which eventually form two main lymphatic ducts – the thoracic and right [28]. According to Petrenko V. M. (2003) the adult lymphatic system consists of 600-800 lymph nodes, which account for approximately 1/100 of the body weight. There are two large groups of lymph nodes; somatic (lymph nodes of the extremities, head, neck) and visceral (lymph nodes of the thoracic and abdominal cavities). The cervical lymph nodes belong to the mixed group, as they receive lymph from the organs of movement and internal organs [31]. There are 50 groups of lymph nodes [32]. The size of the lymph nodes varies from 1.5×2.0 to 21×45 mm [33, 34]. The lymph nodes contain smooth muscle elements located in the capsule, trabeculae and in the area of the gate, which allows the lymph node to contract and decrease in size, move the lymph and actively rearrange itself due to the peculiarities of functioning in different regions and under different influences [35, 30].

In the lymph nodes there is a reticular stroma, characteristic of the hematopoietic organs. Reticular tissue, which is genetically and functionally related to the shaped elements of blood, significantly affects the processes of cell proliferation and differentiation, and the intensity of hematopoiesis [36, 37, 38]. According to Ishchenko I. Yu. (2017), the connective tissue forming the stroma of the lymph nodes (LN) is the microenvironment, the "stromal niche", which plays an important role in the development and activation of immune cells by regulating cell differentiation and proliferation. It consists of various cell types (fibroblasts, macrophages, etc.), extracellular matrix molecules and adhesion molecules that regulate the processes of cell differentiation and proliferation through the production of soluble factors and through interactions between cells. Such interactions are important, since defects within the stromal niche strongly inhibit the function of the lymph nodes. In LN, the following stromal cell subsets are distinguished: fibroblastic reticular cells (FRC) forming a reticular network (stained with podoplanin), endothelial cells of lymphatic vessels (on LYVE-1), endothelial cells of blood vessels (on CD31), macrophages. In turn, FRC represent a heterogeneous subset of stromal cells in the LN: these are FRC -paracortex cells, follicular dendritic cells (FDC) in the lymphoid nodules of the cortex, and contractile FRC -like pericytes. FRC form a reticular network (RN), which not only serves as a mechanical framework for the LN, but also creates a kind of handrail along which dendritic cells, T - and B-lymphocytes move into the LN. MS forms channels for transporting lymph from the subcapsular sinus to the LN parenchyma.

Jia L. et al. (2012) believe that FRC are involved in the formation of the walls of lymphatic labyrinths (LL) in LN. The researchers found that LL arise at the periphery of the deep cortex and at the edge of the follicle, expand towards the medulla and pass into the cerebral sinuses at the cortical-brain border. These structures are populated by densely packed small lymphocytes, do not contain dendritic cells and macrophages. The LL wall consists of three layers: the inner wall is a layer of flattened lymphatic endothelium (stained on LYVE-1); The outer wall is a layer of FRC and their cytoplasmic processes, and the third layer is an amorphous substance and collagen fibers sandwiched

between these two layers. Apparently, the LL are the zones of the most rapid transport of lymphocytes to the LN.

The movement of lymph depends on the following factors: consistency of fluid from plasma to interstitial space, and last – to the lymph vessels, the physiological activity of the organs and the contractility of the walls of lymph vessels and lymph nodes that contain smooth muscle cells; contractions of striated muscles, and all kinds of active and passive movements of the body and individual organs; a negative pressure in the large veins of the neck, which are for collectors of the thoracic lymphatic duct, fluctuations in intrathoracic pressure during breathing; pulsation of the aorta and arteries[28].

The anatomy and physiology of the lymphatic system, as well as its instant reaction to the pathological process of any localization and etiology, opens up broad prospects for the use of lymphotropic therapy in clinical practice.

The main metabolic processes are carried out at the level of the microcirculatory bed, which consists of arterioles with a diameter of 30-200 microns, blood capillaries with a diameter of 2-22 microns, venules with a diameter of 40-100 microns, and lymphatic capillaries with a diameter of 10-200 microns [6, 7]. In the body, the cells do not adhere directly to the blood capillaries, the exchange of substances between the cells and the blood occurs through the connective tissue, which is for them the "tissue of the internal environment" [8]. The connective tissue is filled with an interstitial substance of a colloidal nature, through which there is a movement of water, electrolytes, substances in a state of molecular dispersion, colloids and suspended particles from the bloodstream to the lymphatic system. Normally, interstitial pressure is close to zero or slightly positive [9]. The lymphatic system, absorbing water and dissolved crystalloids, colloidal solutions, protein substances, fats, complements the venous system in the process of tissue metabolism and drainage of the intercellular space. Since the diameter of the lymphatic capillaries exceeds the diameter of the blood capillaries, colloidal particles with a size of 20-80 microns become permeable to the lymphatic system [10]. The role of the endothelium of lymphatic vessels is not limited to the absorption of colloidal solutions and suspensions from tissues, it also participates in reactive changes in connective tissue [11]. Lymphotropic therapy is based on two main components – the principle of regionarity and the principle of increased interstitial pressure.

Petrenko V. M. (2017) points out that the lymphatic system is arranged as a chain of intervalvular segments with different wall structures, organizes a special path of outflow from the organs (collateral drainage to the veins) of tissue fluid in the form of lymph, and in its composition – antigens. The lymphoid system looks like a special prefix of the cardiovascular system: lymphoid couplings of varying complexity of structure surround the tissue channels and vessels as their attachments-biofilters that regulate the cellular and protein composition of the internal environment of the body. At the heart of the lymphoid system are closed in a circle of blood vessels, through which the (re)circulation of lymphocytes occurs. The lymphatic bed drains the lymphoid formations, and brings the lymph to some of them for purification. The lymphoid and lymphatic systems are united at the periphery in an immunoprotective complex: the lymphatic bed and the lymphoid tissue around the blood microvessels cooperate to ensure the genotypic homeostasis of the body, make up the lymphoid-lymphatic apparatus as part of the cardiovascular system.

The lymphatic system plays a leading role in the pathogenesis of purulent-inflammatory diseases (Yu. E. Vyrenkov 1990-2008, Yarema I. V. et al., 1992-2010), since the spread of bacteria and toxins occurs mainly in the lymphatic vessels and lymph nodes, where they are delayed in the

lymphatic system and the so-called toxic depot is formed. In this regard, the lymphotropic administration of antibiotics, immunomodulators, antioxidants, and anticoagulants is pathogenetically justified. Drug saturation of the lymphatic system allows you to create high therapeutic concentrations of antibiotics and other drugs on the pathways of bacterial factors, improve the rheology of the lymph, which makes it possible to unblock inflamed lymph nodes, reduce the likelihood of restriction and abscission of inflammatory infiltrates in the lymphatic system.

The idea of using lymphatic vessels for the administration of drugs, in particular antibiotics, was first expressed in the early 50s by B. V. Ognev. Conducting experimental studies, he discovered the leading role of the lymphatic system in the spread of tumor cells from the site of the primary focus, the migration of microorganisms with the development of lymphangoitis, lymphadenitis and sepsis in inflammation [1].

Experimental research and clinical observations allowed us to use mainly 2 methods of lymphogenic therapy: direct endolymphatic administration of drugs through a catheterized peripheral lymphatic vessel and indirect drug saturation of the lymphatic system. The latter method is minimally invasive, does not require direct surgical intervention, special surgical skills, and is available for doctors to perform in any direction [1]. The results of numerous studies in recent years confirming the presence of a lymphatic bed in the maxillofacial region, as well as the successful application of lymphatic therapy methods in other areas of surgery, contributed to the beginning of their application in dentistry [5].

The advantages of lymphotropic therapy are the following: [12]:

* create a high concentration of drugs in the drug (antitumor, antibiotics, immunomodulators, proteolysis inhibitors, analgesics, etc.), which, when administered normally, do not sufficiently penetrate the drug, are quickly inactivated or removed;
* increase the concentration and duration of action of the drug in the tissues of the pathological focus;
* reduce the toxic effect of the drug;
* increase the passage of the drug in the brain tissue;
* enhance the analgesic effect of the drug.

Based on the direction and nature of treatment, S. U. Dzhumabaev, E. S. Dzhumabaev, and I. R. Fayziev (1986) first developed a classification of lymphatic therapy, according to which it is divided into the following:

I. Kinds:
1. General lymphatic therapy
2. Regional lymphatic therapy
II. Methods of lymphatic therapy:
1. Direct
2. Indirect
III. Methods of drug administration
1. Direct lymphatic therapy-catheterization of
a) the lymphatic vessel
b) the lymph node
2. Indirect lymphatic therapy:
a) through a skin puncture
b) intraoperative puncture c

) percutaneous needle-free injection
d) electrophoresis
IV Mechanism of action:
1. Correction of microcirculation
2. Antibacterial therapy
3. Immunomodulatory therapy
4. Antitumor therapy
5. Detoxification therapy
6. Combined therapy
V. Regions of therapeutic effects of lymphatic therapy.

According to Gurbanov T. V. (2018) indirect saturation of the lymphatic system (lymphotropic therapy) is a promising method of drug infusion. Its essence consists in the introduction of active substances targeted in a zone containing a large number of lymphatic vessels and nodes, which allows you to achieve saturation only of a certain region of the lymphatic system that drains this area.

According to Yu. M. Levin et al. (2012), S. U. Dzhumabayeva, E. S. Dzhumabayeva (2017), endolymphatic therapy, both direct and indirect, is designed to create an optimal concentration of the drug in the lymphatic system "in its pure form", to ensure its maximum contact with pathogenic microorganisms in places of their retention and accumulation, mainly in the lymph nodes.

The study of Kantemirov O. I. (2001) shows that antibiotics are a unique group of pharmacological drugs, the effectiveness of which decreases over time. This aspect requires special attention both when evaluating their effectiveness and when developing evidence-based approaches aimed at prolonging the terms of their clinical use. In this regard, there was a need to find new ways of introducing drugs that would allow them to create long-lasting therapeutic concentrations in the body without increasing the dose. One such route of administration is the lymphatic system. The study of the distribution of drugs introduced into the lymph in different groups of lymph nodes showed that it is possible to achieve their greatest accumulation when administered taking into account the segmental structure of the lymphatic system.

Thanks to the research of the leading lymphologists of our country, S. U. Jumabaev, E. S. Jumabaev, the mechanisms of the influence of drugs introduced into the lymphatic vessels, the effects on the lymphatic system by physical, chemical, biological and other agents became clear.

Jumabaev E. S., Jumabaeva S. E., Saidhodzhaeva D. G. (2017) believe that regional lymphatic therapy, including regional stimulation of lymphatic drainage, antibiotic therapy and immunomodulation, lead to better clinical results in comparison with traditional methods of treatment, reduce the consumption of medicines by 1.5-2 times, reduce the number of injections by 2-3 times, reduce the duration of treatment by 10 - 25% and the cost of inpatient treatment by 25-40%.

As indicated by N. N. Nazarov, E. S. Dzhumabaev, Z. K. Gafurov, A. B. Makhmudov (2018), it is possible to prevent the occurrence of complications in purulent-inflammatory diseases by indirect regional lymphotropic therapy. The proposed indirect administration of antibiotics allows you to create large concentrations of the drug in the regional lymph nodes and keep them in the tissues for a long time.

Semak M. V., Bubnova N. A., Borisova R. P., Shatil M. A. (2017) believe that conducting a course of lymphotropic antibacterial therapy with a temporary pharmacological block with modern antibiotics in patients with chronic osteomyelitis contributes to a faster relief of inflammatory

phenomena. In addition, the relapse of the disease occurs in such patients much less often than in patients who received traditional treatment. According to Zhanalin B. S. et al (2014) introduction of regional lymphotropic therapy in acute odontogenic osteomyelitis of the mandible in children has led to optimization of the structure of direct costs, more efficient use of antibacterial drugs, reducing the number of days of hospital stay and duration of antibiotic therapy, improvement of cost/effectiveness.

Taking into account the anatomical structure of the salivary gland, the use of lymphotropic therapy in inflammatory and dystrophic diseases of the large salivary glands is shown. Thus, the parotid glands contain lymph nodes in their structure. The parotid and submandibular glands are enclosed in dense capsules, which, when the volume of the gland increases, create additional interstitial pressure. Thus, the conditions that promote lymphotropic therapy are met [13].

Today, several methods of drug delivery to the parotid gland have been developed. This is a method similar to novocaine blockade of the salivary glands, in which subcutaneous fat is infiltrated over the parotid salivary gland [13, 14], as well as a method of subcapsular administration of drugs [13, 15]. These methods have a number of disadvantages associated with some anatomical and morphological features of the structure of the parotid salivary glands. The lobes and lobules of the gland are surrounded by their own thin, but dense shells, between which there is a loose connective tissue, which makes it difficult for the drug to penetrate and spread in the areas of the acinar structures of the glands [13, 16]. The results were improved and the treatment of chronic inflammatory and reactive dystrophic diseases of the parotid salivary glands was shortened by indirect lymphotropic therapy using anatomical intragastric injection of the drug into the salivary gland, infiltrating its central, lower and posterior parts. Injections are administered in areas of the gland with a low fiber density that are free from the passage of the branches of the facial nerve [13].

To date, the clinical effectiveness of regional lymphotropic therapy in the complex treatment of patients with purulent-inflammatory complications of mandibular fractures has also been studied. Fractures of the lower jaw account for about 80% of the total number of injuries to the bones of the facial skeleton. Despite some success in the treatment of this category of patients, the percentage of infectious and inflammatory complications in mandibular fractures remains high and varies from 5.5 to 41% [17]. It is clinically proven that lymphotropic therapy significantly reduces the duration of treatment and reduces the course doses of antibiotics by 3 times, as well as the risk of allergic reactions. This technique is easy to use, does not require special equipment and can be recommended for wide practical use [18].

Prikhodnaya V. A. (2008) believes that the method of lymphotropic antibacterial therapy in the complex treatment of open fractures of the lower jaw can influence the etiotropic and pathogenetic mechanisms. Having an advantage over the traditional method of drug administration: it contributes to a longer maintenance of optimal concentrations of the antibiotic in the lymphatic system, blood, in the focus of inflammation, allowing you to significantly reduce endogenous intoxication of the body, normalize the drainage function of the lymphatic system of the maxillofacial region. The method of lymphotropic antibacterial therapy has no significant restrictions in use, is easily accessible, and allows you to reduce the consumption of medicines. Complex therapy of open mandibular fractures with the use of lymphotropic antibacterial therapy promotes rapid relief of inflammation, providing prevention of post-traumatic inflammatory complications.

Currently, it is also proposed to increase the effectiveness of the treatment of periapical abscess with the help of lymphotropic drug therapy using the drugs rocefin and tactivin. Inflammation of the

tissues surrounding the tooth is quite common, which is mainly due to microorganisms that enter the periodontium through the root canal, periodontal pocket, or hematogenous and lymphogenic pathways.

Determining the effectiveness of the results of conservative treatment of exacerbations of chronic periodontitis consists of an analysis of the timing of relief of acute inflammation and the duration of the rehabilitation period of the patient [19]

The evaluation of the obtained results suggests the advantage of using the regional lymphotropic method in the complex treatment of exacerbations of chronic periodontitis in comparison with standard intramuscular administration.

According to Savin E. K. (2011), as a result of clinical radiological studies, a high efficiency of treatment of exacerbations of chronic apical periodontitis, in which lymphotropic therapy was used, was established. Lymphotropic therapy activated the reparative processes in the bone tissue of apical periodontitis, reducing the time for reducing the size and eliminating the periapical pathological focus of destruction in the area of the root apex.

The analysis of the effect of lymphotropic therapy on the local manifestations of osteomyelitis of the lower jaw was performed. It is proved that it more effectively stops them than the known methods of postoperative treatment. This is manifested in an accelerated and more pronounced decrease in the circulatory manifestations of inflammation, such as edema, hyperemia, and the condition of the mucous membrane of the transitional fold of the oral cavity [20]. There was an increase in the antibacterial activity of the antibiotics used, which is indirectly evidenced by a decrease in the number of people with purulent fistula compartments and a decrease in the size of lymph nodes, including those surrounded by perifocal inflammation. In addition, lymphotropic therapy in the treatment of chronic forms of osteomyelitis of the lower jaw promotes bone regeneration, which is confirmed by orthopantomography data [21].

Observations of E. V. Turchina (2017) indicate that in patients with CHLO abscesses, after intramuscular administration of ampicillin in the blood after 4 hours, its concentration decreased by more than three times (1.00±0.44 mcg/ml). Moreover, some of the subjects had a zero ampicillin concentration (from 0 to 6.5 micrograms/ml). In this group of subjects, the half-elimination period ranged from 0.25 to 1.5 hours. Meanwhile, after lymphotropic administration of the antibiotic in the mastoid process of the temporal bone in 4 hours, its concentration reached 4.24 ±0.17 micrograms / ml, and the half-elimination period was from 20.6 to 43.5 hours. The creation of the necessary concentration of the antibiotic throughout the entire period of treatment had a positive effect on the clinical course of the disease.

Lymphotropic administration of an antibiotic 1 cm below the mastoid process of the temporal bone in acute purulent periostitis of the jaw in the molar region leads to earlier, compared with other methods of treatment, elimination of antigenic substances from the site of inflammation, since in the cytogram of leukocyte infiltrates in the deep parts of the gingival mucosa 2 days after the start of treatment, monocytes and macrophages are present in greater numbers, which means that by this time the purulent-necrotic processes are completed and more pronounced reparative [2].

Chronic diseases of the oral mucosa are a serious problem in dentistry. Such diseases include lichen planus, which is characterized by a torpid course, polymorphism of clinical manifestations, complexity of diagnosis and low effectiveness of treatment [22]. In this regard, various methods of complex pathogenetic therapy using a wide variety of methods and means of treatment are proposed.

Under the influence of lymphotropic therapy is not effective and ksantinola the nicotinate improves the clinical course of lichen planus of the mucous membrane of the oral cavity.

The positive dynamics is expressed in the reduction of unpleasant subjective sensations, the degree of hyperemia, the size of the lesion area by 2.5 times, the severity of the papular pattern and the epithelization of erosions. Thus, lymphotropic administration of derinate and xanthinol nicotinate allows to achieve improvement of the local and general condition of the patient, stabilization of immunological parameters, stable clinical results and longer remission [23].

It is advisable to use the lymphotropic method of drug administration to increase the effectiveness of therapeutic measures for oral candidiasis, since this disease causes changes not only in the epithelium of the oral mucosa, but also in the underlying tissues [24]. Regional lymphotropic administration of the antioxidant drug mexidol was used in the complex treatment of oral candidiasis. Mexidol initiates the detoxification function of the oral cavity, restores the antioxidant potential, normalizes the differentiation of epithelial cells and increases their resistance to the adhesion of fungi of the genus Candida. Lymphotropic administration of mexidol shortens the treatment time of patients and reduces the frequency of relapses of the disease [25].

Lymphotropic therapy has great prospects in modern medicine, including in the treatment of many serious infectious, chronic, including oncological diseases. There is an advantage of lymphological methods of drug administration in comparison with traditional ones: faster recovery and recovery of patients, a reduction in bed days, a decrease in the number of complications, and a reduction in the side effects of drugs [4, 26, 27]. The anatomy and physiology of the lymphatic system, as well as its instant reaction to the pathological process of any localization and etiology, opens up broad prospects for the use of lymphotropic therapy in clinical practice. However, many issues of this problem have not been precisely studied, which requires further experimental and clinical study [1].

Conclusion

Thus, with the lymphotropic administration of drugs, they enter directly into the organs and tissues from the lymph and blood due to the slow discharge of the drug from the lymph into the blood. Lymphotropic therapy is widely used in modern medicine in the treatment of infectious, chronic and oncological diseases. Since, the lymphatic system instantly reacts to the pathological process of any localization.

The authors note the positive aspects of the lymphotropic administration of drugs: faster recovery and recovery, a decrease in the number of complications, and a decrease in the side effects of drugs.

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