I.D. Ushnitsky, A.A. Chakhov, I.S. Pinelis, A.V. Yurkevich

CHARACTERISTICS OF LOCAL ANESTHESIA METHODS AND AGENTS IN CLINICAL DENTISTRY

DOI 10.25789/YMJ.2022.78.29

УДК 616.31-089.5

The review examines the current aspects of improving the effectiveness and safety of local anesthesia in dentistry, since specialized care is the most common among the population due to the high prevalence of dental caries, its complications and periodontal diseases. At the same time, a significant proportion of clinical cases require anesthesia, where adequate anesthesia is achieved taking into account the psychoemotional state, comorbidity, age of patients, types of anesthetics and trigeminal nerve ramus block techniques. Currently, this problem has not been completely solved. Therefore, there are the researches increasing the anesthetic effect and safety of local anesthesia.

Keywords: local anesthesia, anesthetics, trigeminal nerve, anesthesia complications, premedication, efficiency and safety of anesthesia.

Nowadays, the priority state task is public health, which includes the preservation, strengthening the health of citizens, as well as increasing the medical care provided and its accessibility, training of qualified personnel. At the same time the preservation of the functional state of the organs and tissues of the oral cavity, as well as the maxillofacial region is one of the necessary indicators of the life quality of the population [14, 43]. In this regard, improving the quality and accessibility of therapeutic and preventive care to the population is a key area of health care development [28, 33].

Currently, dentistry is characterized by historical stages in the development of local anesthesia. In the middle of the last century, anesthesia of the maxillofacial region was carried out with the use of reusable syringes of the "Record" type. Meanwhile, in the 80s of the 20th century, disposable plastic syringes were used in dentistry. At the end of the century, the cartridge syringe technology of local anesthetic injection appeared in practical dentistry, which provided a significant improvement in the quality of anesthesia, due to the convenience and sterility of the solution [6, 41].

Today, we observe the development of medical science, clinical dentistry, including local anesthesia. In this connection the search of effective means and methods of anesthesia aid is carried out for the improvement of treatment and preventive care [17, 43]. High-quality anesthesia during dental interventions helps to reduce the psychoemotional state of patients, which ultimately has a positive impact on the results of treatment [3].

The dental pain-free medical manipulations largely depend on quality anesthesia, which is important for the patient in clinical practice. At the same time, up to 80% of patients need local anesthesia for their indications, which determines the importance of adequate anesthesia. In view of the above, clinical dentistry researches aimed at improving and safety of local anesthesia [25, 34]. Currently, the term "Personalized approach" is most widely used in the practical work of doctors, which is based on the knowledge of individual anatomical-topographic features of oral organs and tissues, as well as maxillofacial region [1, 2, 8, 23]. At the same time, the main factor of inadequate anesthesia in the maxillofacial region is a violation of the technological features of its performance, which requires a personalized approach that takes into account individual anatomical-topographic features of the jaws [7]. Meanwhile, insufficient efficiency of local anesthesia can be associated with variability in topography of trigeminal nerve ramus, which in some cases can be accompanied by traumatic needle damage of nerves, vessels, as well as masticatory muscles. Despite the study of the local anesthesia problems, it has not been yet solved. In this connection, researches improving the quality of local anesthesia are of great importance [3, 8, 18, 25].

Modern dentistry has the necessary level of effective and safe medications to perform adequate anesthesia in the maxillofacial region [3, 31, 35]. In addition, methods controlling psycho-emotional stress before a dental appointment are used to increase the effectiveness of anesthesia [17, 20, 40].

Today, a significant problem in clinical dentistry is the adequate preparation of the patient for medical intervention, since almost all patients experience fear. At the same time, patients with various concomitant somatic diseases require special attention, for whom dental treatment, as a rule, causes negative emotions, which leads to stress, disorganization of the functional systems of the body, changes in mental state [16, 22]. This situation at the stages of doctor's appointment dictates the need to monitor the patient's behavior, his motor skills, emotional and autonomic reactions. At the same time, it is necessary to conduct a thorough questioning, which allows to find out the peculiarities of subjective experiences and the patient's attitude towards medical interventions [3, 10].

It should be noted that various questionnaires and psychometric scales are widely used to determine the psychoemotional status of patients.

At the same time, the professional experience of a specialist plays an important role in the diagnosis and prevention of anxiety at dental appointments, which can allow a timely response to the possible prevention of the occurrence of various genesis of dental phobia [24, 26]. It should be emphasized that in certain clinical situations premedication methods are successfully used for adequate anesthesia in dental interventions [20, 24]. Premedication has several forms, which are characterized as nonspecific and

USHNITSKY Innokentiy D. – M.D., Professor, Head of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Pediatric Dentistry of the Medical Institute of M.K. Ammosov North-Eastern Federal University RS (Yakutia), ORCID ID: 0000-0002-4044-3004; **CHAKHOV Aleksandr A.** – Candidate of Medical Sciences, Associate Professor of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Pediatric Dentistry of the Medical Institute of M.K. Ammosov North-Eastern Federal University, RS (Yakutia), ORCID ID: 0000-0002-6371-0734; **PINELIS Iosiph.S.** – MD, Professor, Department of Surgical Dentistry and Maxillofacial Surgery of the Federal State Budgetary Educational Institution of Higher Education "Chita State Medical Academy"; Zabaikalsky Krai, Chita; **YURKEVICH Aleksandr V.** – MD, Professor, Dean of the Faculty of Dentistry, Head of the Department of Orthopedic Dentistry of the Federal State Budgetary Educational Institution of Higher Education Far Eastern State Medical University MH RF Khabarovsk Krai, Khabarovsk

specific forms. Nonspecific premedication is based on the use of substances that have mainly peripheral M-cholinolytic effect (atropine, scopolamine, methacin), that have sleeping and sedative effects (barbituric acid derivatives), non-barbiturates (noxiron, nembutal), ataractic agents - tranquilizers, neuroleptics and antihistamines [24]. Specific premedication involves the use of drugs that eliminate disorders in the body caused by the underlying disease, or reduce their severity. In this case, the most common simple and convenient method of premedication in outpatient dental practice is the use of pills, powders and solutions per os [20].

Three main groups of drugs are used in clinical practice: benzodiazepines, sedative-hypnotics, and antihistamines, which have a calming effect [12]. Chlordiazepoxide, diazepam, relanium, oxazepam, nitrozepam, medazepam, phenazepam, lorazepam, midazolam, dermicum, etc. are often used among benzodiazepine drugs. Drug action of benzodiazepines group, depending on their dose, is accompanied by inhibition of emotional and vegetative brain centers, which are located in limbic system [24, 37].

It is known that patients with pathological processes of organs and tissues of the oral cavity, as well as of the maxillofacial region are treated with painful symptoms of both local and general nature at dental appointments. Pharmacological methods (remedies, drugs, etc.) are used to relieve pain of the nervous system at different receptor, conductive, nuclear levels. This fact confirms that today medicinal analgesia in dentistry is the most widespread [4, 37]. In addition, pharmacological substances have multifaceted effects of the nervous system at different levels. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in dental practice. The pharmacological activity of these drugs is due to their anti-inflammatory, analgesic, antipyretic, and antiaggregant effects, which together have a positive effect in increasing the effectiveness of local anesthesia [13, 30].

Thus, the prevention of patient distress is important at the dental clinic. For example, nowadays, perfect computerized technology is used for local anesthesia, which provides guaranteed and stable success of anesthesia, full control over the procedure and reduction of patient's fear of injection [17]. Thus, the intensive development of innovative technologies in dentistry allowed the company "Milestone Scientific" (USA) to develop an automated computerized syringe "Wand" in 1997. One of the positive properties of the device is the absence of fear in patients before the injection, as it is not perceived as an ordinary syringe [17]. In addition, electronic injection systems "Sleeper One" and "Quicksleeper" (Dental Hi Tec) are used for local anesthesia, as well as "Amsa" and "P-Asa" block anesthesia. There is also a method of injecting the anesthetic into the tissues using high pressure (needle-free method). For example, in 2001, the new-generation needleless injector of the Injex system sized like a ballpoint pen and weighing 75 grams was developed by Rösch AG Medizintechnik (Germany) [19].

It should be noted that psychological correction is effective in severe forms of physical discomfort at dental appointments for patients with an acute syndrome [10, 15]. In addition, for the prevention of emotional stress and pain at high surgical and anesthetic risk, unmitigated fear, and when an allergic history prevents the administration of local anesthetics, suggestive therapy can be used. One method of dealing with emotional tension at the dental appointment is reflexive action on acupuncture points. This method is used as a means of adaptive management of the body and as a way to prevent the development of stress reactions by triggering more appropriate adaptation reactions, which together with adequate anesthesia increases the quality of medical interventions and their effectiveness [9]. Percutaneous electroneurostimulation (PENS) is successfully used to suppress nociceptive impulses at the level of spinal neurons during stimulation of acupuncture points HE-GU or ZU-SAN-LI. At the same time, the use of the CHENS method in practice reduces the need for analgesics in the postoperative period in some patients. In addition, a pronounced clinical effect can be obtained by electrostimulation (electrodentoanalgesia) of the auricular reflexogenic zones by changing the frequency and duration of stimulating impulses when the analgesic effect occurs during electrostimulation. For this purpose the apparatus "Analgedenta" is successfully used [19, 29].

Local anesthesia with a wide range of drugs is widely used in practical dentistry, which is the most convenient and safe way to control pain in dental practice [21, 42]. Thus, local anesthetics with different compositions and components are used to anesthetize tissues of the maxillofacial region, the improvement of which is the main link in the development of local anesthesia in dentistry [5, 25, 32, 38]. Lidocaine, mepivacaine and articaine preparations are the most widespread in practice [4, 39].

For the last period, a wide range of local anesthetic preparations has been presented in the Russian dental market, which facilitates the choice of means for carrying out interventions [5, 21, 36]. At the same time, there are a number of drugs for anesthesia, both Russian and foreign-made, which are generics - drugs that do not differ by their international nonproprietary name from the original drug, but differ by trade name and manufacturing technology, as well as by the composition of auxiliary substances. Manufacturers take measures to ensure the safety of drugs, use preservatives and stabilizers of the active substance, such as EDTA - a complexing agent that captures the metal ions (Al, Pb), leached from the glass. The presence of EDTA in anesthetics can cause headache, nausea, vomiting, local tissue irritation, kidney damage, cardiac arrhythmia, and allergic reactions [11, 22]. Often generic manufacturers do not offer a full range of forms and dosages, sometimes have different indications for use than for the original drugs. This situation needs to improve the knowledge of dentists on the pharmacokinetics and pharmacodynamics of local anesthetics [5, 27].

Thus, there are a wide range of methods and agents of local anesthesia in dentistry. Despite this, the problems of efficiency and safety of anesthesia in the maxillofacial region have not been completely solved. This situation determines the necessity of further studies increasing the efficiency and safety of local anesthesia and their implementation into the practical activity of doctors of medical preventive institutions of dental profile.

References

1. Iordanishvili A.K., Muzykin M.I., Nagayko A.E., Verbitsky E.S. Anatomiya perednego otdela nizhnej chelyusti u vzroslogo cheloveka [Anatomy of the anterior mandible in an adult]. Kubanskij nauchnyj medicinskij vestnik [Kuban Scientific Medical Bulletin. 2017; 24(3):44-50 (In Russ.).] https://doi.org/10.25207/1608-6228-2017-24-3-44-50

2. Bakhmudov B.R., Vasiliev Y.L., Kuzin A.N. Anatomicheskoe obosnovanie klinicheskoj effektivnosti provodnikovoj anestezii vnutrikostnoj chasti podborodochnogo nerva [Anatomical substantiation of the clinical efficacy of conduction anesthesia of the intraosseous part of the chin nerve]. Stomatologiya [Dentistry. 2018; 97(2):41-43 (In Russ.).]. https://doi.org/10.25207/1608-6228-2017-24-3-44-50

3. Bahmudov B.R., Alieva Z.B., Bahmudov M.B. Rezul'taty mnogoletnego opyta ispol'zovaniya anestetika Ul'trakain D-S pri udalenii zubov u beremennyh zhenshchin [The results of many years of experience in the use of the anesthetic Ultracaine D-S for tooth extraction in pregnant women]. Novoe v stomatologii [New dentistry.

2019; 4:2-7 (In Russ.).] DOI: 10.37988/1811-153X_2019_1_92

4. Belfer M.L. Artikain kak mestnyj anestetik v stomatologii [Articaine as a local anesthetic in dentistry]. Stomatolog-praktik [Dentist-practitioner. 2017; 1:72-73 (In Russ.).]

5. Borisova E.G., Griga E.S., YAgmurov H.O. Klinicheskie i sudebno-medicinskie aspekty primeneniya anestetikov v ambulatornoj stomatologicheskoj praktike [Clinical and forensic aspects of the use of anesthetics in outpatient dental practice] Stomatolog-praktik [Dentist practitioner. 2017; 4:42-43 (In Russ.).]

6. Vasilyev YU.L., Rabinovich S.A. Sostoyanie voprosa i puti resheniya standartizacii karpul'noj tekhnologii (obzor literatury) [The state of the issue and ways to solve the standardization of carpool technology (literature review)]. Anesteziologiya i reanimatologiya [Anesthesiology and resuscitation. 2018; 63(2):139-141 (In Russ.).]

7. Volkov S.I., Lebedev S.N., Lebedeva YU.V. Topografo-anatomicheskoe i klinicheskoe obosnovanie provedeniya mandibulyarnoj anestezii [Topographic-anatomical and clinical justification of mandibular surgery. Morphology. 2018; 153(3):61-64 (In Russ.).]

8. Volkov S.I., Lebedev S.N., Lebedeva YU.V. Sposob provedeniya mandibulyarnoj anestezii na osnovanii topografoanatomicheskih orientirov [Method of mandibular anesthesia based on topographic and anatomical landmarks]. Stomatologiya [Dentistry. 2019; 3:94-96 (In Russ.).] https://doi.org/10.17116/stomat20199803194

9. Grishanin G.G. Stress v stomatologii [Stress in dentistry. Harkov : Karavella, 1998:168 (In Russ.).]

10. Mitin N.E., Rodina T.S., Guskov A.V., Yudin A.V. Issledovanie psihoemocional'nogo sostoyaniya pacientov na stomatologicheskom prieme [Investigation of the psychoemotional state of patients at a dental appointment]. Klinicheskaya stomatologiya [Clinical dentistry. 2018; 4(88):80-82 (In Russ.).]

11. Anisimova E.N., Ermolyev S.N., Pershina L.V. Letunova N.Yu., Orekhova I.V. Issledovanie effektivnosti i bezopasnosti ispol'zovaniya 4% rastvora artikaina s razlichnym soderzhaniem epinefrina [Investigation of the effectiveness and safety of using 4% articaine solution with different epinephrine content]. Institut stomatologii [Institute of dentistry. 2017; 1(74):38-40 (In Russ.).]

12. Ichinohe T. Harakteristika i vybor sedativnyh sredstv i klinicheskih strategij vnutrivennoj umerennoj sedacii pri lechenii zubov [Characteristics and selection of sedatives and clinical strategies for intravenous moderate sedation in dental treatment] Klinicheskaya stomatologiya [Clinical dentistry. 2021; 97(1):75-79 (In Russ.).]

13. Vetkova K.V., Elohina E.V., Lomiashvili L.M., Chekina A.V., Eorev S.M. Kupirovanie boli posle endodonticheskogo lecheniya [Relief of pain after endodontic treatment]. Endodontiya Today [Endodontics Today. 2020; 18(4):10-13 (In Russ.).] DOI: 10.36377/1683-2981-2020-18-4-10-13

14. Lazarev V.V., Haliullin D.M. Anesteziya i ksenon v detskoj stomatologii [Anesthesia and xenon in pediatric dentistry]. Vestnik anesteziologii i reanimatologii [Bulletin of anesthesiology and intensive care. 2019; 4:31-35 (in Russ.).] https://doi.org/10.21292/2078-5658-2019-16-4-31-37

15. Mihalchenko D.V., Makedonova Yu.A., Adamovich E.I., Marymova E.B., Venskel E.V. Lazernaya dopplerovskaya floumetriya kak sposob diagnostiki psihofiziologicheskogo sostoyaniya pacienta na stomatologicheskom prieme [Laser Doppler flowmetry as a way to diagnose the psychophysiological condition of a patient at a dental appointment]. Klinicheskaya stomatologiya [Clinical dentistry. 2020; 95(3):66-71 (In Russ).]. DOI: 10.37988/1811-153X_2020_3_66

16. Rahmatullina N.M., Ahmedzyanova D.G., Sibgatullina N.A. Mesto ostryh reakcij lekarstvennoj giperchuvstvitel'nosti pri ispol'zovanii mestnyh anestetikov v usloviyah mnogoprofil'noj kliniki [The place of acute drug hypersensitivity reactions when using local anesthetics in a multidisciplinary clinic]. Vestnik sovremennoj klinicheskoj mediciny [Bulletin of contemporary clinical medicine. 2018; 11(5):115-118. (In Russ.).] DOI: 10.20969/VSKM.2018.11(5).115-118

17. Ovsepyan A.P. Anesteziya bez boli i straha. Kafedra [Anesthesia without pain and fear]. Stomatologicheskoe obrazovanie [Dentistry education. 2017; 59:10-12 (In Russ).].

18. Rabinovich S.A., Babich T.D., Zinovyev I.A., Zinovyeva A.A., Dashkova O.P., Vasilyev YU.L. Opyt ispol'zovaniya osteocentral'noj metodiki intraseptal'noj anestezii pri lechenii kariesa dentina i pul'pita postoyannyh molyarov na nizhnej chelyusti [Experience of using the osteocentral technique of intraceptal anesthesia in the treatment of dentine caries and pulpitis of permanent molars on the lower jaw]. Klinicheskaya stomatologiya [Clinical dentistry. 2020; 2(94):18-23 (In Russ.).] DOI: 10.37988/1811-153X_2020_2_18

19. Rabinovich S.A., Vasilyev Yu.L., Babich T.D., Zinovyev I.A. Parodontal'noe obezbolivanie. Sovremennye tekhnologii [Periodontal anesthesia. Modern technologies]. M.: GEOTAR-Media, 2019:96 (In Russ.).]

20. Zaitsev A.Yu., Svetlov V.A., Dubrovin K.V., Nazaryan D.N. Prakticheskie aspekty sedacii v stomatologii [Practical aspects of sedation in dentistry]. Stomatologiya [Dentristry]. 2019; 98(4):96-102 (In Russ.).] https://doi.org/10.17116/stomat20199804196

21. Rabinovich S.A., Zavodilenko L.A. Sistemnaya toksichnost' mestnyh anestetikov [Systemic toxicity of local anesthetics]. Stomatologiya [Dentistry]. 2017; 96(2):36-42 (In Russ.).] https://doi.org/10.17116/stomat201796236-42

22. Rabinovich S.A. Zavodilenko L.A. Somaticheskie oslozhneniya v usloviyah stomatologicheskogo kabineta (Diagnostika i neotlozhnaya/ekstrennaya pomoshch') [Somatic complications in a dental office (Diagnosis and emergency / emergency care). M.: Gelioprint, 2017:39 (In Russ.).]

23. Kabak S.L., Melnichenko Yu.M., Savrasova N.A., Zhuravleva N.V. Razdvoennyj kanal nizhnej chelyusti [Bifid mandibular canal]. Stomatologiya [Denistry. 2018; 97(1):63-66 (In Russ.).] https://doi.org/10.17116/stomat201897163-66

24. Bizyaev A.A., Konnov V.V., Maslennikov D.N., Arushanyan A.R., Konnov S.V. Rol' premedikacii i psihoterapevticheskoj podgotovki v profilaktike psihogennyh reakcij pacienta na stomatologicheskom ortopedicheskom prieme [The role of premedication and psychotherapeutic training in the prevention of psychogenic reactions of a patient at a dental orthopedic appointment]. Sovremennye problemy nauki i obrazovaniya [Contemporary issues of science and education. 2016; 3:107-110 (In Russ.).]

25. Kuzin AV, Shafransky AP, Izmaïlova ZM, Remizov GV. Stomatologicheskaya pomoshch' pacientam s riskom razvitiya pobochnyh reakcij na mestnye anestetiki [Dental care for patients at risk of adverse reaction to local anesthetics]. Stomatologiya [Denistry. 2018; 97(6):63-66 (In Russ.).] https://doi.org/10.17116/stomat20189706163

26. Grechko T.Yu., Koreckaya I.V., Uryadnikova V.A. Eremeeva P.S., Oganisyan G.T. Stomatofobiya u podrostkov: metody vyyavleniya i preduprezhdeniya [Stomatophobia in adolescents: methods of detection and prevention]. Prikladnye informacionnye aspekty mediciny [Applied information aspects of medicine. 2018; 21(2):28-32 (In Russ.).]

27. Turkina A.YU. Sostav i svojstva preparatov dlya mestnoj anestezii na osnove artikaina [The composition and properties of drugs for local anesthesia based on articaine]. Dental Tribune Russia. 2018; 1:5-6 (In Russ.).]

28. Hasyanov A.Sh., Vagner V.D., Smirnova L.E. Kachestvo zhizni pacientov, nuzhdayushchihsya v hirurgicheskom ortognaticheskom lechenii [The quality of life of patients in need of surgical orthodontic treatment]. Institut stomatologii [Institute of dentistry. 2017; 1:18-20 (In Russ.).]

29. Shikova E. Aktual'nost' primeneniya nejromyshechnoj koncepcii v ortodontii [The relevance of the application of the neuromuscular concept in orthodontics]. Dental Market. 2017; 3:39-44 (In Russ.).]

30. Blinova EV, Semeleva EV, Shilova AM, Vediaeva AP, Blinov DS, Skachilova SYa, Vasilyev YuL, Vasilkina OV, Samishina EA, Meilanova RD. Eksperimental'noe issledovanie po ocenke effektivnosti mestnoanesteziruyushchej aktivnosti novoj dimetilfenilacetamid-soderzhashchej farmacevticheskoj kompozicii pri hronicheskom periodontite [Experimental study of the effectiveness of local anesthetic activity of a new dimethylphenylacetamide-containing pharmaceutical composition in chronic periodontitis]. Stomatologiya [Denistry. 2020; 99(2):11-16 (In Russ.).] https://doi.org/10.17116/stomat20209902111

31. Allen G., Chan D., Gue S. Investigation and Diagnosis of an Immediate Allergy to Amide Local Anaesthetic in a Paediatric Dental Patient. Australian Dental J. 2017; 62(2):241-245.

32. Anesthetic efficiency of articaine versus lidocaine in the extraction of lower third molars: a meta-analysis and systematic review. Zhang A., Tang H., Liu S., Ma C., Ma S., Zhao H. J. Oral Maxillofac. Surg. 2019; 77:18-28. DOI: 10.1016/j.joms.2018.08.020

33. Bartold P.M. Personalized/Precision Dentistry - The Future of Dentistry? Australian Dental J. 2017; 62(3):257-259.

34. Benefits and harms associated with analgesic medications used in the management of acute dental pain: An overview of systematic reviews / Moore P.A., Ziegler K.M., Lipman R., Aminoshariae A. J. Am. Dent. Assoc. 2018; 149(4):256-265. DOI:10.1016/j.adaj.2018.02.012

35. Brignardello-Petersen R. Local anesthetic administered with a pressure syringe system probably results in less successful and insufficient anesthesia than an inferior alveolar nerve block in patients undergoing mandibular posterior tooth extractions. J. Am. Dent. Assoc. 2018: 149(2):147-149.

36. Comparison of onset anesthesia time and injection discomfort of 4% articaine and 2% mepivacaine during teeth extractions. Gazal G., Alharbi R., Fareed W. Omar E., Alolayan A.B., Al-Zoubi H., Alnazzawi A.A. Saudi J. Anaesth. 2017; 11(2):152-157. doi: 10.4103/1658-354X.203017.

37. Effect of premedication to provide analgesia as a supplement to inferior alveolar nerve block in patients with irreversible pulpitis. Lapidus D., Goldberg J., Edward H. Ram S., Clark G., Enciso R. J. Am. Dent. Assoc. 2016; 147(6):427–437. DOI:https://doi.org/10.1016/j.adaj.2016.01.006

38. Injectable local anaesthetic agents for dental anaesthesia. George St. G., Morgan A., Meechan J., Moles D.R., Needleman I., Ng Y.L., Petrie A. Cochrane Database Syst. Rev. 2018; 7(7):CD006487. doi: 10.1002/14651858.CD006487.pub2.

39. Stirrup P., Crean S. Does articaine, rather than lidocaine, increase the risk of nerve damage when administered for inferior alveolar nerve blocks in patients undergoing local anaesthesia for dental treatment? British Dental Journal. 2019; 226(3):213-223. DOI: 10.1038/sj.bdj.2019.98

40. Shehabi Z., Flood C., Matthew L. Midazolam use for dental conscious sedation: how safe are we? British Dental Journal. 2018; 224(2):98-104. DOI: 10.1038/sj.bdj.2017.1042

41. Trayner K., Nguyen M., Bagg J. Use of safety syringes for administration of local anaesthesia among a sample of UK primary care dental professionals. British Dental Journal. 2018; 225:957-961.

42. Vigneswaran T. Aravind R. Vijay A randomized study of 4% articaine versus 2% lignocaine for surgical removal of the third molar. Drug. Invent. Today. 2019; 12:632-635.

43. Wright F. Local anaesthesia in dentistry, second edition : Book Review. British Dental Journal. 2018; 225:7.

N.A. Khonina, A.V. Fedorova, E.A. Smetanenko, N.M. Pasman, E.R. Chernykh

IMMUNOMODULATORY PROPERTIES OF ANGIOGENIC FACTORS AND MYELOID SUPPRESSOR CELLS: A ROLE IN THE GESTATIONAL PROCESS

DOI 10.25789/YMJ.2022.78.30

УДК 612.017.1 611.018.1 618.3

The review presents data on the immunomodulatory role of angiogenic factors and myeloid suppressor cells. The mechanisms that play a key role in shaping the balance of proangiogenic and antiangiogenic factors, the role of endothelial growth factor (VEGF), placental growth factor (PlGF) and myeloid suppressor cells (MDSC, MS) in the development of gestational immunosuppression are shown. Data are presented on the molecular mechanisms of immunosuppression, the expression of check-point molecules that play a major role in the suppression of cellular immunity reactions. The role of tyrosine kinase receptors for proteins of the VEGF family - VEGF-1 (Flt-1), VEGFR-2 (KDR/Flk-1) in the regulation of immune responses has been characterized. Data are presented on the cross-regulatory interaction of angiogenic factors and myeloid suppressor cells and the immunomodulatory effect on cellular immunity responses. Disturbance of these mechanisms may be associated with the development of gestational complications, in particular preeclampsia. Based on the presented data, the possibility of evaluating VEGF and MS in pregnant women as prognostic biomarkers of preeclampsia is considered.

Keywords: vascular endothelial growth factor (VEGF), placental growth factor (PlGF), myeloid suppressor cells (MDSC), preeclampsia.

The process of formation of new vascular vessels plays an important role in many diseases and pathological conditions. the most intense neoangiogenesis occurs during embryonic development, pregnancy, and tissue repair [32].

Both activating and inhibiting angiogenic factors are involved in the regulation of angiogenesis [28]. Both during the tumor process and during pregnancy, a balance of proangiogenic and antiangiogenic factors is formed [9]. The formation of new organs is carried out due to two mechanisms - angiogenesis and vasculogenesis. Angiogenesis is the process of neovascularization from already inflammatory vessels, while vasculogenesis is the process of colon formation from cells - elevated angioblasts. During pregnancy, the processes of vasculogenesis and angiogenesis develop, including the key role of the growth of vascular endothelial inflammation (VEGF) [28].

Recent studies have expanded our understanding of the role of pro-angiogenic factors, in particular VEGF-A, in the regulation of immune responses. It is known that the cytotoxic activity of VEGF significantly increases the toxic activity of T cells, can increase the number of T cell regulators (Treg) and myeloid suppressor cells (MDSC), and also prevent the differentiation and activation of dendritic cells (DC) [10]. Basically, the VEGF family exerts its influence on T cell function through binding to type 2 receptors (VEGFR-2) [32], while the function of type 1 receptors (VEGFR-1) remains unclear. To identify a selective ligand for VEGFR-1 is placental growth factor (PlGF), also identified for a protein of the VEGF family, a study of the PlGF study to assess the role of VEGFR-1 signaling T-cells in the regulation of T-lymphocyte functions. At the same time, the revealed immunomodulatory properties make it possible to identify new manifestations of T-cell immunosuppression in conditions of neoangiogenesis [2].

Receptors for VEGF. Three types of tyrosine kinase receptors are known for the VEGF family - VEGF-1 (so-called Flt-1), VEGFR-2 (so-called KDR/Flk-1) and VEGFR-3 (Flt-4); and as a coreceptor of neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2) bundles [9]. Neuropilins exhibit an extracellular part, a transmembrane segment, and a short (about 40 amino acid residues) intracellular domain that require enzymatic activity [9]. Also, NRP-1 and NRP-2 form complexes that are included in the composition and form in a cooperative mode [28]. Neuropilins, acting as co-receptors, increased VEGF affinity for VEGFRs [34].

Thus, the VEGF family stimulates the cellular response of binding to receptors with tyrosine kinase activity on the cell surface, and the products are activated due to their transphosphorylation [28]. Each VEGF receptor has an extracellular portion consisting of 7 immunoglobulin-like regions; an intracellular portion containing a tyrosine kinase domain; and one transmembrane region. As a result of alternative splicing, receptors can be membrane-bound and free.

The VEGFR-2 receptor binds VEGF-A with high affinity and can also bind VEGF-C and VEGF-D [32]. It mediates the main properties of VEGF-A - acti-

KHONINA Natalia A. – M.D., leading researcher, laboratory of cellular immunotherapy, Institute of Fundamental and Clinical Immunology, professor of Institute of Medicine and Psychology, Novosibirsk State University, Novosibirsk, RF; **FEDOROVA Anastasia V.** - intern, Institute of Fundamental and Clinical Immunology, embryologist of Clinic Pasman, Novosibirsk, RF; **SMETANENKO Ekatarina A.** - post-graduate student, laboratory of cellular immunotherapy, Institute of Fundamental and Clinical Immunology, embryologist of Clinic Pasman, Novosibirsk, RF; **PASMAN Natalia M.** –M.D., head of Department of Obstetrics and Gynecology of Institute of Medicine and Psychology, Novosibirsk State University, RF; **CHERNYKH Elena R.** – M.D., professor, Corresponding Member of the Russian Academy of Sciences, head of laboratory of cellular immunotherapy, Institute of Fundamental and Clinical Immunology, Novosibirsk, RF