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Comparative Assessment of Vessel Reactivity in Medication-Related Osteonecrosis of the Jaw

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Introduction

Anti-osteoclastic-Associated Osteonecrosis of the Jaw (AAOJ) is a condition associated with the use of antiresorptive drugs, such as RANKL inhibitors (monoclonal antibody-denosumab), nitrogen-containing bisphosphonates (zoledronic acid), and the use of some narcotic phosphate-containing substances (desomorphine). It manifests as a persisting (more than 8 weeks) open wound surface of the jaw bone tissue after dental surgical intervention. Currently, AAOJ is widely discussed in the scientific and clinical community. Since the first description of the disease [1], clinicians and scientists have been focused on identifying its mechanisms of occurrence. The main theories of AAOJ development include: Immune regulation disorders and excessive inflammation [2], accelerated apoptosis of osteoblasts and osteocytes [3], secondary infection [4], microvascular damage [1,5].

There is evidence suggesting a significant influence of antiresorptive drugs on the occurrence of vascular disorders. For instance, the use of aminobisphosphonates leads to enhanced thrombus formation in vessels, active leukocyte migration, and expression of pro-inflammatory cytokines, along with a decrease in nitric oxide synthesis [6-8]. Therefore, assessing the vascular status through functional tests to evaluate endothelial function in patients taking antiresorptive drugs may reveal the relationship of vascular disorders at the systemic level.

There are invasive techniques performed through intra-arterial administration of various vasoactive drugs (acetylcholine, nitroglycerin, sodium nitroprusside, and others). However, the invasiveness of this procedure for additional examination, especially in elderly patients, prohibits its use [2]. Among non-invasive methods, the most widespread are the occlusion test with the application of a cuff on the arm (temporarily occluding the brachial artery) and the acetylcholine test, which either topically or *via* iontophoresis locally affects the superficial vessels of the mucous membrane or skin. Both variants of the functional test allow assessing endothelium-dependent vasodilation through the influence on M1 and M2 endothelial receptors (acetylcholine) or through the mechanism of flow-dependent vasodilation (occlusion test), increasing the formation of NO, PGI2, EDHF [9]. There are also other non-invasive methods for assessing vessel reactivity, including the cold test, which allows evaluating neurogenically mediated reflex vascular reaction [10].

The basis for conducting this study was the lack of data on the condition of the endothelium in patients taking antiresorptive drugs.

Research objective: To investigate the relationship between developed AAOJ and systemic endothelium-dependent vasodilation of vessels.

Materials and Methods

A prospective study of 33 patients hospitalized in the Department of Maxillofacial Surgery of the Pavlov First Saint Petersburg State Medical University, Ministry of Health of the Russian Federation, was conducted. Patients were divided into 2 groups: AAOJ group and Control group.

The inclusion criteria for the study group (AAOJ group, n=18) were as follows:

1) History of taking drugs from one antiresorptive drug class of one pharmacological group (nitrogen-containing aminobisphosphonates were taken by 88.89% (n=16) of individuals, RANKL inhibitors were taken by 6.25% (n=2);

2) History of diagnosis M87.1 osteonecrosis. Avascular bone necrosis, ICD-10 revision from 2014 (100% - n=18);

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3) History of surgical procedures such as tooth extraction, tooth-preserving surgery, implantation, or complaints of missing teeth from 8 weeks to 1 year (n=18);

4) Age of patients: Middle-aged (45-59 years, n=6 (35%)); elderly (60-74 years, n=10 (50%)); geriatric (>75 years, n=2 (15%)) according to WHO classification.

Exclusion criteria from the study:

Presence of severe blood diseases, patients undergoing supportive therapy;

Young age (18-44 years);

Use of drugs from other pharmacological groups; The control group (n=15 individuals-Control group) consisted of patients of middle, elderly, and geriatric age, 67 ± 16 years old, without a history of significant cardiovascular diseases, who had previously removed teeth from 8 weeks to 1 year, and whose medical history did not confirm the intake of antiresorptive drugs.

All participating patients provided written voluntary consent for the study (protocol approved by the Ethics Committee of the Pavlov First Saint Petersburg State Medical University). Microcirculation examination was performed on all patients using high-frequency ultrasound Dopplerography with functional tests: Occlusive (cuff) test with reactive hyperemia and acetylcholine test (application on intact gingiva) [11]. Patients were examined in a fasting state, and before the examination, they rested for 25 min to 30 min in a resting state. The examinations were carried out with patients lying on their backs.

Microcirculation study was conducted using high-frequency ultrasound Dopplerography with a linear sensor with a frequency of 25 MHz and a diameter of the working part of 1.5 mm on an ultrasound device ("Minimax-Doppler-K", St. Petersburg, Russia). The integral value of tissue perfusion of the gingiva (mucous membrane and deeper tissues) and superficial vessels in the area of the nail fold of the index finger of the right hand were determined in the form of linear (Vas-cm/s), volumetric (Qas-ml/min) velocities, and the Pulse Resistant Index (RI-arbitrary units), where RI= (systolic Vas-diastolic Vas)/systolic Vas.

To assess the reactivity of vessels in the microcirculatory bed of intact oral mucosa, acetylcholine-induced endothelium-dependent vasodilation was evaluated. The sensor was positioned in the vestibular surface area of the mucous membrane below the mucogingival line of attached gingiva (upper border), in the underlying tissues devoid of hard tooth tissues-the area between the bi- and tri-furcation of the roots or between teeth (approximate borders), without reaching the transition fold (lower border) [12]. Acetylcholine (ACH) 0.0223 mg of 3% solution (HiMedia Laboratories GmbH, Germany) was applied to the area with cotton swabs, with exposure for one minute. To standardize the volume of drug application, sterile cotton swabs were cut into equal parts sized 10 mm × 10 mm, and then the ACH solution was applied using "Lenpipet" dispensers with a sterile tip (0.1 ml ± 0.0002 ml).

The reactive hyperemia test (occlusive test) has proven itself in clinical diagnosis due to its association with vasodilation-induced nitric oxide synthesis. Before conducting the test, indicators of superficial vessel reactivity in the area of the nail fold of the left index finger were measured [7,12-14]. After measuring tissue perfusion indicators in the specified area, a cuff of a sphygmomanometer was applied to the shoulder, and pressure was pumped until the blood flow spectrum disappeared from the monitor of the device (compression of the brachial artery)- 240 mmHg to 250 mmHg. Compression was maintained for 3 min, followed by rapid decompression of the vessel. Dopplergram recording was performed at 0.30th second, 1st and 2nd, 4th minute after decompression.

Statistical data processing was based on conducting non-parametric statistical analysis under conditions of small sample size within each group (n<30) using Microsoft Excel 2019 MSO (16.0.14026.20202), Paleontological Statistics (v.4.06), and IBM SPSS Statistics (v.26.0.0.1). Considering the non-normality of the Gaussian distribution of factors, quartiles Q1 (25th percentile), Q2 (50th percentile - median), Q3 (75th percentile) were calculated, and the data were presented as median (Q1; Q3) at p<0.05. Pearson correlation analyses were conducted between the occlusion test and the vasoactive acetylcholine test in the area of intact gingiva, and the cold test in the area of the nail fold with the gingiva. During the analysis, the statistical significance of the obtained differences was evaluated when the p-value (significance level) corresponding to the student's t-test was less than 0.05 (95% Confidence Interval), followed by the construction of graphs with polynomial trends, box-and-whisker plots, and pivot tables for data visualization.

Results and Discussion

Occlusion Test

After the cuff was removed from the area of the brachial artery in both groups, the peak reaction was observed in the first minute. However, in the AAOJ group, significantly lower values of blood flow increase were noted compared to the Control group (Figure 1 and Table 1). The maximum amplitude of the reaction in the AAOJ group decreased from 15.33% (Vas) to 17.11% (Qas) compared to the Control group (p<0.05).

Functional test with Acetylcholine (ACH): In both investigated groups, application of acetylcholine to the gingival mucosa resulted in local vasodilation of gingival vessels in the first 2 min, followed by a gradual decrease in blood flow levels and return to baseline values by the 5th min (Figure 2 and Table 2). However, in the AAOJ group, the blood flow level was significantly lower at the peak reaction to ACH- 18.9% (Vas) and 15.99% (Qas) compared to the Control group (p<0.05).

The Pearson correlation coefficient (r1) comparing the results of both tests yielded a positive value: r1=0.821 (p=0.021). These data suggest that the decrease in vascular reactivity in the gum area correlated with the decrease in vascular reactivity in the area of the nail fold, confirming the hypothesis of systemic effects of anti-resorptive drugs in the development of MRONJ. The positive value of the coefficient indicates a strong positive linear relationship between vascular reactivity factors in the gum area and the oral mucosa. The value approaching 1 may support the correlation between these reactions.

Conclusion

We obtained data on the correlation of vascular response impairment in the oral cavity and the hand in patients diagnosed with MRONJ. These results are consistent with the theory proposed by Marx et al. [1] and Peer et al. [5], which describe a possible mechanism for the development of MRONJ as avascular necrosis and

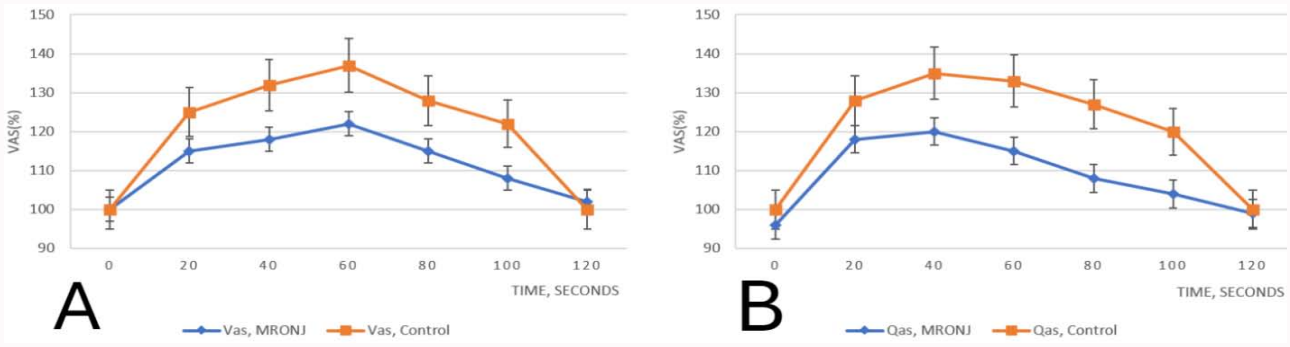

Figure 1: Skin vascular reactivity in the cuff test.
Note: The data are presented as the percentage ratio of linear blood flow velocity measured by high-frequency ultrasound Dopplerography (A - Vas, B - Qas) in % to the parameters of the initial blood flow of the Control group after cuff removal in the area of the brachial artery.

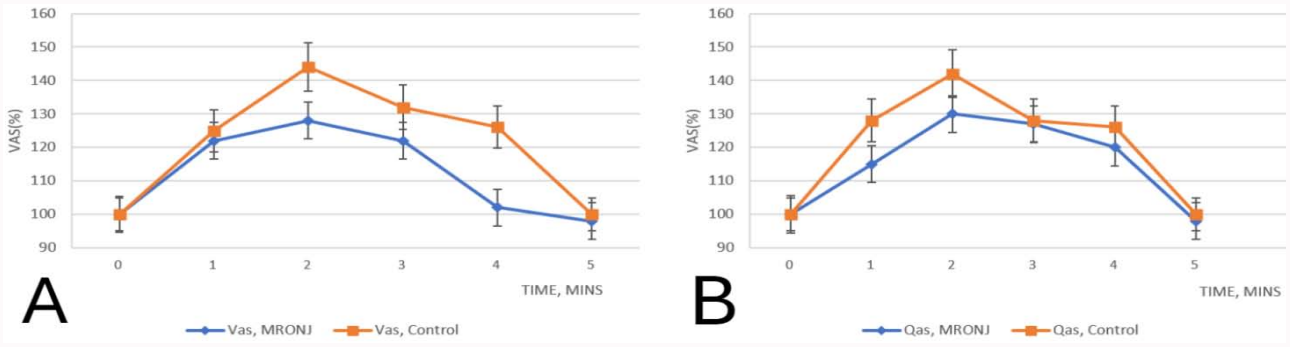

Figure 2: Reactivity of skin vessels in the area of intact gums in the test with acetylcholine.
Note: Data are presented as the percentage ratio of linear blood flow velocity measured by high-frequency ultrasound Dopplerography (A - Vas, B - Qas) in % to the parameters of the initial blood flow of the Control group after ACH application.

Table 1: Blood flow parameters. High Frequency Ultrasound Dopplerography (HFUD) during cuff test.

Parameters	Control	AAOJ	p - AAOJ and Control
Vas initial (cm/sec)	0.52 (0.47; 0.54)	0.31 (0.28; 0.42)	0.02*
Qas initial (ml/min)	0.27 (0.25; 0.31)	0.27 (0.18; 0.26)	0.11
A (Vas max) (cm/sec)	0.71 (0.65; 0.74)	0.65 (0.59; 0.68)	0.01*
A (Qas max) (ml/min)	0.361 (0.343; 0.423)	0.215 (0.162; 0.234)	0.01*
A (Vas max - %)	137.58 (134.97; 139.08)	122.25 (118.75; 124.91)	0.01*
A (Qas max - %)	137.21 (132.41; 142.43)	120.11 (118.92; 122.6)	0.02*
RI (cm/sec)	0.62 (0.58; 0.67)	0.7 (0.63; 0.72)	0.07

Note: Data are presented as Median (Me) (quartile (Q1; Q3)). Significant difference is accepted at p<0.05, *- Control

Table 2: Blood flow parameters. HFUD during a test with acetylcholine in the oral cavity (mucosa).

Parameters	Control	AAOJ	p-value (AAOJ *vs.* Control)
Vas initial (cm/s)	0.74 (0.67; 0.78)	0.53 (0.42; 0.54)	0.02*
Qas initial (ml/min)	0.03 (0.028; 0.032)	0.02 (0.018; 0.023)	0.04*
A (Vas max) (cm/s)	1.08 (0.98; 1.16)	0.68 (0.54; 0.69)	0.01*
A (Qas max) (ml/min)	0.044 (0.041; 0.047)	0.026 (0.023; 0.029)	0.01*
A (Vas max - %)	148.21 (141.11; 151.22)	129.31 (117.94; 124.91)	0.01*
A (Qas max - %)	146.04 (139.25; 150.17)	130.05 (128.91; 133.06)	0.02*
RI (cm/s)	0.52 (0.51; 0.57)	0.26 (0.25; 0.31)	0.04*

Note: Data are presented as the median (Me) (quartile (Q1; Q3)). Significance was accepted at p<0.05, *- Control

microvascular damage.

Previously, we have described models of MRONJ induced in laboratory animals. Vascular reactivity of rat jaw vessels to ACh was significantly reduced in groups receiving anti-resorptive drugs (zoledronic acid, denosumab) before and after tooth extraction [15-17]. It is worth noting that vascular reactivity decreased not only in the superficial vessels of the mucous membrane but also in

underlying tissues, including bone tissue [15]. The results obtained in the experiment are consistent with the findings of the current study. It can be assumed that invasive dental intervention in the form of tooth extraction may be the basis for microvascular disruption, which, in turn, leads to one of the mechanisms of osteonecrosis development in patients receiving anti-Thus, this study revealed a decrease in endothelium-dependent vasodilation of vessels in two anatomically independent areas-the hand and the oral mucosa. The reduction in microvessel response in the gums to acetylcholine application can be explained by the fact that anti-resorptive drugs, particularly aminobisphosphonates, reduce nitric oxide synthesis, enhance thrombosis, and may promote monocyte migration in the cascade of inflammatory reactions [13,14].

Further investigation into the etiology of MRONJ may involve a detailed assessment of the timing, dosages of drug administration, and the nature of dental traumas inflicted on the microvascular system.

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