



Pharmacogenetic Testing: Effectiveness of the Use of the Indirect Anticoagulant Warfarin

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Abstract

There are some particularities of managing patients who have been taking anticoagulants for a long time and who need dental treatment. People who regularly receive oral anticoagulant therapy are at increased risk of bleeding during and after surgery in the oral cavity. Clinicians must constantly weigh the risk of postoperative bleeding with continued therapy, as well as the risk of thromboembolic complications when the drug is discontinued. The purpose of this study is to study the effectiveness and safety of the indirect anticoagulant Warfarin in patients with diseases of the cardiovascular system undergoing dental treatment. In 2017-2018, based on the Moscow dental clinic No. 2 (Russian Federation), studies were conducted in which 350 patients participated, of which 5 were excluded from the sample. Moscow cardiological dispensary No. 1 patients who applied for dental care were involved. The first group consisted of 30 people with a diagnosis of severe diseases of the cardiovascular system (coronary heart disease, etc.), the second - 65 people with an average risk of thrombosis, the remaining 250 people of the 3rd group are patients with a low risk of thrombosis. Instead of Warfarin, the first two groups received low molecular weight heparin, the third - continued the course of Warfarin. In addition to general clinical methods (ECG, maintaining the INR level (international normalized ratio), etc.), examinations used a selection of local anesthetics and vasoconstrictors. Significant differences in the INR level before and after the operation between the three groups were not found - all of them were within normal limits. The maximum number of bleeding cases in patients from the 1st group is 2.1 times higher than in the 2nd group ($p \leq 0.01$), and 3.5 times higher than in the first ($p \leq 0.001$). Between the 2nd and 3rd group the difference was 1.6 times ($p \leq 0.05$). Regardless of the use or rejection of Warfarin, the maximum number of bleeding cases during dental procedures occurs in patients with severe cardiovascular diseases. Refusal from Warfarin is justified in case of severe diseases of the cardiovascular system, but in the case of a low level of thrombosis, therapy with Warfarin is possible. The risk of bleeding is evenly distributed within each group, regardless of the combined use of a vasoconstrictor and anesthetic or only anesthetic, while maintaining the difference between the groups. We have shown that the severity of diseases of the cardiovascular system can also influence the number of cases of bleeding during dental interventions. The complexity of the dental intervention determines the likelihood of bleeding. In the first group, for patients who had one tooth removed, bleeding was observed 5 times less compared with removal of the cyst ($p \leq 0.001$), and 4 times less - compared with operations on the pulp ($p \leq 0.001$). Pearson's correlation between the type of dental intervention and the number of bleeding in this group is the highest (0.91), 0.82 in the 2nd group, 0.56 in the 3rd. The type of dental intervention, regardless of the use of Warfarin, has a direct relationship with the number of bleeding. The maximum number of bleeding is observed in patients with severe pathologies of the cardiovascular system.

Keywords: Effectiveness and safety of dental treatment, Warfarin, INR, Anticoagulants, Anesthetics, vasoconstrictors, Injection pain relief, Pharmacogenetic testing.

Introduction

Warfarin has been used as an anticoagulant for a long time, since the middle of the last century [1]. From this moment until today, there remains an open discussion about the possibility of using Warfarin before invasive interventions. The drug has shown its high efficacy - when it is taken, the likelihood of arterial thromboembolism is reduced by 71%, which can be observed with atrial fibrillation [2].

Taking Warfarin can also almost completely (85%) reduce the risk of venous thrombosis [3]. And yet, given the certain risks that arise with prolonged use of oral coagulants related to vitamin K antagonists (which includes Warfarin), there is a certain problem with the management of patients who need to be operated on. On the one hand, there is a significant risk of bleeding that may occur after surgery if the warfarin therapy is continued.

On the other hand, in the event of withdrawal of Warfarin, the risk of thromboembolic complications increases very significantly [4]. Warfarin is one of the anticoagulant drugs with indirect effects [5]. The action of Warfarin is reduced to blocking the action in the liver of the synthesis of vitamin K-dependent factors that are responsible for blood coagulation processes (namely, II, VII, IX, X factors). The effect of the drug refers to a prolonged, due to a long half-life - about 36 hours [6].

A cardiologist prescribes a dose of Warfarin to each patient based on indicators such as the international normalized ratio (hereinafter referred to as INR). On average, the generally accepted norm of INR lies between 2.0 and 3.0. Such standardization makes it possible to significantly facilitate and adequately evaluate the effectiveness of therapy with anticoagulants [7]. Exceeding the critical INR values may indicate the development of serious bleeding [5].

There are peculiarities in anticoagulant therapy and when patients undergo dental procedures. The main approaches are either to reduce the dose of Warfarin in the 3-5 days preceding the dental procedure, or to completely eliminate the drug [8]. In some cases, it is possible to continue taking Warfarin if the risk of bleeding is minimal [9].

As a rule, the therapy used is associated with two factors- the type of disease in which regular administration of warfarin was prescribed, and the degree of invasiveness of the dental procedure.

Nevertheless, among practicing dentists, the most common opinion is that it is necessary to completely exclude the use of anticoagulant drugs (including Warfarin) in order to completely eliminate possible bleeding [10]. There is a high risk of hematoma when performing invasive procedures, such as local injection pain relief, and there is a risk of bleeding in the treatment of pulpitis, tooth extraction, implantation and minor surgeries [7].

According to Chokesuwattanakul et al [6], the frequency of local bleeding during tooth extraction in patients not taking anticoagulants is about 1%. However, to date, there's an increasing number of patients who are visiting a dentist have problems with the cardiovascular system. The trend over the past decades is that there is "rejuvenation" and a shift in the frequency of occurrence of cardiovascular pathologies to an increasingly young age [11].

In most cases, patients with diseases of the cardiovascular system undergo anticoagulant oral therapy. The activities of an untrained dental implant specialist can lead to serious consequences for the patient, such as bleeding [12]. Over the past ten years, there has been an increase in the number of studies devoted to the advanced training of dentists who treat patients taking anticoagulant drugs [7, 13]. These studies were primarily carried out remotely.

Dentists were interviewed over the telephone, on average; the practice time of the doctor was in the range of 20-30 years, without differences in gender and age composition. The majority of dentists, as a rule, took note of the need for a consultation with a cardiologist (up to 85%). The remaining dentists did not take into account the advice of a cardiologist, adhering to the further administration of warfarin or replacing it with another drug - low molecular weight heparin [14]. The results of such work are reflected in the recommendations for dentists with

therapeutic and surgical profiles, when they manage patients undergoing anticoagulant therapy. Thus, a very important point is the preliminary collection of patient data. In addition to taking anticoagulants, other factors are taken into account: alcohol consumption, medication, the presence of hemorrhagic rashes, etc [15]. In the case of the use of some products that contain a high concentration of vitamin K, especially green vegetables, the effect of anticoagulant therapy can be significantly reduced. In this case, it is necessary to adhere to strict control over the level of INR [16].

One of the typical characteristics of patients undergoing anticoagulant therapy is poor oral hygiene. The consequence of this is the presence of periodontal tissue inflammation. Based on this, full oral hygiene and a professional examination are necessary at least 1 time in 3-4 months [17]. The question of changing the drug before the dental procedure remains, in particular, from Warfarin to low molecular weight heparin. It is during this period, according to some reports, that the maximum number of thromboembolism occurs [18].

But, if the INR value is within the normal range, there is no need to reduce the dose of Warfarin or cancel it [13]. Therefore, before the actual dental procedure, blood coagulation tests are performed. Indicators such as INR level, prothrombin time and partial thromboplastin time are tested. As for local anesthesia, there is a generally accepted opinion that there are no contraindications to the use of articaine or mepivacaine [19].

Articaine has been shown to have greater anesthetic efficacy if dental surgery takes more than 1 hour [16]. There is evidence of tachycardia attacks using vasoconstrictors [17]. However, if the anesthesia is delivered correctly and appropriate instruments are used (e.g., a syringe), the effect of using vasoconstrictors will be maximized [20].

Among modern methods, a special place is occupied by the method of genotyping [7]. This method allows us to identify carriers of the so-called "slow" allelic variants of CYP2C9, as well as VKORC1 genotypes. This examination seems necessary, since this genotype and "slow" alleles are detected in one third (32%) of patients undergoing Warfarin therapy.

In order to minimize the risk of complications (hemorrhagic bleeding), in such patients it is necessary initially, before invasive interventions, to reduce the intake of this drug. The genotyping method is currently available in many large cities, including in Russia [21]. Based on the level of sensitivity to Warfarin, patients can conditionally be divided into three groups [22].

The first group includes patients with a high level of sensitivity. Their INR values quickly come to the range necessary for therapy. On the other hand, patients of this group have high rates of hypocoagulation when taking Warfarin. On the other hand, with the withdrawal of the drug, the INR values decrease rather slowly. Every fifth patient belongs to this group, which makes up the majority of the group of patients with "slow" alleles.

The second group consists of patients whose sensitivity to Warfarin is within normal limits. This is the majority (up to 70%) of patients. Values of INR of the required level are reached at them more slowly in comparison with the first group - at 5-6 days. Finally, in the third group of patients, sensitivity to Warfarin is minimal. Their INR values do not change at different doses of Warfarin, but are quickly restored after its withdrawal. Most studies on dosage and the need for warfarin are related to cardiology and surgery [7].

For dentistry, such studies, primarily regarding the passage of dental procedures by cardiological patients, are not enough [13]. It is necessary to systematize the available approaches, to compare the effectiveness of prolonging or discontinuing the use of Warfarin during dental procedures in patients of different groups with diseases of the cardiovascular system. There is also the problem of failure of anesthetists during invasive interventions in pain relief, based on the fear of hemorrhagic bleeding in patients taking Warfarin. These factors determined the relevance of this work.

The purpose of this study is to study the effectiveness and safety of the indirect anticoagulant Warfarin in patients with diseases of the cardiovascular system undergoing dental treatment. The main objectives of this study included the development of practical recommendations

for anesthesia during dental interventions of different intensities.

Materials and Methods

Materials

The studies were conducted in 2017-2018 on the basis of dental clinic No. 2 of Moscow (Russian Federation). A total of 350 patients were examined who applied here after undergoing treatment at Cardio logical Dispensary No. 1 (Moscow). For each patient, a detailed diagnosis was made from cardiologists. If necessary, they were consulted with cardiologists. Patients took warfarin in different dosages, based on their diagnosis.

The first group included high-risk patients who had a history of atrial fibrillation, coronary heart disease (CHD), ischemic stroke, or pulmonary thromboembolism or had artificial heart valves. There are 35 patients in this group, of which 15 are men and 20 are women, the average age is 56.0 ± 7.5 years. These patients, in order to avoid death or complications, were canceled by warfarin, with the transition to low molecular weight heparin intravenously.

The dose of heparin was prescribed depending on body weight, two days before the proposed dental procedure, initially 80 IU/kg intravenously, then 18 IU/kg/h. 6 hours before surgery, heparin was discontinued. The resumption of administration continued 12 hours after the operation, or stopped altogether, with target INR values of 2.0. The second group consisted of patients with an average risk of thrombosis.

They also canceled Warfarin 3-5 days before surgery, with a switch to low molecular weight heparin, which was administered at the same concentration, but subcutaneously. Warfarin was prescribed on the day of the dental intervention, with the abolition of heparin after reaching the target INR value. This group included 65 patients, 35 women and 30 men; the average age of the group was 51.0 ± 9.0 years.

The third group, the largest in the number of patients (250 people, 129 men and 121 women, the average age of the group was 62.0 ± 10.0 years), consisted of patients with a low risk of thrombosis. For them, Warfarin administration was not canceled, but the dose was reduced until the INR 2.0-2.5 was

achieved, with close monitoring of the level. We found no significant differences in the age and gender composition of patients both within groups and between them. The INR level in all patients, according to the surgical management of the primary care dental patient of Warfarin [23] at the time of the dental intervention did not exceed the maximum value 4.0. During the study, we adhered to generally accepted ethical and moral standards, with each patient, if he agreed to participate in the study, we signed an anonymity and non-disclosure agreement.

Clinical Methods

Each patient underwent a preliminary analysis; upon examination, an assessment was made of the general status and dental status. The ECG was used to assess the state of the cardiovascular system. The processing of information also included the study of medical documentation, which drew attention to extracts from the medical history, and also took into account the conclusions of medical specialists (cardiologists, surgeons, therapists).

When preparing patients for anesthesia, their status was assessed according to recommendations developed by the American Society of Anesthesiologists (ASA). In this case, patients belonging to grades 3 and 4 were sent to a hospital for hospitalization. Such patients were present in group 1, and there were 5 of them (3 women and 2 men), so in the final version, group 1 consisted of 30 people, and the total number of patients was 345. The following types of dental procedures were performed: extraction of individual teeth, pulpitis therapy, with the observed increase in inflammation.

If necessary, stop the hole bleeding. For patients from group 1, especially with coronary heart disease, an ECG was prescribed, in case of doubt or complications; they consulted with a cardiologist and anesthetist. Correction of drug therapy was carried out, as well as control of anesthesia. All dental operations were done under local anesthesia. In patients of the first two groups, hemodynamics was monitored simultaneously with dental intervention using Nihon Kohden (Japan). In addition, measurements of heart rate and blood pressure (systolic, diastolic, average) were performed. This is due to the fact that in all patients from the first two groups and 51

people from the third group, arterial hypertension was observed. In total, there were 146 people with arterial hypertension.

Anesthesia Methods

For an adequate choice of anesthesia methods, the following factors were taken into account: a) the type of dental intervention; b) the severity of the disease of the cardiovascular system. Moreover, the choice of local anesthetics and vasoconstrictors was guided by the algorithm already known from other works [5]. So, for diseases of the cardiovascular system, it is not recommended to introduce doses exceeding 0.04 mg. In our cartridges, the concentration of adrenaline corresponded to a value of 1: 100000, so for the above dose of adrenaline it is necessary to use the contents of about two of these cartridges. For patients with a diagnosis of arterial hypertension and with other diseases of the cardiovascular

system, ultimately the benefit from the results of the operation using pain relief (1 cartridge, anesthetic combined with a vasoconstrictor) for all its time exceeds all possible risks. The use of more than two cartridges can be justified in some cases, but is usually not recommended. We propose the following procedure: if during the slow introduction of the contents of the first cartridge containing the anesthetic and vasoconstrictor, with preliminary aspiration, changes in cardiac activity are not recorded, two options are possible.

Firstly, you can enter the contents of the second cartridge with the same drugs, and secondly, you can limit yourself only to an anesthetic, without a vasoconstrictor (adrenaline). We used ultracain-D or mepivacaine (solution 3%). In the three most severe cases, during osteosynthesis, trigeminal nerve blockade was used, the scheme of which is shown in Fig. 1A-C.



Figure 1: Scheme of anesthesia and blockade of the trigeminal nerve. A - Insertion of a catheter on a needle; B - bringing the catheter to the oval hole; C - blockade through a catheter

Statistical Analysis

Processing the obtained data was carried out using the program Past v. 3.0. The normality of the distribution used the Lillifors test. Given the normal distribution of the sample, parametric analysis methods were used. The tables show the values of the arithmetic mean \pm the error of the mean. To determine the differences between the parameters, the

Fisher two-sample t-test was used. Pearson correlations between features were also calculated. The differences are significant at $p \leq 0.05$.

Results

We have not obtained significant differences between the INR values in patients of each group before and after dental procedures (Table 1).

Table 1: INR values in patients of three groups per day before surgery and one day after surgery

Group	INR values before surgery	INR values after surgery
1	2.1 \pm 0.15	2.2 \pm 0.11
2	2.2 \pm 0.18	2.3 \pm 0.16
3	2.3 \pm 0.13	2.4 \pm 0.19

There were no significant differences between the groups. The INR values did not go beyond those provided by international recommendations. Such results can be explained by careful monitoring of the INR level immediately before the procedure and

in the postoperative period. Significant results were obtained by us when comparing the number of bleeding observed in patients from different groups depending on the type of dental procedure (Table 2).

Table 2: Reported cases of bleeding, depending on the group and on the type of dental procedure, in% (100% - all patients in this group)

Group	Dental procedure	Bleeding
1	Single tooth extraction	4.54
	Extraction of 2-4 teeth	9.67
	Pulpitis therapy against the background of the inflammatory process	16.02
	Cyst autopsy	20.76
Group average		12.74
2	Single tooth extraction	2.01
	Extraction of 2-4 teeth	5.20
	Pulpitis therapy against the background of the inflammatory process	7.11
	Cyst autopsy	9.56
Group average		5.97
3	Single tooth extraction	1.55
	Extraction of 2-4 teeth	3.21
	Pulpitis therapy against the background of the inflammatory process	4.43
	Cyst autopsy	6.66
Group average		3.96

As expected, the maximum number of cases of bleeding between groups was recorded in patients from the 1st group. On average, it exceeded the similar indicators of the 2nd group by 2.1 times ($p \leq 0.01$), and the indicators of the 3rd group by 3.5 times ($p \leq 0.001$). Between the 2nd and 3rd group the difference is less - 1.6 times ($p \leq 0.05$). Thus, regardless of the use or refusal of Warfarin, the maximum number of bleeding cases during dental procedures occurs in patients from the 1st group who are diagnosed with the most severe cardiovascular diseases. From this we can conclude that the rejection of Warfarin is justified in case of severe diseases of the cardiovascular system, but in the case of patients from the 3rd group who

are diagnosed with a low level of thrombosis, its administration is justified. The complexity of the dental intervention also determines the likelihood of bleeding. So, in the first group, in patients who had one tooth removed, bleeding was observed 5 times less compared with removal of the cyst ($p \leq 0.001$), and 4 times less - compared with operations on the pulp ($p \leq 0.001$). For this group, the highest Pearson correlation values between the type of dental intervention and the number of bleeding (0.91) were obtained. In the remaining groups, similar patterns were observed, but with lower correlation values: 0.82 in the 2nd group, 0.56 in the 3rd. Thus, the type of dental intervention, regardless of the use of Warfarin, has a direct

relationship with the number of bleeding. The maximum number of bleeding is observed in patients with severe pathologies of the cardiovascular system. The use of local anesthetics, such as adrenaline, reduced the likelihood of bleeding due to the fact that the anesthetic remains at the injection site, its analgesic effect is manifested here and the anesthetic does not migrate to other parts of the body, where its toxic effect may occur. For a group of patients diagnosed with coronary

heart disease, from the 1st group, the injection included 2% lidocaine solution, or 4% articaine solution, in a ratio of 1: 200000 with adrenaline. On the other hand, the use of an anesthetic without a vasoconstrictor gave statistically indistinguishable results - the risk of bleeding in patients from group 3 who took Warfarin did not differ from that in patients who received anesthetic injections with a vasoconstrictor (Table 3).

Table 3: The risk of bleeding in patients who underwent analgesia with and without a vasoconstrictor, the group average, in% (100% - all patients in this group)

Group	Anesthetic + vasoconstrictor	Anesthetic
1	6.03	6.25
2	2.85	2.74
3	1.21	1.38

As can be seen from the data in Table. 3, the risk of bleeding is evenly distributed within each group, regardless of the combined use of a vasoconstrictor and anesthetic or only anesthetic. The difference in the number of bleeding between groups remains, with a maximum in the 1st group and a minimum in the 3rd

Based on the results obtained, we propose the following anesthesia scheme for patients taking indirect anticoagulants (Warfarin or low molecular weight heparin replacing it). Mandatory actions include a complete medical examination by a cardiologist before local anesthesia and dental procedures are performed.

For the normal course of anesthesia and subsequent dental procedures, it is necessary to eliminate the patient's nervous reactions (excitement, anxiety, etc.). Injection-related procedures must be carried out in the reclining position of the patient, not in a sitting position. An exception is made by patients from the 1st group for whom severe diseases of the cardiovascular system are diagnosed. Before the injection is made, it is necessary to carry out anesthesia at the injection site.

The duration of this procedure should be at least 1 minute. Anesthetic is administered in the minimum recommended amount. Before administering the anesthetic, it is necessary to make a selection based on the duration of action, depending on the type of dental procedure and the patient's diagnosis for diseases of the cardiovascular system.

Vasoconstrictors are excluded on the basis of severe diseases of the cardiovascular system. Immediately before injection, an aspiration test is required, which is carried out in two planes, at an angle of rotation of the needle at 45 degrees. The duration of administration of the anesthetic should be slow, at least 1 minute, if a dose of 1.7 ml is administered.

During anesthesia, a dental procedure and after it, constant monitoring of the patient is necessary to avoid possible negative consequences (bleeding, etc.), with mandatory accompaniment in the form of an ECG, measurement of pulse and heart rate. Co-administration of an anesthetic and a vasoconstrictor can reduce the patient's stress state and maintain adequate pain relief. The use of an anesthetic without a vasoconstrictor and the correct technique for injecting an injection needle into soft tissues reduces the risk of bleeding and hematoma, respectively, in patients taking anticoagulants.

Discussion

Most dental procedures performed daily are not invasive. These include - prosthetics, removal of plaque (stones), as well as filling and installation of bridges and crowns. Accordingly, these types of dental care do not need to determine the level of INR, with the cancellation or replacement of anticoagulants, including Warfarin. Invasive procedures that always require INR monitoring include the removal of one or more teeth, operations with a pulp of the tooth, cyst removal, implantation, removal of tartar from the gums, as well as periodontal treatment associated with surgical procedures [18].

In this case, the determination of the INR level is carried out, as a rule, 4 days before the start of the operation. In the case of blockade of the mandibular nerve, there is a likelihood of hematoma formation, therefore,

special care should be taken when INR values are higher than 3.0. Before monitoring the level of INR was introduced into medical practice, dentists had serious concerns about possible bleeding in patients during and after surgery. According to some reports, the likelihood of complications in patients not taking anticoagulants does not exceed 1%. However, most cases of bleeding occur in patients with INR levels above 4.0 [10].

In other studies, when patients did not stop taking Warfarin, but with an INR level above 4.0, patients were excluded from the study [19]. In our study, the INR threshold did not exceed critical values, both in the groups where warfarin was replaced with low molecular weight heparin and in the group of patients taking warfarin. The authors of the study [12] found that in the group taking Warfarin, the INR values significantly exceeded those in patients who stopped taking Warfarin by 1.5 times.

The difference in the frequency of bleeding was not significant, although in the group taking Warfarin, bleeding was recorded 1.8 times more often. Our data allowed us to establish that it is better to exclude Warfarin in patients with severe and moderate levels of cardiovascular disease. Another study [20] showed that the bleeding rate in patients taking Warfarin was 1.6 times higher compared to patients who stopped taking it 4 days before the dental procedure. Tooth extraction, as shown by another comprehensive study, regardless of the use of anticoagulants or refusal from it, has no significant differences in severity [24].

On the other hand, bleeding was recorded in 12% of patients from the anticoagulant group. The indicators of the INR level in patients from different groups also varied: from 1.74 in the group without anticoagulants to 3.8 in the group where coagulants were taken. Another discovery is the administration of tranexamic acid, along with the administration of anticoagulants (Warfarin and others).

In one study, the authors found statistically significant differences between the number of bleeding in patients in whom the surgical field was irrigated with tranexamic acid and who took anticoagulants compared with that in patients who took only anticoagulants - the number of bleeding in the 1st group was 8 times below [17].

As for Warfarin, there is a series of data on the danger of its cancellation or replacement with heparins, since there is a high risk of thromboembolism [25]. However, these data relate to the surgery of patients with severe diseases of the cardiovascular system. For dental interventions, in most cases, proceeding with much smaller consequences for the patient's health and a shorter rehabilitation period compared to complex surgical operations, such data are insufficient.

Nevertheless, it is known that as a result of abandonment of Warfarin and after dental operations of varying complexity, mortality can reach 1%, mainly as a result of cerebral and venous thromboembolism, myocardial infarction on the 5-19th day after stopping the drug [26]. In any case, before conducting dental operations, especially in people with problems of the cardiovascular system and prone to thromboembolism, a thorough medical history should be performed. We have shown that the severity of diseases of the cardiovascular system can also influence the number of cases of bleeding during dental interventions.

Conclusions

- The use of an anesthetic without a vasoconstrictor and the correct technique for injecting an injection needle into soft tissues reduces the risk of bleeding and hematoma, respectively, in patients taking anticoagulants.
- A thorough history and the addition of questions related to the use of anticoagulants in the "health profile" of the medical record will increase the effectiveness and safety of dental treatment for patients with concomitant pathology and avoid undesirable complications associated with blood clotting disorders.
- The complexity of the dental intervention determines the likelihood of bleeding. So, in the first group, in patients who had one tooth removed, bleeding was observed 5 times less compared with removal of the cyst ($p \leq 0.001$), and 4 times less - compared with operations on the pulp ($p \leq 0.001$). Pearson's correlation between the type of dental intervention and the number of bleeding in this group is the highest (0.91), 0.82 in the 2nd group, 0.56 in the 3rd.

The type of dental intervention, regardless of the use of Warfarin, has a direct relationship with the number of bleeding.

The maximum number of bleeding is observed in patients with severe pathologies of the cardiovascular system.

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