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MANAGEMENT OF ORAL SURGERIES IN PATIENTS ON ANTITHROMBOTIC THERAPY

METHODICAL GUIDELINES

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LIST OF ABBREVIATIONS

AMI – acute myocardial infarction

BP – blood pressure

DVT – deep vein thrombosis

HBP – high blood pressure

IEM – Institute of Emergency Medicine

INR – International Normalized Ratio

IU – international units

OAM – oral anticoagulant medication

OMF – oral and maxillofacial

PDB – postextractional dental bleeding

PE – pulmonary embolism

PTE – pulmonary thromboembolism

RCH – Republican Clinical Hospital

VTE – venous thromboembolism

WHO – World Health Organization

1. BACKGROUND

In recent years the indications for the administration of antithrombotic drugs have been extended [1]. Millions of patients undergo thrombolytic therapy for the prevention and treatment of degenerative and cardiovascular diseases, as well as prophylaxis of thromboembolic accidents etc. [1,2,3,4]. Thus, in the US alone 12,000 tons of salicylates are annually consumed [5]. At the same time, there is an increase in angio- and cardiosurgical assistance rendered to population (heart valve prostheses, coronary bypass, valvuloplasty etc.) [6]. In 1997, 64,000 valvular interventions were performed all over Europe, of which mechanical prostheses were used in 2/3 of the cases [7]. Currently approximately 700 cardiosurgeries are annually performed in the RCH, the Department of Cardiac Surgery in Chisinau [6] and about 150 heart interventions are annually performed in the International Hospital Medpark. It should be noted that mechanical valves are some foreign bodies to the organism, increasing the risk of thromboembolic and infectious complications, thus, requiring lifelong anticoagulation therapy and prophylactic antibiotic therapy [8,9]. Therefore, patients on antithrombotic therapy are at risk of both bleeding complications and thromboembolic events. Bleeding accidents are relatively common in this group of patients [10]. They are favored by the high risk of overdose linked to individual variations in pharmacokinetic behavior as well as interferences dictated by different conditions or associated drugs [10]. The danger of heavy bleeding is high, given the prolonged effect of anticoagulants after stopping treatment [10]. According to the literature data, the frequency of bleeding in patients on OAM varies between 5-10% [11]. The rate of severe bleeding ranges between 2.4 and 8.1%, while the rate of fatal bleeding varies between 0 and 4.8% [11]. On the other hand, thromboembolic disorders are a major complication of the surgical patient. The importance of this health issue is due to, on the one hand, an increased frequency, and on the other hand, difficulties in intravital diagnosis and high lethality [12]. The anatomo-clinical statistics show that massive embolism is the third cause of sudden death in the U.S.. Every year about 300,000 patients are hospitalized with deep vein thrombosis (DVT), producing about 50,000 deaths caused by pulmonary thromboembolism (PTE). In Europe the incidence of DVT reported in recent years reaches 160 cases per 100,000 inhabitants. Over 80,000 PTE occur annually in France, with at least 20,000 deaths [12].

Management of dental extractions in patients on antithrombotic medication is questionable [13,14]. To prevent bleeding, some authors recommend the patients to discontinue antiplatelet therapy and/or oral anticoagulants a few days before extractions [15,16], others recommend to compulsorily substitute antiplatelet therapy with heparin during treatment, until resuming taking oral anticoagulants [17,18]. Other researchers argue to perform tooth extractions in patients on antithrombotic medication without discontinuing these drugs [19, 20, 21, 22, 23,

24]. Therefore, the dilemma discussed amply in recent years in literature: *"Is it necessary to discontinue antithrombotic therapy in patients requiring dental extractions?"* - remains current and any accumulated experience helps develop an optimal therapeutic management of these patients. It should be noted that publications devoted to the problem of dental extractions in patients on antithrombotic therapy are often contradictory and a large number of questions have to be specified.

The conditions under which a tooth extraction is performed in these patients (inpatient or outpatient care) are not definitively clarified. There is no single opinion about the therapeutic approach in urgent cases in patients whose INR is outside of therapeutic range (over- or underdosing) without discontinuing oral anticoagulant, a common situation in patients who do not monitor their anticoagulant effect. The correlation between the frequency of bleedings and various INR values is not studied. It is not definitively determined the best method of ensuring local hemostasis in these patients, given that according to some sources [25], the incidence of postoperative bleeding that can not be controlled by local hemostatic measures in patients on OAM ranges between 0% and 3.5%.

Thus, having a definite practical significance, the assessment of optimal conditions for performing surgery on patients on antithrombotic therapy is a current task in oral surgery and it is insufficiently reflected in literature. This can account for the complications arising in these cases and the varied choice of medical tactics which is often groundless.

2. PHARMACOLOGICAL CHARACTERISTICS OF ANTITHROMBOTICS

Antithrombotics are substances that inhibit blood clotting and enhance the fibrinolytic system [26]. These preparations are administered to prevent and treat thromboembolic complications.

Depending on the mechanism of action, they can be divided into three groups:

1) Anticoagulants:

a) direct-acting anticoagulants: heparin preparations (heparin), low molecular weight heparin preparations (LMWH - dalteparin sodium, nadroparin calcium, enoxaparin, reviparin), sodium citrate, antithrombin III preparations, heparinoids (danaparoid, pentosan, sulodexide), hirudin and its analogues (bivaluridin);

b) indirect-acting anticoagulants: acenocoumarol, warfarin, phenprocoumon, phenindione etc.

2) Antiaggregants (antiplatelets): acetylsalicylic acid, sulfinpirazone, dipyridamole, ticlopidine.

3) Fibrinolytics (thrombolytics):

a) direct-acting fibrinolytics: fibrinolysin, trypsin, chymotrypsin;

b) indirect-acting fibrinolytics: streptokinase, urokinase, streptodecase, anistreplase, alteplase.

Therefore, antithrombotic medication includes several groups of drugs. Of them, the dentist more frequently deals with patients on oral anticoagulants (acenocoumarol, warfarin, etc.) and/or antiplatelet drugs (acetylsalicylic acid, etc.)

2.1. CHARACTERSITICS OF ORAL ANTICOAGULANTS

Indirect-acting anticoagulants are drugs which inhibit the activation of plasma coagulation factors. Their effect sets in slowly and is long lasting, being present only *in vivo* [26].

Pharmacodynamics

Having the same structure as vitamin K_1, oral anticoagulants take the place of vitamin K_1 in enzyme systems (inhibit vitamin K epoxide reductase necessary for the synthesis of some procoagulant proteins in the liver), being involved in the formation of coagulation factors (II, VII, IX, X), thus impairing the formation of vitamin K1 molecules and inactivating them. After the inhibition of epoxide reductase by OAM, the liver synthesizes and secretes partially carboxylated or undercarboxylated procoagulants that are inactive.

Inactivated factors (II, VII, IX, X) are primarily required for the venous thrombus formation, therefore OAM has great importance in the prevention and treatment of diseases related to red thrombus formation in the veins (white platelet thrombus forms in the arterial system).

Pharmacokinetics

OAM is absorbed rapidly from the gastrointestinal tract. 90-99% bind to serum albumins in the blood. They are metabolized in the liver. The metabolites are eliminated through the bile into the intestine, where they are reabsorbed and then eliminated through urine and partially with faeces. They penetrate the placental barrier as well as breast milk in small amounts.

Currently, some oral coumarinic or indandionic anticoagulants are used. They differ in the onset of action, active doses and duration of effect (Table 1). By the virtue of its favorable pharmacological features (it is less toxic and has an appropriate plasma $T_{1/2}$), warfarin has become in recent years the first-choice drug of long-term oral anticoagulant therapy in most European countries and the U.S. [11]. Acenocoumarol (thrombostop) is the only oral anticoagulant currently registered in Romania [27]. At the same time, from the full spectrum of antithrombotic agents, acetylsalicylic acid ranks first [2,11]. Our studies [28] reported that of 38 patients on antithrombotic medication, the majority (21 patients or 55.3%) of patients were on acenocoumarol therapy, followed by those on warfarin (9 patients or 23.7%), aspirin (5 patients or 13.1%) and phenindione (3 patients or 7.9%).

Table 1. Latent period, duration of effect, half-life and daily doses of oral anticoagulants

Name of OAM	Latent period	Duration of effect	$T^1/_2$	Daily doses	
				Initial dose	Maintenance dose
Acenocoumarol	24-36 hours	48-72 hours	8.5-24 hours	4 mg	1-2 mg
Ethyl biscoumacetate	18-24 hours	36-48 hours	2-3.5 hours	0.6-1.2 g	0.3-0.45 g
Warfarin	37-60 hours	5-7 days	37 hours	10-15 mg	2-15 mg
Phenprocoumon	48-72 hours	8-10 days	2.7-7 days	15-21 mg	0.5-4.5 mg
Diphenadione	36-72 hours	20 days	2-3 weeks	20 mg	2.5-5 mg

Factors that may influence the effect of OAM

I. Factors that increase the effect of OAM:

1. Endogenous factors: hyperthermia, hyperthyroidism, vitamin K deficiency, diarrhea, collagenosis, liver disease, malignant tumors, chronic heart failure.

2. Exogenous factors: antibiotics (aminoglycosides, penicillins, tetracyclines, cephalosporins, fluoroquinolones, macrolides), NSAIDs (aspirin, analgin, indomethacin, diclofenac, ibuprofen, paracetamol), anabolic steroids, heparin and heparinoids, metronidazole, omeprazole, pentoxifylline, oral antidiabetic drugs, streptokinase, urokinase, ticlopidine, thyroid hormones, tricyclic antidepressants, phenothiazines, quinidine, cimetidine, estrogens, allopurinol, amiodarone, influenza vaccine, lipid-lowering drugs.

II. Factors that reduce the effect of OAM:

1. Endogenous factors: congenital resistance, hyperlipidemia, hypothyroidism, edematous syndrome, malabsorbtion.

2. Exogenous factors: antacids, antihistamines, vitamins C, K1 and K2, barbiturates, haloperidol, griseofulvin, carbamazepine, oral contraceptives, rifampicin, cholestyramine, cyclosporine.

III. Factors with both effects: alcohol, diuretics, diphenidine, moricizine, ranitidine.

Indications for OAM:

OAM is indicated to prolongably reduce blood clotting, which allows to decrease the likelihood of thrombus development, and in the event of its development, to stop its further growth. Thus, OAM is indicated to prevent and treat venous thromboembolism in patients with valvular heart disease (to prevent and treat acute myocardial infarction in patients with prosthetic heart valves, e.g. prosthetic mitral and aortic valves, bioprosthetic heart valves as well as atrial fibrillation).

In our research [28] antithrombotic drugs were administered in: cardiosurgeries (prosthetic heart valves, implantation of artificial cardiac pacemaker) in 32 cases (84.2%),

ischemic heart disease in 4 cases (10.5%), history of thromboembolism in 1 case (2.6%) and (2.6%) thrombophlebitis of the lower limb in 1 patient (Figure 1).
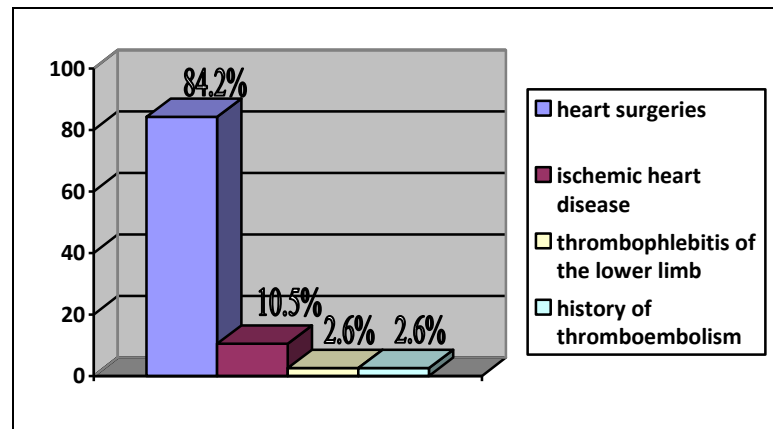
Fig.1. Causes of administration of antithrombotic medication in patients at risk of thromboembolism (%)

Contraindications to OAM:

➢ hemorrhagic syndromes
➢ blood clotting disorders (hypocoagulation disorders)
➢ hemorrhagic strokes
➢ specific allergy
➢ pericarditis
➢ severe hypertension
➢ active gastroduodenal ulcer
➢ neurological and ophthalmological surgeries
➢ severe kidney and liver dysfunctions
➢ pregnancy, lactation
➢ lack of possibility of regular blood clotting tests.

2.2. CHARACTERISTICS OF ANTIPLATELET DRUGS

Antiplatelet drugs (antiaggregants) are drugs that inhibit platelet aggregation and other processes responsible for platelet thrombus formation [26].

Classification of antiplatelet drugs

I. Inhibitors of platelet arachidonic acid metabolism:

1. Inhibitors of phospholipase - glucocorticoids (hydrocortisone, prednisolone), papaverine.

2. Cyclooxygenase inhibitors - NSAIDs (acetylsalicylic acid, indomethacin, ibuprofen, diclofenac sodium), sulfinpyrazone.

3. Selective inhibitors of thromboxane A synthase - indobufen, imidazoline derivatives levamisole, imidazole).

II. Drugs that increase cAMP (cyclic adenosine monophosphate) concentration and duration of action:

1. Adenylate cyclase activators - prostacyclin, epoprostenol, alprostadil, etc.

2. Inhibitors of phosphodiesterase and adenosine deaminase - dipyridamole, xanthine derivatives (pentoxifylline, aminophylline, xantinol nicotinate), vinpocetine etc.

III. Drugs that influence thromboxane A_2 receptors - dextran 40 and dextran 70.

IV. Drugs that block specific platelet receptors - ticlopidine, clopidogrel.

V. Drugs that stimulate prostacyclin synthesis - pyrazoline derivatives, coumarin, nicotinic acid, pentoxifylline.

VI. Inhibitors of the platelet components release - piracetam.

VII. Other drugs with antiaggregation mechanisms:

1. Calcium channel blockers - verapamil, nifedipine, diltiazem, cinnarizine.

2. Antihistamines and antiserotoninics - lidoflazine, cytisine.

3. Tricyclic antidepressants - amitriptyline, imipramine.

4. Antibiotics of penicillin family.

5. Sodium nitroprusside.

Pharmacodynamics

Acetylsalicylic acid (aspirin), most commonly administered antiplatelet drug (antiaggregant), blocks thromboxane A_2 synthesis due to irreversible inactivation by acetylation of cyclooxygenase. It inhibits platelet aggregation caused by collagen, ADP (adenosine diphosphate), epinephrine, and serotonin. Acetylsalicylic acid inhibits both thromboxane formation (favorable therapeutic effect) and prostacyclin formation (adverse effect). In small doses, prostacyclin in vascular endothelial cells can recover as these cells contain the required set of organelles for resynthesis of cyclooxygenase. Platelets are anucleate and do not have any set of organelles for protein synthesis, thus being not capable of restoring either cyclooxygenase or thromboxane. High doses of acetylsalicylic acid considerably suppress the synthesis of endothelial prostacyclin, it being quite disadvantageous. This accounts for a high efficacy of low-dose acetylsalicylic acid as an antiplatelet drug.

It is to be noted that patients have different sensitivity to aspirin. According to the patients` sensitivity to aspirin, there are the following groups of patients: responsive (0.5 g of aspirin contributes to reduction of aggregation by 40-50%); hyperresponsive (aspirin inhibits aggregation completely or up to 80-90%) and non-responsive (lack of antiplatelet effect).

Pharmacokinetics

When administered orally, acetylsalicylic acid is extensively hydrolyzed in the gastrointestinal mucosa, blood and liver. The unchanged and active form (capable of acetylation) reaches small concentrations in blood, sufficient to be highly efficient. About 50% of the drug binds to proteins, in particular albumin. The half-life is 15-30 minutes. During the first passage of acetylsalicylic acid through the liver, salicylic acid is formed which is less active. Acetylsalicylic acid is partially eliminated with urine in pure form and conjugated with glycine and glucuronic acid.

Indications for acetylsalicylic acid therapy:

1. Prevention and treatment of cerebral circulation disorders.

2. Prevention of thrombosis and embolism in:

➢ arterial thrombosis, hypertension, atherosclerosis, diabetes mellitus, excessive smoking, hypodynamia;

➢ thrombophlebitis, varices, postoperative period, prolonged immobilization;

➢ patients after heart valve or blood vessel prosthesis intervention.

3. Unstable angina, acute myocardial infarction, secondary prevention of myocardial infarction.

It should be noted that if thrombus formation in the venous system is equally related to participation of platelets and plasma coagulation factors, then platelets have the basic role in thrombus formation in the arteries. Therefore, antiplatelet agents are preferred for use in the prophylaxis and treatment of arterial thrombosis, while anticoagulants are used for the prophylaxis and treatment of venous thrombosis.

Contraindications to antiplatelet drugs:

➢ bleeding diathesis

➢ gastric and duodenal ulcers

➢ acute and subacute hemorrhagic stroke

➢ hypocoagulation disorders

➢ specific allergy

➢ severe renal or hepatic dysfunction.

3. INR VALUE IN IDENTIFICATION OF BLEEDING AND THROMBOEMBOLIC RISK

A frequent monitoring of anticoagulation therapy is mandatory to constantly know the necessary individual drug dose to achieve the therapeutic effect, the potential influence on coagulation of other associated factors and the appreciable risk of bleeding when anticoagulation exceeds the therapeutic limits [11]. To this end, the anticoagulant effect of coumarins is assessed

through monitoring of the prothrombin time, represented by the *International Normalized Ratio* (INR) [29]. The INR was introduced in 1983 by the World Health Organization Committee on Biological Standards [30]. The INR is calculated by the ratio of the prothrombin time (PT) of the patient and the PT of the normal control plasma, raised to the power of the *International Sensitivity Index* (ISI) [29]. Data on ISI are attached to the description of all sets to determine the PT [29]. A patient with normal coagulation system has an INR of 1.0 or close to 1.0 (between 0.7 and 1.3) [29]. It is increased in patients with liver diseases, vitamin K deficiency, disseminated intravascular coagulation, deficiencies of factors VII, X, V, as well as patients on oral anticoagulants [29].

Ideally, the INR should be assessed within 24 hours prior to any oral surgery [31,32], but in patients with a stable INR its assessment is acceptable within 72 hours before the surgery.

The therapeutic level of anticoagulation depends on the indication for which it is administered and the INR values range between 2.0 and 4.0 [29]. The indications for OAM therapy, the recommended INR values and the duration of treatment are listed in the following table (Table 2).

Table 2. Indications for oral anticoagulant therapy, recommended INR values
and duration of treatment

Indication	INR	Duration
1. VTE prophylaxis: - neoplasia - gynecological surgery - orthopedic surgery	2-3	≥ 6 weeks
2. VTE treatment: a. proximal DVT b. PE, idiopathic deep venous thrombosis c. idiopathic recurrent DVT - recurrent PE - genetic disorders of coagulation (deficiency of proteins C and S; factor V Leiden) - antiphospholipid antibodies syndrome - DVT associated neoplasia d. combination of factors of 2c category	2-3 2-3 2-3 3-4,5	≥ 3 months ≥ 6 months continuously continuously
3. Heart and valvular diseases: a. prevention of AMI in coronary patients b. acute myocardial infarction c. heart valve prostheses - mitral - aortic - bioprosthetic heart valves d. atrial fibrillation	1,5 2-3 3-4,5 2,5-3 2-3 2-3	continuously continuously continuously 6 months continuously continuously

The higher the INR, the more pronounced hypercoagulation is, and therefore bleeding complications are more frequent and dangerous, and vice versa, a fall in the INR values below the therapeutic range will increase the risk of thromboembolic events [29].

The frequency of the INR measurement has to be:

➢ daily after the treatment initiation until the desired INR value is obtained at least 2 days consecutively;

➢ weekly during the first month of treatment;

➢ monthly after the treatment initiation.

It should be noted that by virtue of its pharmacological properties, acetylsalicylic acid, unlike indirect anticoagulants (acenocoumarol, warfarin), does not require laboratory monitoring of coagulation [11]. Despite this, patients on antiplatelet therapy do not require monitoring of the INR and its assessment.

Although multiple thromboprophylaxis guidelines and recommendations are published, the way the recommendations are applied in medical practice is a problem only partially solved. The studies focused on this issue suggest that the pharmacological thromboprophylaxis is underused in 30-50% of patients with thromboembolic risk [27,33]. Thus, the patients are exposed to both an increased bleeding and thromboembolic risk. In our research [28], of 33 patients on OAM, 11 (33.3%) patients were not monitored for the effect of oral anticoagulants. In this context, 6 patients were not assessed the INR values for 2 or 3 months, 3 patients between 4 and 6 months and 2 patients > 12 months.

Discontinuation of anticoagulants is often groundless in clinical practice. In 1995 M. Wahl and J. Howell conducted a survey and found that the majority of physicians (73%) recommended discontinuing warfarin therapy in some dental procedures, including tooth extractions [34]. However, the discontinuation of these drugs puts the patient at a serious risk of thromboembolic complications with a significant potential of morbidity [35,36,37,38].

Thus, M. Wahl (1998) [39] studied the impact of discontinuing anticoagulant therapy in dentistry, analyzing 542 documented cases, involving 493 patients in whom the anticoagulant therapy was discontinued before varied dental procedures. He reported that 4 patients had lethal thromboembolic events (cerebral thrombosis (2), myocardial infarction (1), unidentified embolism (1)); one patient experienced two non-lethal thromboembolic complications (cerebral embolism and brachial artery embolism). The incidence of severe thromboembolic complications was 1%. This research was much criticized because the anticoagulant was withdrawn for longer than usually (from 5 to 19 days) or the period of anticoagulant withdrawal was unknown [40]. However, there are a lot of documented cases of severe embolic complications in patients in whom warfarin has been withdrawn for dental treatment [1,41]. In this context, some sources

[39] have reported that 14 of 17 patients (71% of cases), in whom warfarin was withdrawn, experienced embolic events. Three cases of embolism occurred within 5 days after warfarin discontinuation. Moreover, some bibliographical sources mention that patients with mechanical heart valves, even on warfarin therapy (maintaining the INR values between 3.0 and 4.5), have an increased risk of thromboembolism (especially during the first year after surgical intervention). The risk of fatal incidents represents 0.2%, while the risk of non-fatal incidents is 2% per year [42].

Although theoretically possible, however there are not well documented severe cases of postoperative bleeding complications after dental surgeries in patients on oral anticoagulant therapy within the therapeutic range. M. Wahl (2000) [43] estimated the incidence of bleeding in 950 patients on anticoagulation therapy subjected to 2400 individual dental procedures. Only 12 patients (<1.3%) had bleeding not controlled through local measures and no patient died. Of the 12 patients, seven had a higher anticoagulation level than the recommended one, 3 patients followed a course of antibiotics postoperatively, which probably interacted with warfarin, 2 patients rinsed their mouth 4 times/day immediately after surgery, which contradicts standard recommendations. According to standard recommendations, mouth rinses are contraindicated up to 24 hours.

Thus, assessment of the INR values is a mandatory method for preoperative evaluation of the effect of oral anticoagulants in this group of patients.

4. PECULIARITIES OF DENTAL EXTRACTIONS

Multiple studies are reported in the literature evaluating tooth extractions in patients on OAM, various approaches being proposed, namely:

1. Discontinuing oral anticoagulation therapy a few days before extraction [15,16];
2. Discontinuing oral anticoagulation therapy and administration of heparin before the dental treatment [17,18];
3. Cutting down on (without discontinuing) anticoagulation therapy [44];
4. Maintaining unchanged anticoagulation therapy and applying different local hemostatic measures, with the INR<2.5 [14,45] or INR<4.0 [46,47].

Although theoretically possible, however there are no well documented serious cases of postoperative bleeding complications after dental surgeries in patients receiving OAM within the therapeutic range. But there are documented cases of thromboembolic complications with fatal incidents or disability following discontinuation of OAM. According to our studies carried out [28] on patients whose INR (at admission) was below the therapeutic range (<2), to prevent thromboembolic accidents the dose of anticoagulant was increased individually (including before

extraction) until the INR was adjusted to the therapeutic range. The results of the oral anticoagulant dose adjustment are shown in Table 3.

As seen in the table, the INR (at admission) ≤ 1.9 was estimated in 15 (45.5 ± 8.7%) patients, in whom, in order to decrease the risk of thromboembolic events, the dose of anticoagulant was increased until the INR values were adjusted to the therapeutic range (2.0-4.0). In 15 (45.5 ± 8.7%) cases the INR was within the therapeutic range and the dose of anticoagulant was not changed. Three (9.1 ± 5.0%) patients were reported to have an overdose of indirect anticoagulants, at admission the INR values being between 4.6 and 5.0.

Table 3. Values of INR at admission and discharge of patients on OAM (n = 33)

INR values	At admission		At discharge		P
	N	P±ES%	N	P±ES%	
1.0 – 1.9	15	45.5 ± 8.7	-	-	****
2.0 – 2.5	10	30.3 ± 7.9	28	84.8 ± 6.2	****
2.6 – 3.0	3	9.1 ± 5.0	4	12.1 ± 5.7	*
3.1 – 3.5	1	3.0 ± 2.9	1	3.0 ± 2.9	*
3.6 – 4.0	1	3.0 ± 2.9	-	-	*
4.1 – 4.5	-	-	-	-	-
4.6 – 5.0	3	9.1 ± 5.0	-	-	*

* $p > 0.05$ **** $p < 0.001$

The dose of anticoagulant was reduced and subsequently maintained within the therapeutic range in overdosed patients. As a result, we determined that all patients after the administration of an individual dose of anticoagulant were discharged with the INR between 2.0 and 3.5, i.e. within the therapeutic range. Thus, the thromboembolic complications were avoided, particularly in patients hospitalized with the INR values below the therapeutic range.

The preextractional change (increase) of OAM dose in patients with INR (at admission) below the therapeutic range is reflected in the following clinical case.

Patient C. V., aged 57, medical record no. 21485, was admitted to the Department of OMF Surgery on November 18, 2008 presenting the following complaints: presence of tooth root residues on the left mandible, regularly causing tenderness and discomfort; pronounced general weakness.

The medical history recorded dental painful sensations some 10-11 days before seeing the dentist. The respective teeth were endodontically treated 8 years ago. According to the data from the outpatient medical record, in 2005 the patient was performed a cardiac surgery (mitral valve prosthesis), after which he was administered thrombostop (2 mg/day). The last INR assessment

was conducted on March 15, 2007, its values being equal to 2.0. It was found that the effect of thrombostop had not been monitored for one year, though at discharge of the patient from the RCH, Department of Cardiac Surgery, the treating physician recommended monthly INR assessment, maintaining it between 2.5 and 3.5.

The physical examination revealed: symmetrical face, pale pink facial skin, impalpable regional lymph nodes, mouth opening freely. The endobuccal exam found the roots of teeth 35 and 36 painless and immobile during vertical percussion. The bilateral palpation of the alveolar process of teeth 35 and 36 was painless. Hemodynamic indices at presentation: BP=110/70 mmHg, heart rate=78 b/min; the bleeding time by the Duke method=3 minutes, the coagulation time by the Lee-White method=12 minutes. The patient was examined by the general practitioner. The orthopantomography recorded: presence of oval and radiolucent formations with well-defined contour around the apexes of teeth 35 and 36 with a size <0.5 cm.

The diagnosis was established on the basis of clinical and laboratory examination: *Chronic granulomatous periodontitis in teeth 35 and 36. Rheumatic heart disease. Condition after mitral valve prosthesis (2005). Oral anticoagulants (thrombostop).*

Given the lack of OAM monitoring and the presence of major risks of both bleeding and thromboembolism, the venous blood was collected at admission to assess the coagulation indices. The following results were obtained: prothrombin index=93%; fibrinogen=2.4 g/l; activated partial thromboplastin time=37 sec.; thrombin time=24 sec.; "negative" ethanol test; INR=1.10. While assessing the respective index, an increase in the prothrombin index (93%) and a decrease in the INR values (1.10) below the therapeutic range were observed, being indicative of the presence of a major risk of thromboembolic events. This finding served as an indication for increasing the dose of thrombostop from 2 mg/day to 3 mg/day with a follow-up control of the INR.

It is well known that mechanical valves are some foreign bodies to the organism, carrying an increased risk of infectious complications, therefore prophylactic antibiotic therapy is required [8,9,48]. Despite this, antimicrobial treatment was administered before the extraction.

The results of laboratory tests performed (blood test, urinalysis, biochemical analysis of blood) were within normal values.

On November 19, 2008, the root extraction of teeth 35 and 36 was performed, the level of the INR being 1.14. Immediately after the extraction the alveoli of the extracted teeth filled with blood that overflew outside the socket. The bleeding time was 30-40 sec., the intensity being insignificant. Blood clot formation was assessed in the 3rd minute after the extraction, after the blood transformed from liquid into gel (Figure 2.A). At the same time, it was observed that the newly formed clot was homogeneous in the socket and it came into contact with the alveolar

edges. In the 10th minute after the extraction a light red line was observed at the periphery compared to dark red in the center of the clot. Thus, an inhomogeneous clot was revealed, which "migrated" under the edge of the socket (Figure 2.B).

The postoperative period evolved without any unusual manifestations: wound inspection performed 12 hours after the extraction revealed the presence of retracted blood clots (Figure 2.C) and 36 hours after the extraction the gum integrity practically restored (Figure 2.D).

On November 21, 2008, following the increase in the dose of thrombostop, the INR restored within the therapeutic range (2.84). Thus, the patient was not at risk of thromboembolic complications. Moreover, the patient`s general weakness disappeared, it being probably due to the improvement of rheological properties of the blood after the INR adjustment to therapeutic values. On November 22, 2008 the patient was discharged in a satisfactory general condition.

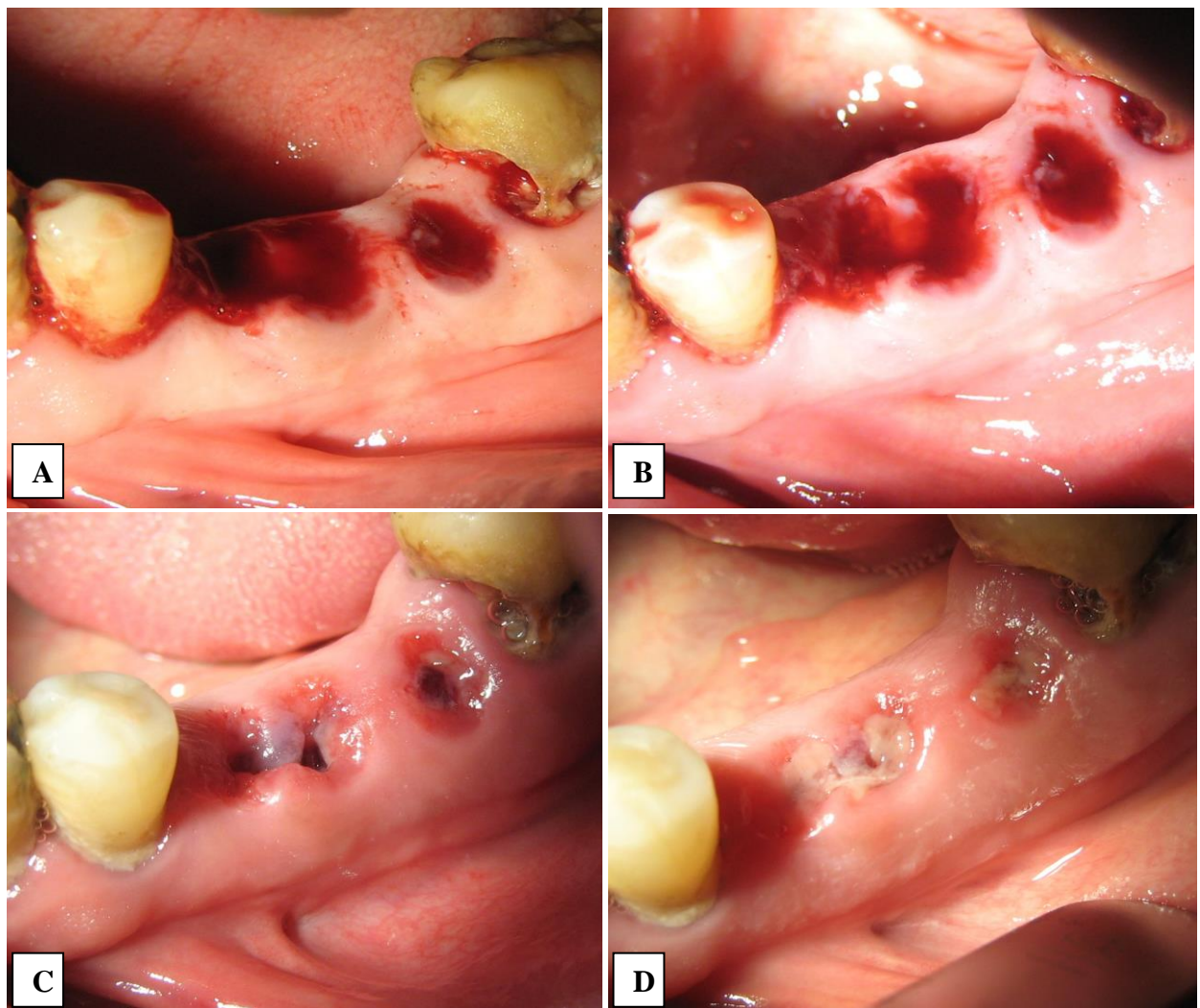Fig.2. Blood clot formation and its appearance after the extraction of the roots of teeth 35 and 36 in patient C.V. on oral anticoagulant medication (thrombostop)

A - Blood clot formation in the 3rd minute after extraction; B - Appearance of the homogeneous clot and its position under the edge of the socket; C - Appearance of the wound 12 hours after extraction; D - Appearance of the wound 36 hours after extraction

From the above mentioned, we can conclude that in case the INR values are below the therapeutic range in patients on OAM, the dose of these preparations can and should be increased (including before extraction) to prevent thromboembolic complications. Moreover, excessive blood clotting (hypercoagulation) was recorded in this patient after the evaluation of the postextractional dental hemostasis. It was assessed by:

- a short duration of postoperative wound bleeding (30-40 seconds) compared to a mean duration of bleeding in patients with an uncompromised hemostatic system (1.2±0.2 minutes);
- an early formation of blood clot (in the 3rd minute after extraction) compared to a mean time of blood clot formation in patients with an uncompromised hemostatic system (in the 5.2±0.1 minute).

5. PECULIARITIES OF DENTAL IMPLANTS PLACEMENT

The indications for dental implants use have been extended in recent years and the share of dental implants in the prosthetic rehabilitation of patients has considerably increased. Although dental implantology has rapidly evolved and achieved remarkable success in the rehabilitation of patients with various edentations, there are still many controversial and debatable issues which require further studies. Disputes cover not only the application of minimally invasive procedures in oral implantology [49,50,51], but also ways (terms) of dental implants placement in patients with a compromised general health status [52,53]. Thus, certain systemic factors or medication associated with underlying diseases could influence the surgery performing, creating difficulties in proper healing of the soft and hard tissues and subsequently compromising the tissue integration of dental implants.

Currently a number of issues have remained to be elucidated which are related to the peculiarities of dental implants placement in patients on OAM. As a result of the available literature analysis, we have faced both the lack of detailed data on the choice of optimal conditions for placement of dental implants in these patients and the presence of multiple gaps or conflicting views on this issue. Considering the ideas mentioned before, some questions have arisen: Is it possible to rehabilitate edentulous patients (on anticoagulant therapy) by placing dental implants without discontinuing these drugs? Is it possible to perform grafting of the maxillary sinus (MS) through a window created in the side wall or MS floor elevation by transalveolar approach without discontinuing the anticoagulant? What therapeutic approach has to be applied in bleedings in the bone wound of the MS floor or endo-sinus bleedings without compromising the integrity of the Schneiderian membrane? Will local hemostatic measures suffice for intra and/or postoperative bleedings in this group of patients? Is a massive life-threatening hematoma possible to develop after surgery?

D. Huang and H.L. Wang (2006) consider that one of the absolute contraindications to placing dental implants are patients with heart valve prostheses and coagulopathy [54]. However, C. Madrid and M. Sanz (2009) found no contraindication to placing dental implants in patients on OAM [53]. Moreover, they opine that dental implants in patients on antithrombotic medication can be placed without discontinuing these drugs, provided they are placed without any extended flaps. It is to be noted that to avoid excessive operative trauma of the standard method of dental implant placement (mucoperiosteal flap raising) some techniques have been proposed to place the implants without raising flaps (flapless surgery). In this context, some local studies [50] have shown that the method of implant placement in two-stage surgery without mucoperiosteal flaps is minimally invasive and the probability of hematoma development in the postoperative period and other indices studied (intensity of pain syndrome, prevalence of edema and its regression) are significantly ($p<0.001$) lower than in placing implants by raising mucoperiosteal flaps. In this connection, we welcome the use of this method of dental implants placement (flapless), including healing abutment [51], thus avoiding the second surgical stage in patients on antithrombotic medication. At the same time, it should be mentioned that the flapless placement of endosseous dental implants is difficult and may be used by the implant dentist with a proper experience in oral implantology. In a study conducted in 2011, C. Baccci et al. [52] evaluated the incidence of bleeding complications after flap implant placement as well as lateral and crestal sinus lift in 50 patients on OAM (warfarin) without discontinuing anticoagulant medication or modifying the dose. It is to be noted that the preoperative INR values of the patients studied ranged between 1.8 and 2.98. The authors reported that of the 50 patients, only 2 (4%) had a delayed bleeding (on the 2nd postoperative day). The bleeding was easily stopped by applying a compressive cotton swab impregnated with tranexamic acid. The patients did not require hospitalization or systemic therapy.

V. Topalo et al. performed the following interventions on 4 patients on anticoagulant therapy (acenocoumarol, warfarin): two-stage dental implants placement conventionally without raising mucoperiosteal flaps [50], crestal sinus lift [55], and lateral sinus lift (Table 4).

Table 4. Volume of surgical intervention performed on each patient (n=4)

No	Volume of surgery
1	10 implants placed by flap surgery
2	3 implants placed by flap surgery
3	2 implants - crestal sinus lift without flap raising
4	4 implants - bilateral lateral sinus lift 2 one-stage flapless implants

After assessing the INR values preoperatively, it was found that of the 4 patients included in the study, 3 patients had the INR between 1.3 and 1.6, it being below the therapeutic range (<2.0). In these cases, to prevent thromboembolic accidents the dose of anticoagulant was increased with a follow-up control of the INR. The INR values recorded in the third patient were 2.1, i.e. within the therapeutic range (between 2.0 and 4.0), the dose of medication being not changed. Thus, none of the patients were discontinued the anticoagulant medication, the dose being modified depending on the INR values. No signs of increased bleeding were detected during surgical inerventions. On the 2nd postoperative day a hematoma was detected in the neighboring regions in patients 1, 2 and 4 (Figure 3).

Fig.3. Presence of a postoperative hematoma in the neighboring regions

The edema of the gums and adjacent soft tissues was more pronounced in cases with flap versus flapless surgery. During the postoperative period, a minor bleeding occurred in patient 1 (Figure 4A), it being easily stopped by the topical application of human thrombin and 5% aminocaproic acid (Figure 4B). For this purpose, dry powder of thrombin, supplied in 125 IU vials, was dissolved immediately before use in about 2 ml of sterile saline solution.

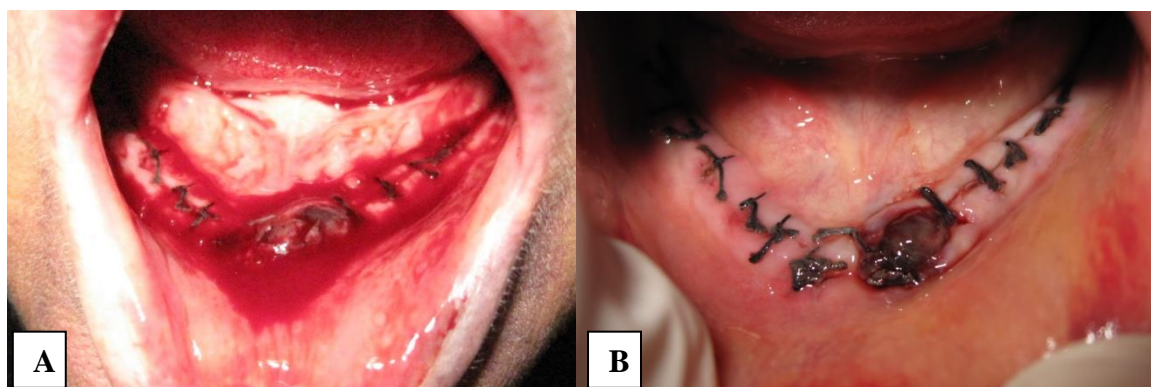Fig.4. Appearance of bleeding area (A) presence of the blood clot formed after the topical application of human thrombin (B)

Thrombin contributes to the conversion of fibrinogen into fibrin and stimulates platelet aggregation [56]. Topically applied, 5% aminocaproic acid is deposited on fibrin and protects it from the fibrinolytic action of plasma and saliva, thereby preserving the thrombus. We believe

that this method of providing local hemostasis is minimally invasive, allowing both the formation and protection of the blood clot.

According to the results obtained in our study, placement of dental implants in patients on OAM is possible without discontinuing these drugs. The INR assessment 24 hours before the surgery is a prerequisite. In this study surgeries were performed at the INR values between 1.3 and 2.1. To prevent thromboembolic events, the dose of medication was increased if necessary (INR<2), including preoperatively. At the same time, increased intraoperative bleeding signs (both bone support and soft tissues) were not detected. This phenomenon can be accounted for the fact that the endosseous implant, through its pressure upon the bone, allows the bone wound to close immediately, this probably contributing to a better hemostasis with a lower potential of bleeding complications. Although in the postoperative period a case of delayed bleeding was recorded (on the 7th day after implant placement), it was insignificant by intensity and was easily controlled by the topical application of human thrombin and 5% aminocaproic acid.

6. MANAGEMENT OF ORAL SURGERY

The analysis of the results obtained in the study served as an impetus for developing the management of oral surgery in patients receiving antithrombotic treatment (Figure 5). According to the proposed algorithm, rendering of dental care to patients on antiplatelet medication entails initial assessment of the bleeding time by the Duke method. In the case of normal values (2-4 min.) of the test, we recommend performing the surgery on an outpatient basis. Conversely, patients with a prolonged bleeding time by the Duke method (>5 min.) require the surgery to be performed in the hospital. The preoperative INR assessment is required in patients receiving OAM (acenocoumarol and warfarin), which may be within different (subtherapeutic, therapeutic and supratherapeutic) ranges.

Given the huge increase in frequency and lethality of thromboembolic complications, the decision to alter the anticoagulant therapy, in our opinion, must be assessed in terms of risk and benefit. In this context, to prevent thromboembolic accidents in patients whose INR (preoperatively) is below the therapeutic range (<2), the dose of anticoagulant should be increased until the INR is adjusted to the therapeutic range. Conversely, if the INR value is greater than the individual therapeutic range recommended by the general practitioner, the dose of anticoagulant will be reduced and the surgery will be delayed. In patients whose INR is within the therapeutic range, the dose of medication will be kept within the same range. Thus, to prevent bleeding and thromboembolic accidents we recommend changing the dose of anticoagulant, it depending on the INR with the follow-up control of the respective coefficient.

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┌─────────────────────────────────────────────────────────────────────────┐
│                 PATIENT ON ANTITHROMBOTIC TREATMENT                       │
└─────────────────────────────────────────────────────────────────────────┘
           │                                          │
           ▼                                          ▼
┌──────────────────────────┐          ┌──────────────────────────────────┐
│ Patient on antiaggregant │          │ Patient on oral anticoagulant    │
│ medication               │          │ medication                       │
│ (acetylsalicylic acid    │          │ (acenocoumarol, warfarin etc.)   │
│ etc.)                    │          └──────────────────────────────────┘
└──────────────────────────┘                          │
           │                                           ▼
           ▼                          ┌──────────────────────────────────┐
┌──────────────────────────┐          │     Assessment of INR values     │
│ Assessment of bleeding   │          └──────────────────────────────────┘
│ time by the Duke`s method│            │          │            │
└──────────────────────────┘            ▼          ▼            ▼
      │            │          ┌───────────┐ ┌───────────┐ ┌───────────┐
      ▼            ▼          │Subtherap. │ │Therapeutic│ │Supratherap│
┌──────────┐ ┌──────────┐    │INR (INR<2)│ │INR(INR=2-4)│ │INR(INR>4)│
│ Within   │ │Prolonged │    └───────────┘ └───────────┘ └───────────┘
│ normal   │ │(>5 min.) │          │            │            │
│ range(2-4)│ │          │          ▼            ▼            ▼
└──────────┘ └──────────┘    ┌──────────┐ ┌──────────┐ ┌──────────┐
      │            │         │OAM dose  │ │OAM dose  │ │OAM dose  │
      ▼            ▼         │increase  │ │continuat.│ │decrease  │
┌──────────┐ ┌──────────┐    └──────────┘ └──────────┘ └──────────┘
│Performing│ │Performing│          │
│surgery on│ │surgery on│          ▼
│an        │ │an        │    ┌──────────────────────────────────┐
│outpatient│ │inpatient │    │Antibiotic prophylaxis of infective│
│basis     │ │basis     │    │endocarditis                       │
└──────────┘ └──────────┘    └──────────────────────────────────┘
                                          │
                                          ▼
                             ┌──────────────────────────────────┐
                             │Performing surgery on an in-patient│
                             │basis and maintaining INR within   │
                             │the therapeutic range              │
                             └──────────────────────────────────┘
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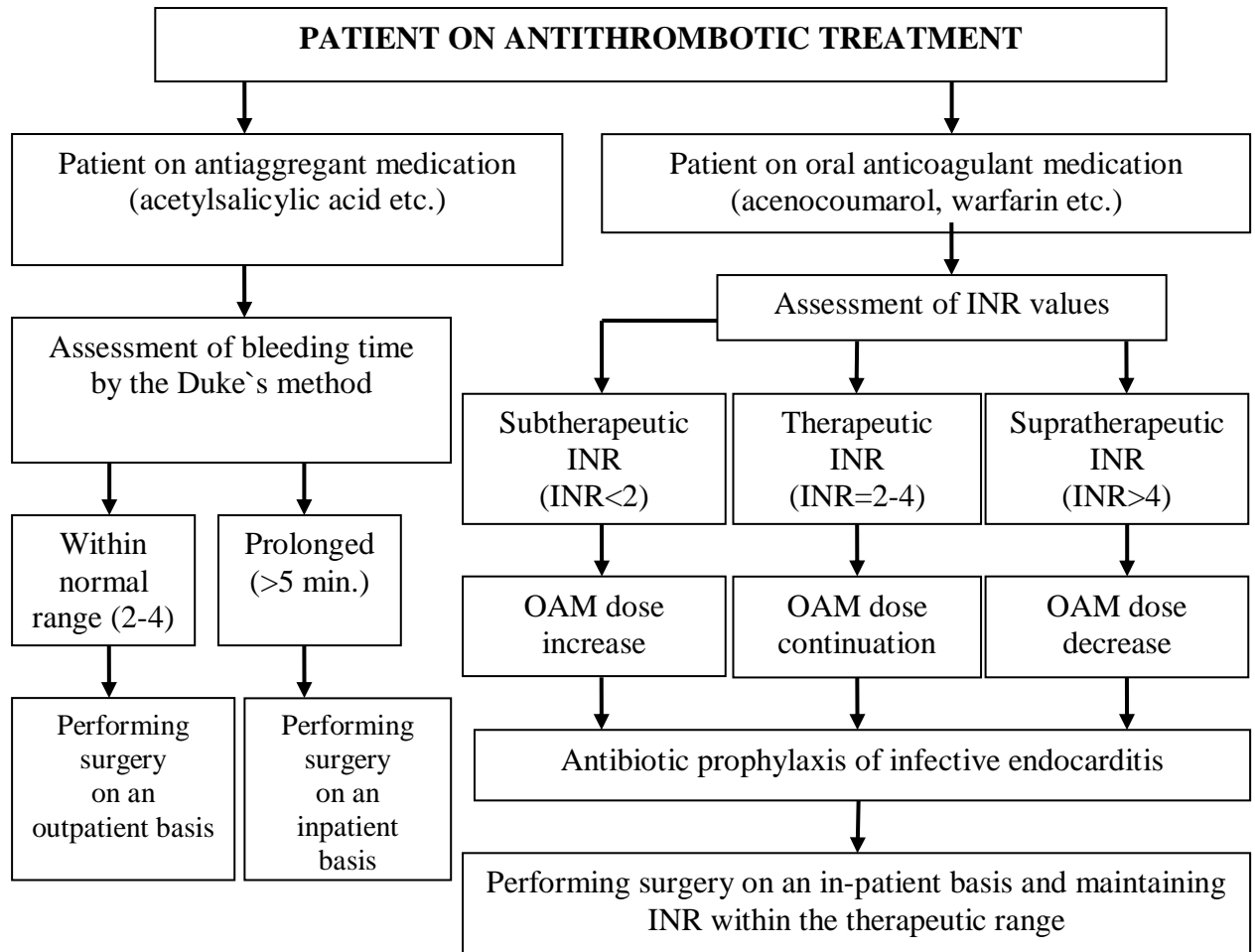
Fig.5. Management of oral surgery in patients receiving antithrombotic medication

It should be noted that to prevent infective endocarditis in people with infectious risk, including patients with cardiovascular disease, it is necessary to administer Amoxicillin or Ampicillin 2.0 g p/o or i/v preoperatively (30-60 minutes before surgery). Clindamycin 600 mg p/o or i/v is administered in case of allergy to Penicillin or Ampicillin [8,57].

7. CONCLUSIONS

1. Dental extractions, dental implants placement and other oral surgeries (transcrestal sinus lift, lateral sinus lift) in patients on antithrombotic medication are possible without discontinuing these drugs.

2. The assessment of the INR values is a mandatory method for preoperative evaluation of the effect of anticoagulants in patients on OAM.

3. To prevent severe bleeding and thromboembolic accidents the dose of anticoagulant will be adjusted depending on the INR values, maintaining them within the therapeutic range as recommended by the general practitioner.

4. Bleedings occuring within the therapeutic range of INR are insignificant by intensity and do not differ from bleedings occurring in patients with an uncompromised hemostatic system, but, if necessary they can be easily controlled by local hemostatic measures.

8. SELF-ASSESSMENT TESTS

1. M.C. Antithrombotics are substances that:
    A. inhibit blood clotting;
    B. stimulate blood clotting;
    C. enhance the fibrinolytic system;
    D. inhibit the fibrinolytic system;
    E. inhibit specifically thrombin formation.

2. M.C. Depending on the mechanism of action on the pathogenesis of thrombosis, antithrombotics can be divided into the following groups:
    A. anticoagulants;
    B. angioprotectors;
    C. antiplatelets;
    D. aggregants;
    E. fibrinolytics.

3. S.C. Anticoagulants are a group of drugs that:
    A. prevent the formation of fibrin;
    B. inhibit platelet adhesion;
    C. inhibit platelet aggregation;
    D. inhibit platelet adhesion and aggregation;
    E. lyse fibrin clot by activating the fibrinolytic system.

4. S.C. Antiplatelets are a group of drugs which:
    A. prevent the formation of fibrin;
    B. stimulate platelet adhesion;
    C. stimulate platelet aggregation;
    D. inhibit platelet adhesion and aggregation;
    E. lyse fibrin clot by activating the fibrinolytic system.

5. S.C. Fibrinolytic agents (thrombolytics) are a group of drugs which:
    A. prevent the formation of fibrin;
    B. stimulate platelet adhesion;
    C. stimulate platelet aggregation;
    D. inhibit platelet adhesion and aggregation;
    E. lyse fibrin clot by activating the fibrinolytic system.

6. M.C. The group of direct-acting anticoagulants include:
    A. standard heparin preparations (heparin);
    B. low molecular weight heparin preparations (LMWH);
    C. sodium citrate;
    D. heparinoids;
    E. hirudin and its analogues.

7. S.C. The most common complications of heparin therapy are:
    A. bleeding complications (melena, hematoma, haematuria);
    B. thrombosis;
    C. allergic reactions;
    D. osteoporosis;
    E. none of the above.

8. M.C. The group of indirect-acting anticoagulants are:
    A. acenocoumarol;
    B. warfarin (coumadin, panwarfin);
    C. ethyl biscoumacetate (neodicoumarin, pelentan);
    D. phenprocoumon (marcoumar, falithrom);
    E. phenindione.

9. S.C. Indirect-acting anticoagulants are drugs that:
    A. inhibit the activation of plasma coagulation;
    B. stimulate blood clotting;
    C. enhance the fibrinolytic system;
    D. inhibit the fibrinolytic system;
    E. inhibit specifically thrombin formation.

10. M.C. The effect of indirect-acting anticoagulants:
    A. sets in slowly;
    B. sets in quickly;
    C. is long;
    D. is short;
    E. is present only *in vivo*.

11. S.C. Acenocoumarol belongs to the group of:
    A. direct-acting anticoagulants;
    B. indirect-acting anticoagulants;
    C. standard heparin preparations;
    D. low molecular weight heparin preparations (LMWH);
    E. none of the above.

12. S.C. The latent period of acenocoumarol administration lasts for:
    A. 1-12 hours;
    B. 12-24 hours;
    C. 24-36 hours;
    D. 48-72 hours;
    E. 5-7 days.

13. S.C. Warfarin belongs to the group of:
    A. direct-acting anticoagulants;
    B. indirect-acting anticoagulants;
    C. standard heparin preparations;
    D. low molecular weight heparin preparations (LMWH);
    E. none of the above.

14. S.C. The latent period of warfarin administration lasts for:
    A. 1-12 hours;
    B. 12-24 hours;

C. 24-36 hours;
D. 37-60 hours;
E. 5-7 days.

15. S.C. After discontinuing the treatment with acenocoumarol, the anticoagulant effect is maintained for:
A. 1-12 hours;
B. 12-24 hours;
C. 24-48 hours;
D. 48-72 hours;
E. 5-7 days.

16. S.C. After discontinuing the treatment with warfarin, the anticoagulation effect is maintained for:
A. 1-12 hours;
B. 12-24 hours;
C. 24-48 hours;
D. 48-72 hours;
E. 5-7 days.

17. S.C. The antiplatelet effect of acetylsalicylic acid is maintained for:
A. 1-5 hours;
B. 6-12 hours;
C. 12-24 hours;
D. 24-48 hours;
E. a few days (not less than 3 or 4 days).

18. S.C. The endogenous factors that increase the effect of oral anticoagulant therapy include:
A. deficiency of vitamin K;
B. liver disease;
C. malignant tumors;
D. diarrhea;
E. all of the above.

19. S.C. The exogenous factors that increase the effect of oral anticoagulant therapy include:
A. penicillins;
B. NSAIDs;
C. heparin and heparinoids;
D. oral antidiabetic drugs;
E. all of the above.

20. M.C. The endogenous factors that reduce the effect of oral anticoagulant therapy include:
A. congenital resistance;
B. hyperlipidemia;
C. hypothyroidism;
D. edematous syndrome;
E. malabsorption.

21. M.C. The exogenous factors that reduce the effect of oral anticoagulant therapy include:
A. antihistamines;
B. vitamins C, K1 and K2;
C. oral contraceptives;

D. edematous syndrome;

E. malabsorption.

22. M.C. The indications for oral anticoagulant therapy are:
   A. prophylaxis of venous thromboembolism;
   B. treatment of venous thromboembolism;
   C. prevention and treatment of acute myocardial infarction;
   D. patients with prosthetic heart valves;
   E. atrial fibrillation.

23. M.C. The indications for oral anticoagulant therapy are:
   A. patients with prosthetic heart valves;
   B. implantation of artificial cardiac pacemaker;
   C. ischemic heart disease;
   D. history of thromboembolism;
   E. thrombophlebitis of the lower limbs.

24. S.C. The contraindications to oral anticoagulant therapy are:
   A. patients with prosthetic heart valves;
   B. implantation of artificial cardiac pacemaker;
   C. ischemic heart disease;
   D. history of thromboembolism;
   E. none of the above.

25. M.C. The contraindications to oral anticoagulant therapy are:
   A. hemorrhagic syndromes;
   B. hypocoagulation disorders;
   C. hemorrhagic stroke;
   D. history of thromboembolism;
   E. thrombophlebitis of the lower limbs.

26. M.C. The contraindications to oral anticoagulant therapy are:
   A. specific allergy;
   B. active gastric and duodenal ulcer;
   C. severe kidney and liver dysfunction;
   D. pregnancy and lactation;
   E. lack of possibility of periodic clotting tests.

27. M.C. Thrombin initiates thrombogenesis through:
   A. conversion of fibrinogen of the underlying tissue into fibrin;
   B. stimulation of extrinsic pathway of blood coagulation;
   C. stimulation of platelet aggregation;
   D. stimulation of intrinsic pathway of blood coagulation;
   E. formation of prothrombin activators.

28. M.C. The antifibrinolytic effect of aminocaproic acid is due to:
   A. inhibition of plasminogen activator (fibrinolisyn);
   B. direct suppression (to a lesser extent) of plasmin;
   C. inhibition of extrinsic pathway of blood coagulation;
   D. inhibition of intrinsic pathway of blood coagulation;
   E. inhibition of prothrombin activators.

29. S.C. The anticoagulant effect of coumarins is assessed by monitoring:
   A. prothrombin time, represented by the International Normalized Ratio;
   B. thrombin time;
   C. activated partial thromboplastin time;
   D. concentration of fibrinogen in peripheral blood;
   E. none of the above.

30. M.C. The frequency of INR measurement has to be checked:
   A. daily after treatment initiation;
   B. weekly during the first month of treatment;
   C. monthly after treatment initiation;
   D. annually;
   E. none of the above.

31. S.C. The frequency of INR measurement has to be checked:
   A. daily;
   B. weekly;
   C. monthly, and more frequently if necessary;
   D. annually;
   E. none of the above.

32. S.C. The INR has to be assessed within:
   A. 24 hours before any oral surgery;
   B. 24 hours after any oral surgery;
   C. 24-48 hours after any oral surgery;
   D. 48-72 hours after any oral surgery;
   E. none of the above.

33. S.C. Cessation of anticoagulant therapy aiming at preventing bleedings puts the patient at risk of:
   A. thromboembolic complications with a significant potential of morbidity;
   B. allergic reactions;
   C. neuroendocrine changes;
   D. all of the above
   E. none of the above.

34. S.C. Patients receiving oral anticoagulants have an increased risk of:
   A. bleeding;
   B. thromboembolism;
   C. both bleeding and thromboembolism;
   D. dysmetabolism;
   E. none of the above.

35. S.C. The INR values below 2 in patients on oral anticoagulant medication show the presence of a possible risk of:
   A. bleeding;
   B. thromboembolism;
   C. both bleeding and thromboembolism;
   D. dysmetabolism;
   E. none of the above.

36. S.C. The INR values between 2 and 4 in patients receiving oral anticoagulants indicate a possible risk of :
    A. severe bleeding;
    B. thromboembolism;
    C. both severe bleeding and thromboembolism;
    D. dysmetabolism;
    E. none of the above.

37. S.C. The INR values above 4 in patients on oral anticoagulant medication indicate a possible risk of:
    A. severe bleeding;
    B. thromboembolism;
    C. both bleeding and thromboembolism;
    D. dysmetabolism;
    E. none of the above.

38. S.C. The optimal level of oral anticoagulants is assessed by:
    A. monitoring prothrombin time, represented by the International Normalized Ratio;
    B. determining fibrinogen content;
    C. assessing thrombin time;
    D. determining the Duke bleeding time;
    E. determining the Lee-White blood clotting time.

39. S.C. The INR values of the individuals with an uncompromised coagulation system are:
    A. 0.3 - 0.6;
    B. 1.0 or close to 1.0 (0.7 - 1.3);
    C. 1.5 - 2.0;
    D. 2.0 - 3.0;
    E. 3.0 - 4.0.

40. S.C. The therapeutic level of anticoagulation depends on the indication for which it is administered and the INR values of patients with prosthetic heart valves vary between:
    A. 0.5 and 1.0;
    B. 1.0 and 2.0;
    C. 2.0 and 4.0;
    D. 4.0 and 5.0;
    E. 5.0 and 6.0.

41. S.C. To prevent severe bleeding and thromboembolism the effect of anticoagulant is assessed determining the INR values:
    A. 5-7 days before surgery;
    B. 2-5 days before surgery;
    C. on the day of surgery;
    D. immediately after surgery;
    E. none of the above.

42. S.C. What has to be done if the INR values are preextractionally below the therapeutic range (<2):
    A. the dose of anticoagulant has to be increased until the INR is adjusted to the therapeutic range and then the tooth extraction is performed;
    B. the dose of anticoagulant has to be reduced and then the tooth extraction is performed;

C. the anticoagulant has to be discontinued and then the tooth extraction is performed;

D. the dose has to be gradually reduced, then the anticoagulant is dicontinued and the dental extraction is performed;

E. none of the above.

43. S.C. What has to be done if the INR value is higher than the individual therapeutic range recommended by the general practitioner:

A. the dose of anticoagulant has to be increased until the INR is adjusted to the therapeutic range and then the dental extraction is performed;

B. the dose of anticoagulant has to be reduced until the INR is adjusted to the therapeutic range and then the dental extraction is performed;

C. the anticoagulant has to be discontinued and then the dental extraction is performed;

D. the dose has to be gradually reduced until the anticoagulant is discontinued and then the dental extraction is performed;

E. none of the above.

44. S.C. What has to be done if the INR before the extraction is within the therapeutic range:

A. the dose of anticoagulant has to be increased and then the dental extraction is performed;

B. the dose of anticoagulant has to be reduced and then the dental extraction is performed;

C. the anticoagulant has to be discontinued and then the dental extraction is performed;

D. the dose has to be gradually reduced, the anticoagulant is discontinued and then the dental extraction is performed;

E. the tooth extraction is performed and the dose of anticoagulant is maintained within the same limits.

45. S.C. Is it possible to rehabilitate edentulous patients (on anticoagulant therapy) by placing dental implants without discontinuing these drugs:

A. yes, if the INR values are within the therapeutic range;

B. yes, if the INR values are below the therapeutic range;

C. yes, if the INR values are above the therapeutic range;

D. yes, without assessing the INR values;

E. none of the above.

46. S.C. Is it possible to rehabilitate edentulous patients by placing dental implants without discontinuing the anticoagulant therapy:

A. yes, under the control of the INR;

B. no;

C. it depends on the clinical situation;

D. yes, without assessing the INR values;

E. none of the above.

47. S.C. Is it possible to perform a lateral sinus lift in patients on oral anticoagulants without discontinuing these drugs:

A. yes, under the control of INR, maintaining it within the therapeutic range;

B. no;

C. it depends on the clinical situation;

D. yes, without assessing the INR values;

E. none of the above.

48. S.C. Is it possible to perform a crestal sinus lift in patients on oral anticoagulants without discontinuing these drugs:
    A. yes, under the control of the INR, maintaining it within the therapeutic range;
    B. no;
    C. it depends on the clinical situation;
    D. yes, without assessing the INR values;
    E. none of the above.

49. M.C. Antibiotic prophylactic regimen for patients with prosthetic heart valves includes:
    A. Amoxicillin 2.0 g orally 1 hour before surgery;
    B. Ampicillin 2.0 g im/iv 30 minutes before surgery;
    C. Clindamycin 600 mg orally 1 hour before the surgery and 300 mg 6 hours after surgery;
    D. Azithromycin or Clarithromycin 500 mg 1 hour before surgery;
    E. Cefazolin 1.0 g im/iv 30 minutes before surgery.

50. M.C. The patients with cardiovascular disease requiring mandatory antibiotic prophylaxis are:
    A. patients with prosthetic heart valves;
    B. patients with valvular heart disease;
    C. patients with a history of bacterial endocarditis;
    D. patients with cyanotic congenital heart disease;
    E. patients with acyanotic congenital heart disease.

9. KEY

1. A, C.
2. A, C, E.
3. A.
4. D.
5. E.
6. A, B, C, D, E.
7. A.
8. A, B, C, D, E.
9. A.
10. A, C, E.
11. B.
12. C.
13. B.
14. D.
15. D.
16. E.
17. E.
18. E.
19. E.
20. A, B, C, D, E.
21. A, B, C.
22. A, B, C, D, E.
23. A, B, C, D, E.
24. E.
25. A, B, C.

26. A, B, C, D, E.
27. A, C.
28. A, B.
29. A.
30. A, B, C.
31. C.
32. A.
33. A.
34. C.
35. B.
36. E.
37. A.
38. A.
39. B.
40. C.
41. C.
42. A.
43. B.
44. E.
45. A.
46. A.
47. A.
48. A.
49. A, B, C, D, E.
50. A, B, C, D, E.

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