

PRE-EXTRACTATIONAL VALUE OF THE INTERNATIONAL NORMALIZED RATIO IN IDENTIFICATION OF THE HEMORRHAGIC AND THROMBOEMBOLIC RISK IN PATIENTS UNDERGOING ORAL ANTICOAGULANT TREATMENT

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Abstract: The study comprised 38 patients undergoing antithrombotic treatment. Relying on the research which we have carried out, we can conclude that patients who undergo unsupervised anticoagulant treatment have an increased both hemorrhagic and thromboembolic risk. The incidence of bleeding after dental extraction in patients undergoing antithrombotic therapy who have been extracted teeth without any prior withdrawal of these drugs, is $30,8 \pm 10,2\%$. These hemorrhages, having recorded the values $INR < 2,4$, have an insignificant intensity. As a prophylaxis of the severe hemorrhagic and thromboembolic events the dose of the anticoagulant drug will be modified depending on INR.

Key words: tooth extraction, bleeding after dental extraction, thromboembolism, international normalized ratio.

INTRODUCTION

Thrombolytic therapy is known to be one of the most important 10 achievements of cardiology in the XXth century (N.J. Mehta and I.A. Khan, 2002). Nowadays some oral anticoagulants with coumarinic or inandionic structure are used. They differ by the time of their action, active doses, effect duration [1]. Due to its advantageous pharmacological peculiarities (it is less toxic, it has an adequate plasmatic $T_{1/2}$) warfarin has become in the last years, in the majority of European countries and USA, the drug of the first choice in the prolonged therapy with oral anticoagulants [2]. In Romania, the only oral anticoagulant registered at present is acenocoumarol (thrombostop) [3]. At the same time, of all antithrombotic drugs, acetylsalicylic acid (aspirin) has a central place.

In the last years the indications for treatment with oral anticoagulant drugs have extended [4]. This is due to an increase of the angio/and cardiosurgical assistance rendered to population (cardiac valve prosthesis, coronary by-pass, valvuloplasty as well as the number of people who are carriers of artificial cardiac valves and valve prosthesis, with

disturbances of the cardiac rhythm etc. [5]. In 1997 there were performed 64000 valvular surgeries in the whole Europe. Mechanic prostheses were used in 2/3 of these cases [6]. At present 500 cardiosurgeries are annually performed in MSPI Center of Heart Surgery from Chisinau.

It is known that mechanic valves are foreign bodies for the organism which have a high risk of infections and thromboembolic complications. This fact requires an anticoagulant therapy and prophylactic antibiotic therapy during the whole life [7]. Sometimes these patients require to be rendered stomatological assistance including dental extractions. The latter can lead to hemorrhagic complications. The hemorrhagic events are relatively frequent in this group of patients [1]. They are fostered by a high risk of overdose, linked with the individual variations in the pharmacokinetic behaviour, as well as interferences connected with different pathologic conditions or associated drugs [1,2]. According to data taken from literature, the incidence of hemorrhages in patients undergoing a treatment with indirect anticoagulants varies between 5-10% [2].

The rate of severe bleedings is 2,4-8,1%, while the rate of the fatal outcomes is 0-4,8% [2].

Thrombotic disease represents a major complication of the surgical patient. The importance of this medical problem, on the one hand is due to the increase of frequency, on the other hand it is due to the difficulties of intravital diagnosis and increased lethality [8]. Anatomico-clinical statistics of USA shows that massive embolism is the third cause of sudden death. About 300 thousand patients are annually hospitalized with profound venous thrombosis (PVT) which causes approximately 50 thousand deaths from pulmonary thromboembolism (PTE). The incidence of PVT in Europe which was recorded in the last years, reached 160 cases at 100 thousand population. Over 80 thousand of PTE occur annually in France, while, at least 20 thousand deaths are recorded.

In order to prevent occurrence of hemorrhagic and thromboembolic accidents, patients following anticoagulant treatment are compelled to monitor their monthly anticoagulant effect of coumarinic drugs [1,2,9]. With this purpose the optimum level of oral anticoagulant drugs is assessed by monitoring the time of prothrombin which is represented by the international normalized ratio (INR) [2,9]. The therapeutic level of anticoagulants depends on the indication for which it was administered. INR values range within 2,0-4,0 [9]. The higher this coefficient is the more marked hypocoagulation is and, consequently, the hemorrhagic complications are more frequent and more dangerous. Conversely, reduction of INR values below the therapeutic range limits leads to increase of the risk of thromboembolic events occurrence [9].

Management of teeth extraction in patients under antithrombotic therapy is disputable [10,11]. In order to prevent hemorrhagic accidents some doctors recommend their patients to cancel oral

antiplatelet and/or anticoagulant therapy some days prior to operation (pre-surgically and pre-extractionally) [12], others recommend a compulsory substitution with heparin during the whole period of treatment, up to oral anticoagulants return [13]. Other researchers suggest to perform dental extractions in patients undergoing antithrombotic therapy without suspending these remedies [14]. Thus, the dilemma widely disputable within the last years in the medical literature: „Is it necessary to discontinue anticoagulant treatment in patients who are subjected to tooth extractions?” – is still actual and any gained experience contribute to elaboration of an optimal treatment management of these patients.

So, the problem of tooth extraction in patients undergoing antithrombotic therapy has a major practical importance and is insufficiently approached in the medical literature. Therefore there are complications which occur in these cases and varied choice of medical tactics, which is often groundless.

PURPOSE OF STUDY

To assess the frequency of the post-operative hemorrhage, hemorrhagic and thromboembolic risk in patients undergoing antithrombotic therapy who are subjected to dental extractions without cancelling these drugs.

MATERIALS AND METHODS

The study comprised 38 patients under antithrombotic therapy. They were admitted to Oro-maxillo-facial Surgery Department from the National Scientific Practical Centre of Emergency Medicine (NSPCEM) from Chişinău in April 2007 – November 2009. Men (18) constituted 47,4 ± 8,1%, while women (20) - 52,6 ± 7,6% (p>0,05). Mean age was 54,8 ± 1,7 years (p<0,001). Of 38 patients, 26 (68,4 ± 7,5%) were hospitalized in order to be performed surgical manipulations in the oral cavity (34 dental extractions were

carried out). 12 patients ($31,6 \pm 7,9\%$) ($p < 0,01$) – complained of hemorrhage in the oral cavity: 8 (66,7%) had post-extraction dental hemorrhage (PDH), 3 (25,0%) hemorrhage resulting from periosteotomy and 1 (8,3%) patient with gingival hemorrhage.

Clinical examination was carried out according to the traditional methods of patients examination. The routine parameters of general and biochemical blood analyses, urine analysis, coagulogram indices (prothrombin index, fibrinogen content, time of partially activated thromboplastin (TPAT), thrombin time, ethanol test), panoramic and retroalveolar radiography, electrocardiography were examined.

To have an orientative examination of the haemostatic system, the examined patients were determined the bleeding time according to Duke and blood coagulation time according to Lee-White.

The effect of oral anticoagulants was assessed at admission and in dynamics through determination of INR values. Due to its pharmacological properties, aspirin, unlike indirect anticoagulants (thrombostop, warfarin, fenilin) does not require laboratory monitoring of coagulations [2]. Despite this fact in 5 patients who were administering aspirin, the anticoagulant effect was not estimated through assessment of INR values.

The mathematical processing of the study results was carried out by means of the statistical set of programs: EXCELL and STATISTICA. Obtained results were presented by the respective tables.

RESULTS AND DISCUSSIONS

Our studies have reported that of 38 patients undergoing antithrombotic therapy, the majority of patients (21 patients or 55,3%) were administered thrombostop, being followed by those who were receiving warfarin (9 or 23,7%), aspirin (5 patients or 13,1%) and fenilin (3 patients or 7,9%). The causes of administration of antithrombotic therapy

were the following : cardiosurgical interventions (valve prosthesis) - in 32 cases (84,2%); ischemic cardiopathies – in 4 (10,5%); thromboembolic case history – in 1 (2,6%); thrombophlebitis of the lower extremity – in 1 patient (2,6%).

Although multiple guides and recommendations on thromboprophylaxis are published, the way these recommendations are applied into the medical practice represents only a partially solved problem. Studies that have observed this aspect, suggest that pharmacological thromboprophylaxis is underutilized in 30-50% of patients with thromboembolic risk [3]. This fact was stated in the current study as well. Thus, after anamnesis taking it was stated that of 33 patients receiving oral anticoagulant therapy, in 11 (33,3%) patients the effect of these drugs was not monitored. Consequently during 2-3 months INR values were not estimated in 6 patients, between 4-6 months – in 3 patients and > 12 months in 2 patients.

Moreover, in the medical practice anticoagulant therapy interruption is frequently groundless. Thus, after history taking it was established that of 38 patients in 7 cases ($18,4 \pm 6,3\%$) the oral anticoagulant therapy was cancelled one day prior to dental extraction in order to prevent hemorrhage occurrence. In 4 (57,1%) cases the patient himself discontinued receiving the anticoagulant, in 2 (28,6%) cases the patients were recommended by the dentist to discontinue the therapy; in 1 case (14,3%) – the patient got the indication from the family doctor. Despite the fact that the duration of thrombostop effect after treatment interruption is 48-72 hours, unlike warfarin which has a longer effect duration (5-7 days) [1], we can state that interruption of these drugs one day prior to operation hasn't been justified, at least from the theoretical point of view. Postoperative wound bleeding having continued, patients required specialized medical assistance. At the same time it

should be recognized the fact that having groundlessly interrupted the anticoagulant therapy, these patients were exposed to a major thromboembolic risk.

Of those 38 examined patients positive hemorrhagic anamnesis was revealed in 33 cases ($86,8 \pm 5,9\%$, $p < 0,001$). It manifested by occurrence of bruises without any marked lesions in 19 (57.6%) patients, post-extractional dental hemorrhages in 7 (21,2%) patients, excessive menstrual hemorrhage in 4 (12,1%) cases. Hemorrhagipar syndrome was less frequent (9,1%), it manifested in the anamnesis by epistaxis, hemorrhage after periosteotomy and petechiae hemorrhages in places where clothes were tightly adherent to skin. Thus, clinical manifestations of hemorrhagipar syndrome, which previously had been recorded (within anamnesis) in patients following antithrombotic therapy, were marked by multiple symptoms of hemorrhagic character. At the same time, the most frequent symptom (in $57,6 \pm 8,6\%$ cases) recorded in these patients was occurrence of bruises without any evident lesions or after insignificant traumatism. It is necessary to mention the fact that negative hemorrhagic anamnesis was established in those 5 patients ($13,2 \pm 5,5\%$, $p < 0,05$) following antiplatelet (acetylsalicylic acid) therapy. Perhaps, this fact is due to different patients sensitiveness to aspirin. In this respect, the patients are divided into some groups according to their sensitiveness [15]: reactive (aspirine in dose of 0.5g diminishes aggregation by 50-40%); hyperreactive (aspirin inhibits the aggregation maximally or up to 80-90%)

and areactive (antiplatelet effect is absent). According to some sources it was established that only 20-25% of patients receiving antiplatelet drugs have abnormal bleeding time (a prolonged one) [16].

Initial evaluation of the haemostatic system was carried out through determination of the bleeding time according to Duke and the coagulation time according to Lee-White. Thus, of 38 patients, 36 ($94,7 \pm 3,6\%$) patients had bleeding time according to Duke within the limits of normal values (2-4 minutes). Only 2 patients ($5,3 \pm 3,6\%$) ($p < 0,001$) were suspected with alteration of the primary haemostasis through increase of the bleeding time (5 and 6 minutes), it being subsequently confirmed by decrease of the platelets count ($58,0 \cdot 10^9/l$ și $84,0 \cdot 10^9/l$). After having estimated the coagulation time according to Lee-White, it was stated that in 3 patients ($7,9 \pm 4,3\%$) the values of this test exceeded the upper limit of the norm (>12 minutes), INR being 4,6; 4,7 and 4,8. By means of these two tests, initially there were suspected, then confirmed marked disturbances in the primary vasculo-thrombocyte haemostasis (severe thrombocytopenia) and in the secondary haemostasis (overdosage of indirect anticoagulants).

In patients whose INR (at admission) was below the therapeutic range limits (< 2), the anticoagulant dose was individually increased (pre-extractionally as well) to prevent thromboembolic accidents. It was increased up to INR adjustment within the therapeutic limits. The results obtained from adjustment of dose of the oral anticoagulant therapy are presented in Tabel 1.

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	-	-	*

Tabel 1. INR values at admission and discharge in patients receiving oral anticoagulant therapy (n = 33) (p > 0,05 **** p < 0,001)*

The data from the tabel show that INR (at admission) $\leq 1,9$ was revealed in 15 patients ($45,5 \pm 8,7\%$). To reduce the risk of occurrence of the thromboembolic events, the anticoagulant dose was increased up to INR adjustment to the therapeutic range values (2,0-4,0). In 15 ($45,5 \pm 8,7\%$) cases INR was within the therapeutic range limits and anticoagulants dose was not modified. It was stated an overdosage of indirect anticoagulants in 3 patients ($9,1 \pm 5,0\%$). INR values at admission were 4.6-4.8. In patients with overdosage, the anticoagulant dose was reduced and subsequently kept within the therapeutic limits. There was one exception when the anticoagulant was cancelled by general physician's indication. In the result we have determined that after having been administered the individual anticoagulant dose, all the patients were discharged with INR within the limits of 2.0-3.5, that is within the therapeutic range limits. Thus, thromboembolic complications have been avoided, especially in patients hospitalized with INR values below the therapeutic limits.

Pre-extractional modification (increase) of the oral anticoagulant dose in

patients with INR (at admission) below the therapeutic range limits is reflected in the following clinical case.

Patient C.V., aged 57 years, medical card nr.21485, was admitted to the Department of OMF Surgery on November 18, 2008 complaining of presence of the root debris on the mandible on the left side which periodically caused painful sensations and discomfort; marked general weakness. From the anamnesis – painful dental sensations appeared 10-11 days prior to admission. The respective teeth were endodontically treated 8 years ago. As the patient stated and according to the data from the medical outpatient card in 2005 the patient had undergone a cardiosurgical intervention (mitral valve prosthesis) after which he received thrombostop (2mg/day). The last check-up of INR was done on March 15, 2007. Its values were 2.0. Thus, it was established that trombostop effect had not been monitored for one year, although at patient's discharge from MSPI Center of Heart Surgery, the patient was recommended by his physician to monthly assess INR and to keep it within the limits of 2,5-3,5. Objective examination: symmetrical face, pale-rose colour of the

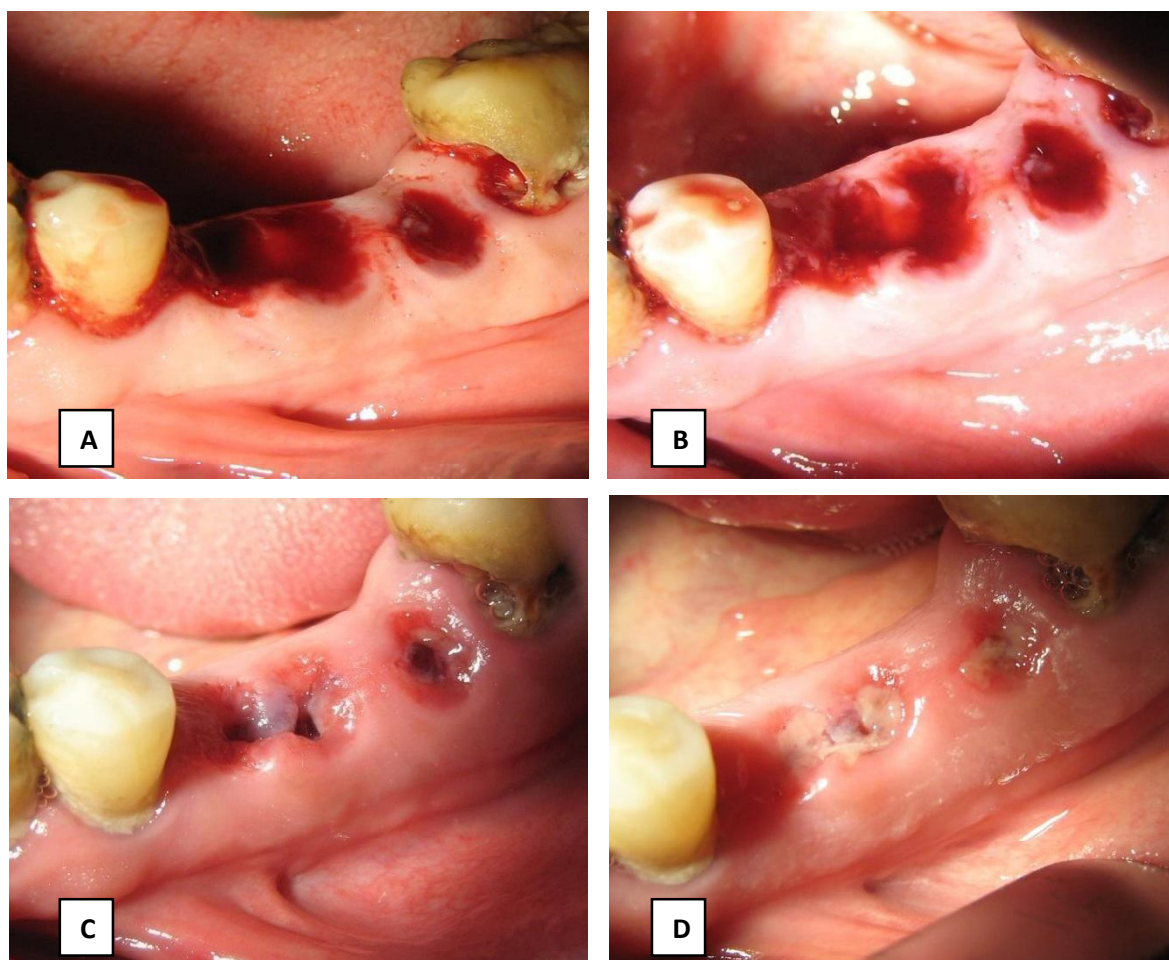
skin. The regional lymphatic nodes were not palpable. Mouth opened easily. The endobuccal examination revealed presence of the 35th, 36th teeth roots. They were not tender to percussion in the axis. They were immobile. Palpation of both slopes of alveolar apophysis of the 35th, 36th teeth was painless. The haemodynamic indices at admission: AP= 110/70 mmHg, puls = 78 b/min. Bleeding time according to Duke = 3 minutes, while the blood coagulation time according to Lee-White = 12 minutes. The patient was consulted by the internist. Orthopantomography revealed presence of oval, radiotransparent formations, with a well-defined contour around the 35th, 36th teeth apices, with a size of < 0,5 cm.

The diagnosis was established on the basis of the clinical and paraclinical examination: „Chronic granulomatous periodontitis of the 36th, 36th teeth. Rheumatic valvulopathy. Condition associated with mitral valve prosthesis (2005)”.

Due to absence of monitoring over the anticoagulant therapy and presence of the major risk both hemorrhagic and thromboembolic, venous blood was taken at admission to assess the indices of coagulogram. The following results were obtained: prothrombin index = 93%; fibrinogen = 2,4 g/l; TTPA = 37 sec.; thrombin time = 24 sec.; ethanol test was „negative”; INR = 1,10. While assessing respective indices it was observed the increase of prothrombin index (93%) and decrease of INR values (1.10) below the therapeutic limits. This suggested existence of the major risk of occurrence

of the thromboembolic events. This served as an indication for increase of thrombostop dose from 2 mg/day to 3 mg/day under a control in dynamics of INR.

The results of paraclinical analyses (general blood analysis) urine analysis, biochemical blood analysis) were within the limits of normal values. On November 19, 2008, at the INR level of 1.14, the extraction of the 35th, 36th teeth roots was carried out. Immediately the alveoli of the extracted teeth filled post-extractionally with blood which flowed on the bottom of the vestibular and lingual sac. Bleeding lasted for 30-40 sec. Its intensity was insignificant. The formation of the blood clot was post-extractionally assessed in the 3rd minute after transformation of the blood from liquid state into gel-like state (Picture 1.A). At the same time, it was observed that the newly formed clot was homogenous. Being at the level of the alveolus, the clot had a contact with the alveolus edges. In the 10th post-extractional minute there was observed the appearance of a light-red gingival line at the periphery compared with the dark-red colour from the clot center. Thus, it was stated that a scratchy clot had appeared. This coincided with its „migration” under the alveolar edge (Picture 1.B). Post-operative period lasted without any peculiarities: at inspection of the post-extractional wound, which was carried out 12 hours after the extraction, it was determined the presence of retracted blood clots (Picture 1.C). Restoration of the gingival integrity was practically recorded 36 hours after the extraction (Picture 1.D).



Picture 1. Blood clot formation and its appearance after the extraction of 35th, 36th teeth roots in patient C.V. receiving oral anticoagulant therapy (Thrombostop).

A – Blood clot formation in the 3rd post-extractional minute; B – Appearance of the scratchy clot and its position under the alveolar edge; C – Appearance of the post-extractional wound after 12 hours of extraction; D - Appearance of the post-extractional wound after 36 hours of extraction.

On November 21, 2008, after the increase of thrombostop dose, it was stated the restoration of INR within the therapeutic range limits (2,84). Thus, the patient was not subjected to risk of occurrence of the thromboembolic complications. The patient stated that his general weakness had disappeared. Perhaps, it was due to improvement of rheological properties of the blood after INR adjustment to therapeutic values. On November 22, 2008 the patient was

discharged, his general condition being satisfactory.

From those mentioned above we can conclude that when patients receiving oral anticoagulant therapy have INR values below the therapeutic range limits, the dose of these drugs can and must be increased (including pre-extractationally) to prevent the thromboembolic complications. Moreover, after assessment of the post-extractional dental haemostasis, the patient was found to have blood hypercoagulation which was evaluated by:

➤ short bleeding duration of the post-extractional dental wound (30-40 seconds) opposite the mean bleeding duration in patients with an uncompromised haemostatic system [17] ($1,2 \pm 0,2$ minutes);

➤ early formation of the blood clot (in the 3rd post-extractional minute) opposite the mean time of the blood clot formation in patients with an uncompromised haemostatic system [17] (in the $5.2 \pm 0,1$ minutes).

After dental extractions (34) performed on 26 patients under antithrombotic therapy it was stated the absence of BADE in the majority (18) of cases ($69,2 \pm 9,1\%$). Of those 18 patients, 14 (77.8%) received oral anticoagulants (thrombostop – 9 (64,3%), warfarin – 5 (35,7%)) and 4 patients (22,2%) received antiplatelet therapy (aspirin). INR values estimated on the day of dental extractions in patients receiving oral anticoagulants without BADE were within the following limits: INR = 2,0-2,6 was established in 6 (42,9%) cases, while INR < 1,9 – in 8 (57,1%) patients.

At the same time, it was observed absence of this contact in $30,8 \pm 10,2\%$ patients (8), in whom bleeding continued after 15-20 minutes. This condition was appreciated as BADE. This was a capillary bleeding. Its intensity was insignificant. Bleeding continued from the soft tissues through the space between the clot and the alveolus edge. Of 8 patients with BADE, 6(75,0%) received oral anticoagulant therapy (thrombostop – 4 (66,7%), warfarin – 2 (33,3%); one patient (12,5%) received antiplatelet therapy (aspirin) and one patient (12,5%) –

received both oral anticoagulant (thrombostop) and antiplatelet (aspirin) therapy. In patients with BADE receiving thrombostop and warfarin (7) INR values assessed on the day of the dental extractions were within the following limits: INR = 2,0-2,4 was established in 5 (71,4%) cases, while INR < 1,9 – in 2 (28,6%) patients. Although it is considered that blood coagulation increases in patients who are below the therapeutic range limits (INR < 2,0) [9], the analysis of the obtained data has proved that in 2 patients (28,6%) BADE appeared at INR values of 1,8 and 1,4. This phenomenon can be explained by the fact that in one clinical case appearance of BADE was conditioned by the simultaneous presence in the patient of thrombocytopenia (thrombocyte count was $84,0 \cdot 10^9/l$). In another clinical case it has been conditioned by associated antithrombotic therapy (thrombostop and aspirin) which significantly increases the risk of appearance of BADE [18].

Thus the presented data show that hemorrhagic accidents in patients receiving oral anticoagulant therapy can occur at any INR value. The frequency of this post-operative complication in patients under antithrombotic therapy subjected to dental extractions without cancellation of these drugs was $30,8 \pm 10,2\%$. It is necessary to mention that BADE which occurred at the level of INR values <2.4 was a capillary bleeding. Its intensity was insignificant. According to some studies, these hemorrhages are easily kept under control through local applications of human thrombin and aminocaproic acid of 5% [19]. At the same

time, it is necessary to mention that BADE occurring in patients who have had an overdosage of oral anticoagulants are extremely severe and can jeopardize people's health [9]. To prevent the severe hemorrhagic accidents in this group of patients, our study has proved that overdosage with indirect anticoagulants can be pre-extractionally assessed through determination of both INR values and time of the blood coagulation according to Lee-White. Some authors mention that the optimal value of INR for performing dental extractions is 2.5, because this limit reduces the risk of occurrence of both hemorrhagic accidents and thromboembolic events [20]. Despite this we consider that dental extractions can be successfully performed at the level of individual INR values recommended to the patients by the general physician. At the same time we are aware of the local haemostatic measures that should be undertaken and are necessary in order to control the bleeding.

Taking into consideration the increase of frequency and high lethality of thromboembolic complications, we think that the decision of modifying the anticoagulant therapy should be deliberated after a careful consideration of risk and benefit. In this respect, when INR value is higher than 4.0, the dental

extraction will be delayed and the dose of the anticoagulant will be reduced. Conversely, when INR values are below the therapeutic range limits, the dose of these drugs should be increased (including pre-extractionally) to prevent thromboembolic complications.

CONCLUSIONS

1. Assessment of INR is a compulsory method of pre-extractional evaluation of the effect of oral anticoagulants.

2. Patients under unmonitored anticoagulant therapy are exposed to an increased risk both hemorrhagic and thromboembolic.

3. Frequency of BADE in patients receiving antithrombotic therapy who undergo dental extraction without cancellation of these drugs constitutes $30,8 \pm 10,2\%$. These hemorrhages, at INR values $< 2,4$, have an insignificant intensity.

4. As a prophylactic measure in prevention of severe thromboembolic and hemorrhagic accidents the dose of the anticoagulant will be modified depending on INR.

5. Dental extraction in these patients can be performed without interruption of the anticoagulant therapy by maintaining INR within the limits of individual therapeutic values.

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