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Laboratory Predictors of Hemorrhagic Complications in Patients with Total Hip Arthroplasty and Treatment with Direct Oral Anticoagulants

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INTRODUCTION Direct oral anticoagulants (DOAC) rivaroxaban and apixaban have significantly reduced the risk of developing venous thromboembolic complications (VTEC). However, the use of DOAC may be associated with a higher risk of bleeding, especially actual in patients after total hip arthroplasty (THA).

MATERIAL AND METHODS We enrolled 38 patients with moderate osteoarthritis of the hip joints undergoing THA. The mean age of patients was 58 (33; 85) years. All the patients received rivaroxaban or apixaban in the doses specified by Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolic complications (VTEC). Retrospectively, in the postoperative period, the patients were divided into two groups: Group 1 — 31 patients (20 women and 11 men), who had no hemorrhagic complications after hip replacement; and Group 2 — 7 patients (4 women and 3 men) who experienced hemorrhagic events in the form of hematomas in the wound area.

Laboratory tests were performed for all patient baseline (1st day of hospitalization), after surgery (1st day after THA), and on the 7th day after THA. Analyses included the determination of hemostasis parameters (INR, aPPT, fibrinogen, D-dimer), hematological (HGB, PLT, RBC) and biochemical parameters (calcium, ionized calcium, serum iron, hs-CRP).

RESULTS The analysis of biochemical parameters in patients with hemorrhagic complications revealed a significant increase of fibrinogen (p=0,023) compared with uncomplicated cases. Serum iron concentration in men with hemorrhagic complications in the postoperative period was significantly lower than in patients without complications. In patients with hemorrhagic complications, the ionized calcium was lower (p=0,032) than in patients without complications, but within the reference values. The hs-CRP concentration in the group with hemorrhagic complications was twice higher than in the group without complication and eight times above the reference values.

CONCLUSION The concentration of iron in the blood serum in men below 11 mmol/l and a slight hyperfibrinogenemia of 4.65 g/l in all the patients are the risks of developing hematomas in the area of surgery. These parameters should be used to predict the risk of hemorrhagic complications in patients before THA and recommended for control before the surgery and on the 1st day after THA (hs-CRP).

Keywords: rivaroxaban, apixaban, total hip arthroplasty, hemostasis, bleeding

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APTT—activated partial thromboplastin time
CRP - C-reactive protein
GFR - glomerular filtration rate
INR - international normalized ratio
PJI - periprosthetic joint infection
THA – total hip arthroplasty
VTEC - venous thromboembolic complications

INTRODUCTION

Large joint replacement may carry risks of various negative consequences, including both hemorrhagic and venous thromboembolic complications (VTEC) [1–4].

Total hip arthroplasty is often accompanied by significant perioperative blood loss, reaching an average of 670–1040 ml [5]. At the same time, prevention of thromboembolic complications using new oral anticoagulants also carries a risk of bleeding. Taking anticoagulants to prevent venous thromboembolism in patients undergoing total hip arthroplasty (THA) during inpatient and outpatient stages can lead to the development of hemorrhagic complications.

The pharmacodynamic features of modern oral anticoagulants - rivaroxaban and apixaban - are that their maximum plasma concentrations are quickly reached, they inhibit factor Xa and are its direct and reversible inhibitors, and are also characterized by a fairly high bioavailability from 50% (apixaban) to 80–100 % (rivaroxaban), and half-lives of 8–15 hours and 5–13 hours, respectively [6]. Despite the advantages of new oral anticoagulants, the use of these drugs in patients with decreased renal function is not recommended due to the risk of bleeding. According to T.A. Zhirovoy (2014), in the group of patients after endoscopic surgery who took rivaroxaban to prevent VTEC, bleeding occurred in 3% of cases [1].

In addition, hematoma formation in the area of surgical intervention is one of the factors causing the occurrence of periprosthetic joint infection (PJI) [7]. A.A. Myasoedov et al. [8] showed a correlation of PJI development with the duration (more than 95 min) and injury rate of the surgical intervention; and, accordingly, the volume of blood loss (more than 410 ml), initially low hemoglobin levels and high body mass index [8].

According to some authors, the development of hemorrhagic complications at the site of the surgical wound in the form of a wound hematoma is 4.5% [5], and profuse bleeding during operations is 3.2% [9].

Despite the improvement of arthroplasty techniques, the use of modern pharmacological agents and adequate anesthesiological support, the risk of developing hemorrhagic complications continues to this day [10]. According to I.P. Antropova (2011), this is due to tissue damage during surgery, features of bleeding from cancellous bone and the medullary canal, and hypocoagulative shifts in the hemostatic system [10].

Therefore, it is advisable to assess the risk of developing hemorrhagic complications in patients taking new oral anticoagulants after endoscopic surgery using laboratory markers, which are determined during the period of preparation for surgery.

Aim: to determine laboratory predictors of the risk of bleeding in patients after total hip arthroplasty (THA) while taking oral anticoagulants.

MATERIAL AND METHODS

The study included 38 patients who stayed in the traumatology and orthopedics clinic of the North-Western State Medical University named after I.I. Mechnikov and underwent elective THA due to stage III osteoarthritis. The average age of the patients was 58±15 (33; 85) years.

Upon admission to the hospital and before undergoing elective THA, all patients underwent a clinical and laboratory examination.

On the first day after surgery, patients received direct inhibitors of coagulation factor Xa: rivaroxaban (10 mg 1 time / day) or apixaban (2.5 mg 2 times / day) for 5 weeks in accordance with the Russian clinical guidelines for diagnosis, treatment and prevention of VTEC (2015) [11].

Retrospectively, in the postoperative period, the patients were divided into two groups: group 1 - 31 patients (20 women and 11 men) who had no hemorrhagic complications after THA, and group 2 - 7 patients (4 women and 3 men) who experienced hemorrhagic events in the form of hematomas in the wound site.

All the patients underwent laboratory tests before surgery (baseline), after surgery (on the 1st day of taking the anticoagulant), and before discharge (10th day after surgery). The laboratory testing included determination of the state of hemostasis (international normalized ratio, INR; activated partial thromboplastin time, APTT; fibrinogen, D-dimer) on a STA-Compact analyzer (Stago, France). Biochemical parameters in the blood (total calcium; ionized calcium; serum iron; C-reactive protein, CRP; creatinine) were studied on a COBAS Integra 400plus analyzer (Roche, Switzerland) with the appropriate sets of reagents. Clinical blood analysis was carried out on a DxH-800 analyzer (Beckman Coulter, USA) with the calculation of erythrocyte and platelet indices.

To assess the effectiveness of anticoagulant therapy in the blood plasma of patients, the concentration of rivaroxaban and apixaban was determined using an ACL TOP 500CTS analyzer (Werfen, USA) on the 1st day after surgery and at discharge. All procedures were carried out according to the corresponding instructions for the kits and analyzers. The residual anticoagulant effect of direct factor Xa inhibitors (rivaroxaban and apixaban) was assessed by drug concentration in blood plasma. The effectiveness of action was judged by the maximum concentration (Cmax) of the drug in plasma (blood was drawn at the moment the expected maximum concentration was reached). Simultaneously, renal function was assessed by glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease Study) formula [12].

Statistical data was processed using the Jamovi software. Numerical values are presented as median Me (25; 75)%. The Friedman test was used to compare related quantitative indicators. Correlations between indicators were determined using Spearman's rank correlation coefficient. Differences were considered statistically significant at $p<0.05$. ROC analysis was performed on the identified variables to determine a prognostic cutoff point. The diagnostic value of the tests was determined using the likelihood ratio (LR). LR(+) shows how many times more often positive results of a given diagnostic test are detected in patients than in healthy people. If the positive likelihood ratio value was more than 100, the probability was defined as “extremely high”, 33–100 as “excellent”, 10–33 as “good”, 3–10 as “satisfactory”, 1–3 as “unsatisfactory”. LR(–) shows how many times less often negative results of a given diagnostic test are found in patients than in healthy people: with a negative likelihood ratio value of 1 to 0.3, the probability was considered “unsatisfactory”, 0.3–0.1 - “satisfactory” ", 0.1–0.03 “good”, 0.03–0.01 - “excellent”, less than 0.01 - “extremely high” (Y.R. Magnus, 2004).

RESULTS AND DISCUSSION

On the first day after THA, the average Cmax of rivaroxaban in the blood plasma was 122.4 ng/ml (94; 178), and at discharge - 186.47 (152.8; 239) ng/ml; in patients receiving apixaban - 60.3 (14; 95.2) ng/ml, and 79.85 (14; 196.4) ng/ml, respectively. These anticoagulant concentrations corresponded to therapeutic intervals. Simultaneously, creatinine and GFR values were assessed before surgery (Table 1) and at discharge, and they were within the reference values, which, together with adequate therapeutic doses of rivaroxaban and apixaban, was regarded as an effective and, at the same time, safe use of direct oral anticoagulants.

Table 1

Biochemical parameters of patients before elective hip replacement, taking into account subsequent development of hemorrhages

Indicator and reference interval		Group 1 (no complications)	Group 2 (with complications)	*p*
INR (0.85–1.2)		1.00 [0.98; 1.06]	0.97 [0.97; 0.99]	0.192
APTT, sec (25–33)		31.2 [29.6; 33.9]	30.5 [28.9; 31.9]	0.275
Fibrinogen, g/l (2–4)		3.67 [3.44; 4.32]	5.18 [4.05; 5.85]	0.023
D-dimer, μg/ml (0–0.5)		0.18 [0.137; 0.257]	0.32 [0.191; 0.512]	0.181
Ca, mmol/l (2.2–2.7)		2.42 [2.34; 2.49]	2.34 [2.33; 2.46]	0.624
Ca^{2+}, mmol/l (1.12–1.32)		1.30 [1.28; 1.32]	1.27 [1.25; 1.28]	0.032
Fe, μmol/l (M - 10.6–28.3; F - 6.6–24.6)	females	12.6 [9.13; 17.6]	9.30 [8.95; 11.7]	0.514
	males	17.1 [13.7;21.2]	9.00 [8.03; 11.0]	0.043
CRP, mg/l (0–5)		2.9 [2.16; 4.51]	4.66 [2.1; 5.22]	0.679
Creatinine, μmol/l (M—62–115; F—44–97)	females	75.3±10.3	75.5 [68.5; 120]	0.850
	males	74 [69; 91.5]	73.7±7.02	0.732
GFR, ml/min (80–120)	females	73.5±12.7	65±32.3	0.399
	males	92.9±27.8	102±15.6	0.602

Notes: APTT — activated partial thromboplastin time; INR — international normalized ratio; GFR — glomerular filtration rate; CRP - C-reactive protein

Thus, patients after orthopedic surgery received effective and safe anticoagulant therapy.

During retrospectively dividing patients into two groups depending on the development of hemorrhagic complications, a comparison was made of the initial biochemical, including some markers of hemostasis, and hematological parameters.

In most patients before surgery, laboratory parameters were within the reference values, with the exception of 11 patients who had a slight increase in fibrinogen blood levels - up to 5.85 g/l; three male patients who had a decrease in serum iron levels in the blood; and one woman with a decrease in hemoglobin concentration (110 g/l). When retrospectively divided into two groups, 11 patients with elevated initial fibrinogen levels were distributed so that 7 patients were in group 1 (without complications), and 4 patients were in group 2 (with complications). One patient with initially low iron levels in the blood was included in group 1, and 2 men were included in group 2. Only in one observation before surgery, the hemoglobin level was below the reference interval (group 2).

When analyzing biochemical parameters (Table 1), patients in group 2 revealed a statistically significant increase in fibrinogen concentration ($p = 0.023$) compared to group 1, in whom hemorrhagic complications were not observed in the postoperative period. A slight increase in fibrinogen in patients before surgery may have been due to inflammatory processes associated with concomitant diseases.

Serum iron concentration in male patients with hemorrhagic events (group 2) in the postoperative period was statistically significantly lower than in patients of group 1. There were no statistically significant differences in this indicator among women.

Statistically significant changes in the level of ionized calcium (Ca2+) were also established. In patients of group 2, its concentration was statistically significantly lower ($p = 0.032$) than in patients of group 1, but within the reference values.

Therefore, among patients who underwent elective THA and subsequently developed hemorrhagic complications, there was a decrease in serum iron levels in men, and an increase in fibrinogen concentration in all the group. Despite the statistically significant increase in the content of ionized calcium in the blood, this indicator cannot be prognostically significant, since its value was within the reference interval.

To increase the predictive value of laboratory parameters in assessing the risk of bleeding before surgery, ROC analysis was performed with ROC curve constructing, calculating the area under the curve (AUC) and likelihood ratio (LR) for serum iron and fibrinogen.

For serum iron concentration in men, the diagnostic criterion between patients with and without complications was determined to be a “cutoff” level below 11 μmol/l with a sensitivity of 85.7%, specificity of

99%, area under the curve of 0.939 and a likelihood ratio LR(+) of 85 .7 and LR(–) 0.14. Serum iron deficiency in men before surgery is, therefore, a significant factor for the development of hemorrhagic complications in the postoperative period after THA.

The diagnostic value of fibrinogen levels in the patients was determined above 4.65 g/l with a sensitivity of 57.1%, specificity of 87.1%, area under the curve of 0.728 and likelihood ratios LR(+) 4.43 and LR(–) 0.49. Hyperfibrinogenemia, in our opinion, should be considered as an additional criterion for including patients at risk for developing complications after the surgery.

When analyzing hematological parameters, no statistically significant differences were found between the 1st and 2nd groups. Although it is noteworthy that in group 2 the average hemoglobin concentration in women was slightly lower than the reference values.

Thus, it has been established that in hospitalized patients before the surgery it is necessary to carry out laboratory monitoring of the concentration of serum iron in the blood in men and the level of fibrinogen in all the patients. Attention should be paid to both the decrease in fibrinogen concentration as a marker of hypocoagulation, and its increase due to concomitant chronic inflammatory diseases. According to a number of authors, concomitant cardiovascular diseases (49%), obesity (31%), diabetes mellitus (47%) and gastrointestinal pathology (67%) are quite common in patients with osteoarthritis [13, 14]. In 90% of geriatric trauma patients, there was a combination of several chronic diseases, mainly pathology of the cardiovascular system (arterial hypertension - 73%, coronary heart disease - 46.7%), diseases of the digestive system (55%), etc. [14].

When analyzing laboratory parameters in two groups of patients after surgery (Table 2), statistically significant differences were revealed between the 1st group of patients without complications and the 2nd group with the development of complications by similar indicators (the content of fibrinogen and serum iron in the blood in men), as well as by the level of CRP in the blood. In patients of group 2 with complications, the concentration of CRP was 2 times higher than in group 1 (without complications) and 8 times higher compared to reference values.

Table 2

Biochemical and hematological parameters of patients after elective hip replacement, taking into account subsequent development of hemorrhages

Indicator and reference interval		Group 1 (no complications)	Group 2 (with complications)	*p*
INR, (0.85–1.2)		1,20 [1,06; 1,46]	1,15 [1,13; 1,21]	0,559
APTT, sec (25–33)		32,2 [30,3; 33,5]	29,6 [29,5; 33,9]	0,940
Fibrinogen, g/l (2–4)		5,85 [5,05; 6,38]	7,64 [7,37; 8,79]	0,001
D-dimer, μg/ml (0–0.5)		2,54 [1,85; 3,77]	1,62 [1,25; 2,5]	0,192
Ca, mmol/l (2,2–2,7)		2,23 [2,16; 2,34]	2,27 [2,17; 2,29]	0,940
Ca^{2+}, mmol/l (1.12–1.32)		1,25 [1,21; 1,27]	1,23 [1,21; 1,25]	0,575
Fe, μmol/l (M - 10.6–28.3; F - 6.6–24.6)	females	8,90 [6,42; 9,85]	4,20 [3,45; 5,45]	0,056
	males	9,1 [7,15; 10,9]	5,35 [4,63; 6,13]	0,048
CRP, g/l (0–5)		21,5[12,1; 29,8]	41,3 [31,7; 69,9]	0,001
PLT, 109/ l (150–450)		193 [182; 220]	207 [194; 280]	0,346
MPV, fl (7.4–10.4)		8,1 [7,85; 8,55]	8,5 [7,8; 8,75]	0,597
RBC,10^{12}/ l (M – 4–5; F – 3.7–4.7)	females	3,65 [3,30; 4,08]	3,48 [3,34; 3,58]	0,222
	males	3,67 [3,32; 4,11]	3,55 [3,17; 3,95]	0,947
HGB, g/l (M—130–160; F—120–140)	females	106 [99,5; 116]	105 [100; 106]	0,477
	males	109 [101; 108]	106 [99,5; 111]	0,716

Notes: APTT – activated partial thromboplastin time; INR —international normalized ratio; CRP – C-reactive protein; PLT—platelet count; MPV—mean platelet volume; RBC - red blood cell count; HGB - hemoglobin concentration

The patients showed decrease in hemoglobin concentration and the number of red blood cells on the first day after surgery, due to blood loss during surgery [5, 15].

There were no statistically significant deviations in hemostasis between the groups and in comparison with reference intervals, except for fibrinogen, the increase of which is associated with the traumatic nature of the surgery [8, 10, 16].

Thanks to laboratory-confirmed effective and safe anticoagulant therapy, no venous thromboembolism or profuse bleeding was observed in the patients in the postoperative period; wound hematomas were verified in only 7 patients, which confirms the need to assess the risks of hemorrhages using laboratory tests.

CONCLUSIONS

1. It has been established that a serum iron concentration below 11 μmol/l in men is an important criterion for including the patient at risk of developing hematomas in the site of surgical intervention; and fibrinogen levels above 4.65 g/l should be considered as an additional indicator for monitoring the patient's condition to exclude the occurrence of hemorrhagic complications.
2. It is recommended to monitor these indicators before surgery (fibrinogen and serum iron levels in men) and on the first day after surgery (C-reactive protein content in the blood).

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