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Research Article

Role of Rivaroxaban and Apixaban in Hip Replacement

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Abstract

Introduction: Direct oral anticoagulants significantly reduce the risk of venous thromboembolic complications. However, in some cases in patients with latent hemostasis disorders, the use of drugs of this group (most often rivaroxaban and apixaban) may be accompanied by an increased risk of postoperative bleeding after hip arthroplasty.

Materials and Methods: 38 patients were under observation, from the clinic of traumatology and orthopedics of the North-western State Medical University named after I.I. Mechnikov, Saint Petersburg, in connection with the planned hip replacement for osteoarthritis. The average age of patients was 58 ± 15 (33; 85) years. Depending upon the anticoagulant taken, patients were divided into 2 groups. The first group - 25 patients receiving rivaroxaban and the second - 13 patients - apixaban. All patients underwent laboratory tests before surgery (baseline), on the first day after surgery (while taking anticoagulant) and on the 7th day after surgery. The laboratory study included determination of hemostasis parameters (INR, APTT, Fibrinogen, D-dimer) on the STA Compact analyzer (Stago, France), biochemical parameters (total calcium, ionized calcium, serum iron, C-reactive protein) on the COBAS Integra 400plus analyzer and hematological parameters on the LH-500 analyzer (Beckman Coulter, USA).

Results and Discussion: When evaluating biochemical parameters, patients in both groups had statistically significant decreases in total calcium, ionized calcium, serum iron after surgery compared with baseline data. At the same time, the concentration of C-reactive protein was significantly increased in both groups. Patients treated with rivaroxaban showed a statistically significant increase in INR ($p < 0.05$) in contrast to the group of patients treated with apixaban. After surgery, patients treated with rivaroxaban and apixaban showed a significant increase in fibrinogen and D-dimer concentrations.

Conclusions: The use of direct oral anticoagulants after hip replacement is not accompanied by hemorrhagic complications. The evaluation of plasma concentrations of apixaban and rivaroxaban demonstrated the efficacy of anticoagulant effects of direct coagulation factor Xa inhibitors and proved the need for their use in the prevention of thrombotic complications in patients after hip arthroplasty.

Keywords: Hip Replacement; Direct Anticoagulants; Rivaroxaban; Apixaban; Bleeding

Introduction

In developed countries, there is an annual increase in the number of hip replacement operations. Now more than 1 million such interventions are carried out annually [1-3]. In the Russian Federation, the need for endoprosthesis of major joints is about 300 thousand [4]. At the current level of demand, 113,220 hip and knee arthroplasty operations were performed in the Russian Federation in 2017 [5]. Complications of hip replacement, according to different authors, range from 2 to 27% [6,7,16].

Thromboembolic disease occupies a special place in the structure of arthroplasty complications. Venous thromboembolic complications of varying severity are verified in 40-60% of patients after hip replacement [8,9]. Pulmonary embolism after hip replacement is 2-20%, and mortality rates are 0.7-4% of cases [4,10,11].

Anticoagulant therapy is the most important component in the prevention of thrombotic and thromboembolic complications in patients undergoing hip replacement. At the same time, hip arthroplasty may be accompanied by the development of postoperative bleeding and hematomas in 0.7-4.3% of cases [12]. Direct inhibitors of coagulation factors for oral administration, developed and implemented in everyday clinical practice in recent decades, significantly reduce the risk of venous thromboembolic complications [13,15]. However, in some cases, in patients with latent hemostasis disorders, the use of direct oral anticoagulants may be accompanied by an increased risk of postoperative bleeding and hematomas after hip arthroplasty.

Materials and Methods

The study was conducted in 38 patients who were being treated in the clinic of traumatology and orthopedics of the Northwestern State Medical University named after I.I. Mechnikov, Saint Petersburg Russia. All these patients underwent a planned hip replacement due to osteoarthritis. The average age of patients is 58 ± 15 [33; 85] years. Depending on the anticoagulant taken, 2 groups were formed. The first included 25 patients treated with rivaroxaban; the second was formed by 13 patients in whom apixaban was used. Laboratory tests were performed at baseline (before surgery), on the first day after the intervention (while taking anticoagulant) and on the 7th day after hip replacement. The following parameters were studied: hemostasis parameters (INR, APTT, Fibrinogen, D-dimer) on the STA Compact analyzer (Stago, France), biochemical parameters (total calcium, ionized calcium, serum iron, C-reactive protein) on the COBAS Integra 400 plus analyzer and hematological parameters on the LH-500 analyzer (Beckman Coulter, USA).

On the ACL TOP 500CTS analyzer (Werfen, USA), the concentrations of rivaroxaban and apixaban were determined in plasma on Day 1 after surgery and at discharge. All procedures were carried out according to the relevant instructions for the kits and analyzers.

All examined individuals gave voluntary informed consent to participate in the study.

Statistical processing of the data was carried out using the Jamovi statistical program. Numerical values are presented as median Me, 25 and 75 percentiles. The Friedman test was used to compare the associated quantitative measures. Correlations between the parameters were determined by Spearman. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Comparative characteristics of oral direct inhibitors of coagulation factors: rivaroxaban and apixaban are given in table 1.

The advantage of rivaroxaban is its single dose, which contributes not only to patient adherence to treatment, but also to increase the safety of pharmacotherapy in relation to the development of bleeding [13].

Upon admission to all patients, a clinical and laboratory examination was carried out. In all patients, laboratory hemostasis parameters, hematological and biochemical markers were within the reference values, except for fibrinogen, the concentration of which in group 2 was higher than 4.53 [3.05; 4.93] g/L (Table 2).

In order to prevent venous thromboembolic complications, all patients received rivaroxaban or apixaban at the recommended doses after surgery. The blood concentration of the drugs was determined on the day of admission, on the 1st day after arthroplasty and on the 7th day after surgery.

The residual anticoagulant effect of direct factor Xa inhibitors (rivaroxaban and apixaban) was assessed by determining the plasma concentration of the drug. The efficacy of the action was evalu-

Parameters to be studied	Rivaroxaban	Apixaban
Target protein	Factor Xa	Factor Xa
Reception rate	Once daily	Twice daily
Bioavailability	80%	50%
Peak Concentration Time	2,5-4 hours	3-4 hours
Approximate half-life	5-9 hours (9-13 hours in elderly)	8-15
Metabolism/Excretion	Cytochrome R-450 (30%) and P-glycoprotein transporter/33% kidney excretion	Cytochrome R-450 (15%) and P-glycoprotein transporter/27% kidney excretion
Drug interactions	With inhibitors and inducers of P-glycoprotein; CYP 3A4- CYP 2J2 inhibitors	With inhibitors and inducers of P-glycoprotein; CYP 3A4- CYP 2J2 inhibitors
Dose monitoring	If necessary - by anti-Xa activity test	If necessary - by anti-Xa activity test

Table 1: Comparative characterization of oral direct coagulation factor inhibitors.

Parameter and reference intervals	Group 1-Rivaroxaban 2-Apiksaban	Outcome (on admission)	1st day after surgery	7th day after surgery
INR (0.85-1.2)	Group 1	1.00[0.98;1.06]	1.33[1.13;1.53]*	1.19 [1.07;1.37]**
	Group 2	1.00[0.95;1.04]	1.11[1.05;1.14]	1.15[1.00;1.22]
Activated partial thromboplastin time, sec. (25-33)	Group 1	31.5[30.8;33.1]	33[31.0;34.0]	33[31.3;34.7]
	Group 2	29.6[28;32.2]	30.2[28.7;32.9]	33.4[31.3;40.5]**/***
Fibrinogen, g/L (2-4)	Group 1	3.78[3.59;4.05]	5.85[5.08;6.46]*	4.97[4.74;5.99]**/***
	Group 2	4.53[3.05;4.93]	6.14[5.4;6.21]*	6.46[4.78;7.42]**
D-dimer, μg/mL (0-0,5)	Group 1	0.19[0.15;0.25]	2.54[1.96;3.71]*	1.33[0.91;2.11]**/***
	Group 2	0.18[0.09;0.34]	3.03[1.17;4.26]*	1.12[0.67;1.81]**/***

Table 2: Indicators of the hemostasis when taking direct inhibitors of blood clotting factor Xa.

Note:

* - significant differences between the outcome and 1 day after surgery ($p < 0.05$);

* * - reliable differences between the outcome and 7 days after surgery ($p < 0.05$);

* * * - reliable differences between 1 and 7 days after surgery ($p < 0.05$);

ated according to the maximum concentration (Cmax) of the drug in plasma (blood was taken at the time of reaching the estimated maximum concentration). In patients treated with rivaroxaban, on the first day after hip replacement in plasma, the mean Cmax of rivaroxaban was 122.4 ng/mL [94; 178] and at discharge -186.47 [152.8; 239] ng/mL, which corresponded to therapeutic intervals. In patients treated with apixaban on the first day after hip replacement in plasma, the mean Cmax of apixaban was 60.3 [14; 95.2] ng/mL; at discharge - 79.85 [14; 196.4] ng/mL, respectively, which also corresponded to therapeutic intervals.

After surgery, hemostasis parameters in patients (Table 2) treated with rivaroxaban and apixaban showed a significant increase in fibrinogen and D-dimer concentrations from baseline due to surgery. Patients treated with rivaroxaban showed a statistically significant increase in INR ($p < 0.05$) compared to the group of patients treated with apixaban. However, according to various authors, there is no unified coagulation test that indicates the effectiveness of the anticoagulant activity of rivaroxaban or apixaban [14].

Before discharge, D-dimer significantly decreased in both groups, but did not reach the reference intervals, while fibrinogen and APTT in patients treated with apixaban remained high. The increase in fibrinogen as an acute phase protein may be due to the inflammatory process. Thus, in patients taking apixaban, the inflammatory response did not decrease during therapy.

When evaluating biochemical parameters (Table 3), patients in both groups had statistically significant decreases in total calcium, ionized calcium and serum iron after surgery from baseline. At the same time, the concentration of C-reactive protein was significantly increased in both groups. Before discharge, all biochemical parameters changed towards the initial data, however, the concentration of C-reactive protein in patients treated with apixaban remained high, while in patients treated with rivaroxaban it decreased compared to the value immediately after surgery. Thus, in the group of patients treated with apixaban, the index characterizing inflammation was also higher than in the 1st group.

Parameter and reference intervals	Group 1-Rivaroxaban 2-Apiksaban	Outcome (on admission)	1st day after surgery	7th day after surgery
Total calcium, mmol/L (2.2-2.7)	Group 1	2.39[2.32;2.45]	2.19[2.16;2.29]*	2.31[2.27;2.41]**/***
	Group 2	2.43[2.42;2.51]	2.26[2.22;2.34]*	2.27[2.20;2.33]**
Ionized calcium, mmol/L (1.12-1.32)	Group 1	1.30[1.28;1.32]	1.24[1.21;1.26]*	1.27[1.24;1.29]**/***
	Group 2	1.29[1.28;1.32]	1.26[1.25;1.27]*	1.26[1.18;1.28]**
Serum iron, µmol/L (M-10.6-28.3 F-6.6-24.6)	Group 1	15.4[9.65;17.8]	9.1[7.8;11.8]*	12.4[10.5;14.9]***
	Group 2	10.4[7.5;13.3]	6.7[5.3;8.7]*	9.1[6.2;9.4]
C-reactive protein, mg/L (0-5)	Group 1	3.15[2.14;4.66]	26.4[15.4;30.8]*	14.2[7.38;19.9]**/***
	Group 2	2.9[2.21;5.03]	13.5[12.2;20.2]*	15.43[6.38;24.8]**

Table 3: Biochemical parameters when taking direct inhibitors of blood clotting factor Xa.

Note:

* - significant differences between the outcome and 1 day after surgery ($p < 0.05$);

* * - reliable differences between the outcome and 7 days after surgery ($p < 0.05$);

* * * - reliable differences between 1 and 7 days after surgery ($p < 0.05$).

Analysis of hematology parameters (Table 4) revealed a significant decrease in red blood cell count and hemoglobin (Hb) concentration immediately after surgery compared with baseline data in patients of both groups. In patients treated with rivaroxaban, platelet count and mean platelet volume (MPV) decreased significantly, while in patients treated with apixaban, these indicators did not significantly change after surgery. Before discharge, the number of red blood cells and hemoglobin concentration increased, but remained below the reference values. Before discharge, platelet count (PLT) and mean platelet volume (MPV) were restored to baseline values in both groups. Thus, patients in both groups showed signs of anemia (low hemoglobin and red blood cell count) before discharge.

It should be noted that in patients treated with apixaban, in addition to changes in hematological parameters, there were signs of inflammation. This group of patients required more attention than Group 1 patients.

Conclusions

Thus, new oral anticoagulants for the prevention of venous thromboembolic complications - rivaroxaban and apixaban according to the selected dosing regimens provided a favorable risk-benefit ratio during the therapy of patients after orthopedic surgery, which is confirmed by the authors about the efficacy and safety of these anticoagulants. Both drugs showed high efficacy and safety

Parameter and reference intervals	Group 1-Rivaroxaban 2-Apiksaban	Outcome (on admission)	1st day after surgery	7th day after surgery
Red Blood Cell count, RBC,10^12/L (M-4-5 F-3, 7-4,7)	Group 1	4.68[4.21;4.89]	3.67[3.31;4.16]*	3.74[3.49;4.26]**
	Group 2	4.64[4.31;4.66]	3.36[3.22;3.69]*	3.71[3.45;4.51]**/***
Hemoglobin concentration, Hb,g/L (M-130-160 F-120-140)	Group 1	133[129;144]	109[102;118]*	113[104;124]**
	Group 2	127[125;133]	95[92;113]*	112[97;127]**
Platelet count, PLT,10^9/L (150-450)	Group 1	230[203;264]	200[184;207]*	237[204;298]***
	Group 2	267[227;307]	218[191;280]	263[227;281]
MPV, fL (7,4-10,4)	Group 1	8.9[8.5; 9.4]	8.2[7.5; 8.3]*	8.6[7.6;8.9]**
	Group 2	8.5[8.0;8.8]	8.2[7.6;8.3]	8.4[7.4;8.9]

Table 4: Indicators of a clinical blood test when taking direct inhibitors of blood clotting factor Xa.

Note:

* - significant differences between the outcome and 1 day after surgery ($p < 0.05$);

* * - reliable differences between the outcome and 7 days after surgery ($p < 0.05$);

* * * - reliable differences between 1 and 7 days after surgery ($p < 0.05$).

in the development of bleeding. However, according to the results of our study, patients treated with apixaban had higher inflammation rates than patients treated with rivaroxaban. In our opinion, rivaroxaban is preferable to patients after surgery due to its proven efficacy and safety, as well as a single dose convenient for patients.

When using rivaroxaban and apixaban in patients after hip replacement, no hemorrhagic complications were observed. The evaluation of plasma concentrations of apixaban and rivaroxaban demonstrated the efficacy of anticoagulant effects of direct coagulation factor Xa inhibitors and proved the need for their use to prevent thrombotic complications at their high risk in patients after orthopedic surgery.

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