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ORIGINAL PAPER

THROMBO-PROPHYLAXIS IN TOTAL HIP ARTHROPLASTY USING ORAL ANTI-THROMBOTICS ANTICOAGULAT – RIVAROXABAN

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Abstract. Rivaroxaban, a novel anti-thrombotic drug, has been described as having a highly potent activity on the coagulation mechanism, due to its reversible inhibiting action on the central point of the coagulation cascade, Factor Xa. Published studies reveal some advantages of Rivaroxaban compared to previously used anti-thrombotics: it is orally administered and rapidly absorbed and it allows a fixed dose regimen as its pharmacokinetic and pharmacodynamic profile is predictable. Having similar cardiovascular and hepatic side effects to other anti-thrombotic drugs and a low risk of bleeding, as shown by the published studies, Rivaroxaban can be considered well tolerated and effective in prevention of thrombembolic events. The authors present some aspects regarding their experience with this drug used in thrombo-prophylaxis following hip arthroplasty, a high thrombo-embolic risk procedure with increasing frequency in modern orthopedics. The results of this prospective study –post-operative blood loss, the incidence of thrombo-embolic events, side effects confirm the data presented in literature regarding the efficacy and safety of Rivaroxaban in major orthopedic surgery.
Keywords: hip arthroplasty, thrombo-prophylaxis, oral anti-thrombotics, Rivaroxaban

Introduction

Thrombo-Embolic Disease (TED) including Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE) as well as their complications, Post-Thrombotic Syndrome (PTS) and Pulmonary Hypertension (PHT) represent a major cause of morbidity and mortality in modern medicine. Compared to the situation some decades ago, the interest for preventing Thrombo-Embolism (TE) significantly increased as studies revealed that it can occur after any type of pathology, regardless the organ involved.

Venous Thrombosis is based on an abnormal activation of the coagulation cascade, which has several steps; that is why research has been oriented towards finding drugs effective in different steps of this cascade to be used treatment and especially in thrombosis prophylaxis[1] .As major orthopedic surgery is unanimously recognized as having a high thrombo-embolic risk, thrombo-prophylaxis is of particular interest for the physicians involved in this activity, surgeons and anesthetists, as well. After arthroplasty (hip, knee), the current standard is nowadays represented by Low Molecular Weight Heparins (LMWH), replacing the "classical". Unfractioned Heparine (UFH) nowadays used mainly in the treatment of TE, and less in prophylaxis, due to its numerous side effects (most of them balanced when LMWH are used).[2] Also indicated by the guides, Fondaparinux sodium, which indirectly affects Factor Xa, has been suggested to proved to have a high risk of bleeding; as for the Vitamin K Antagonists (VKA), they have some inconvenients :non-specific mechanism of action, slow onset and offset of the anticoagulating activity, and a narrow therapeutic window, frequent laboratory monitoring being required. [3]

Thus, the major demands for TE prophylaxis were drugs with higher specificity and predictable effect after a fixed unique oral dose with less bleeding risk. One group of drugs meeting this demand is represented by Direct Inhibitors, acting on Factor

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IIa and Factor Xa. As the inhibition of one single molecule of Factor Xa (the activated form of Factor X) produces the inhibition of 50 molecules of thrombin, it is considered to have the central role in the coagulation cascade[4]. Thus, Direct Inhibitors of Factor Xa were introduced in clinical practice; in orthopedics, their main indication was TE prophylaxis after elective surgery (hip and knee arthroplasty)

One of these is Rivaroxaban which directly, specifically and competitively binds to human Factor Xa; its selectivity was evaluated to be more than 10 000-fold greater selectivity than for other serine proteases. It rapidly and reversibly inhibits factor Xa (both free and fibrin-bound), without needing without antithrombin as a cofactor, as well as the prothrombinase complex, but is has no direct effect on thrombin activity or platelet aggregation.[5]

After oral administration, the absorbtion of Rivaroxaban is rapid, with Cmax reached within 2–4 hours after; it has a plasma protein binding of 92–95% and there are no major or active circulating metabolites as it is two-thirds metabolized, and one-third excreted as unchanged active substance in urine. From the two-thirds metabolized, half is eliminated renally and half is eliminated by faecal route. No dose adjustment is necessary in patients with mild or moderate renal impairment. Rivaroxaban is contraindicated in patients with clinically relevant bleeding risk, such as those having hepatic disease associated with coagulopathy and it may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy.[6]

The efficiency and safety of Rivaroxaban were the objectives of the RECORD

(Regulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE) I, II, III and IV studies which prospectively evaluated the efficacy and safety of a fixed daily dose of 10 mg of Rivaroxaban as thrombo-prophylaxis after hip and knee arthroplasty .[7-10]

Since hip and knee arthroplasty represent an important part of our activity, there has been a continuously growing interest in modern methods of thrombo-prophylaxis within our Clinic [11].This study presents our experience regarding the prevention of thrombembolic events using RIVAROXABAN as XARELTO (10 mg Rivaroxaban per tablet)

Material and method

This prospective study evaluates 46 patients operated between 01.01.2010 and 01.01.2013 in the Clinical Emergency Hospital Bucharest, Orthopedic and Trauma Clinic, who received Xarelto (Rivaroxaban 10mg) as thrombo-prophylactic agent. The study

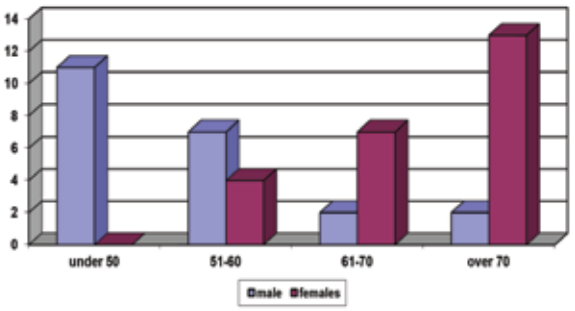

Figure 1. The group of patients – age and gender

group included 24 males and 22 females, with ages between 42 and 76 years (mean age 64 yrs). (Figure 1)

The operation performed was the same for all the patient- Total Hip Arthroplasty (THA)and the indication for surgery was represented by hip osteoarthritis (OA), which was primary (30 cases-16 males, 14 females) and secondary (16 cases- 6 males, 10 females).

From the 30 patients with primary OA, there were involvement of the hip was unilaterally in 28 patients (18 males, 10 females) and bilaterally in 2 patients, all females, while in the "secondary OA group" the involvement was unilaterally in 13 cases (5 males, 8 females) and bilaterally in 3 cases (1 male, 3 females).(Table I)

Pre-operative all the patients followed the same standard protocol established together with the anesthetists.

I. Standard pre-operative evaluation, consisting of:

a. anamnesis - in the study group , 32 patients had significant medical history, with one or more of the following comorbidities: arterial hypertension

Type of OA	males	Females	Total
Primary unilaterally	20	14	34
Primary bilaterally	0	2	2
Secondary unilaterally	2	4	6
Secondary bilaterally	2	2	4
Total	24	22	46

Table I. Etiology of the OA in the studied group

(20 patients), ischemic coronary disease (8 cases), atrial fibrillation (4 patients), allergic reaction to penicillin (1 patient), diabetes mellitus (4 patients), arterial occlusive disease (1 patient), gout (2 patients), ankylosing spondilitis (1 patient), rheumatoid arthritis (5 patients), leukemia (1 case), psoriasis (3 cases). There were 21 patients smoking in the study group (8 of them more than 20 cigarettes daily). None of the patients had had relevant clinical evidence/ medical history for DVT or PE, nor for liver or renal impairment. There were no patients within the study group receiving anti-coagulants in the last 6 months prior to surgery, but 8 patients received chronic treatment with Low-Dose–Aspirin 325mg (4 for atrial fibrillation and 4 for ischemic coronary disease), which was not considered as contra-indication for post-operative prophylaxis with Rivaroxaban

b. clinical examination-relevant for TED- 12 patients had varicose veins, 3 patients had clinical signs of chronic cardiac failure

c. paraclinical evaluation - ECG, pulmonary X-ray, lab tests for blood and urine; blood - hemoleucogram, serum glucose, urea, creatinine, ionogramme, liver function tests, proteins, albumin, CK (creatin-kinase), LDH(lactic-dehydrogenase/, alkaline phosphatase, ESR (erythrocyte sedimentation rate), fibrinogen, coagulation tests); urine-biochemical,cellular and bacteriologic exam

d. pre-operative anesthetist evaluation, assessing the risk.

e. no pre-operative pharmacological thrombo-prophylaxis was performed; non-pharmacological anti-thrombotic measures were applied (proper hydration, elastic stocks for the patients with varicose veins).

Spinal anesthesia was used in 34 patients and general anesthesia in 12 cases; antibiotic treatment was administered to the patients at induction:

- cephalosporin with aminoglycosides in 14 cases
- cephalosporin alone in 6 cases
- quinolone with aminoglycosides in 12 cases
- quinolones alone in 8 cases
- quinolones with glycopeptides in 6 cases

Lateral hip approach was performed in all the cases, except 3 cases, when the posterior approach was used because it had had been previously used for stabilizing the fracture of the posterior wall.

The type of the prosthesis was chosen depending the known criteria: age, bone stock (the quality and the quantity of bone) and the ability of the patient to respect the weight bearing recommendations; the correlation between age and the type of the prosthesis is represented in Figure 2.

Active suction was used in all the cases during surgery and **Intraoperative Red Blood-Cell Salvage**-Reinfusion System (so called "Cell Saver") was used in 20 of the 46 cases; intra-operative blood loss was 500- 1050 ml (mean value 650 ml) (Figure 3)

Re-infusion was performed in two variants:

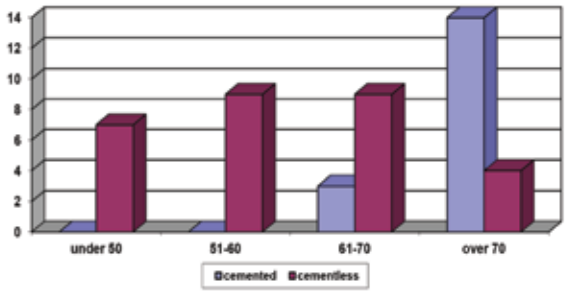

Figure 2. Correlation between age and the type of prosthesis

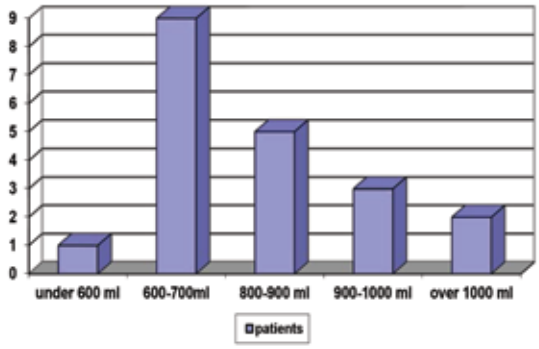

Figure 3. Blood loss during surgery

- reinfusion at the end of the operation (usually, after fascial suture), after collecting and processing all intra-operative blood – when intra-operative blood loss did not exceed 800 ml, or
- collecting 800 ml, processing and re-infusing the resulted product, then collect, process and reinfuse the rest of the blood at the end of surgery.

Transfusion with total blood or RBC (red blood cells) was intra-operatively indicated in 16 cases (12 cases operated without reinfusion system and 4 cases when reinfusion system was used, but there were more than 500 ml blood lost before finishing the acetabular preparation).

Peri-prosthetic and subfascial active drainages were installed; post-operative blood loss was monitored; the first outcome of this monitoring was to establish the moment of starting thrombo-prophylaxis, as the indication for that is the moment when hemostasis is proven to had been completed; the second outcome was to evaluate post-operative blood loss. Elastic bilateral stockings were used at the end of surgery in all the patients.

Rivaroxaban 10 mg daily (fixed dose) was given to the patients, starting after a mean time of 9.2 hrs post-operative, since in all the patients it was proven that haemostasis had been established before that. The moment of first administration was between 8-10 hours post-operative, depending on the post-operative drainage.

The patients were monitorised post-operative by:

1. clinical evaluation once daily and whenever it was considered necessary, general and local (the aspect of the legs and wound surveillance with

drainage removal 48 hrs after surgery).

2. laboratory tests: the same complete pre-operative tests were routinely performed in the evening of the operation day (4-6 hours after the end of the suture) and the next morning

3. Hemoleucograms and coagulation tests were perfumed for all the patients at discharge

4. Recommended control for suture removal, then 35-42 days after surgery

5. Compression ultrasound routinely performed for all the patients at discharge (which was after a mean time of 9.5 days in this group of patients, from 8-16 days) , then 35 - 42 days after surgery (when the treatment with Rivaroxaban was stopped); exceptionally, Compression Ultrasound was indicated whenever there was a suspicion of DVT

Results

The duration of Rivaroxaban treatment was 35- 42 days after surgery (mean time 39.2 days), no discontinuation of the treatment was described in the study group.

From the studied group, 6 patients developed persistent edema of the operated leg; all of them after more than 3 weeks from surgery (after 24, 25, 29, 30, 31 and 34 days correspondingly). Doppler compression ultrasound was performed and it detected thrombosis of the peroneal veins in one of the patients, and of the anterior tibial veins in 2 patients, so Unfractioned Heparine (UFH) treatment of DVT was started, following known protocols.

Doppler Compression Ultrasound was performed at 2,4, 8 and 12 weeks after Heparine treatment was started; the thrombi progressively reduced and disappeared 12 weeks after DVT onset; venography confirmed thrombus disappearance.

PE appeared in 1 patient(62 yrs, heavy smoker with varicose veins) 6 days after surgery.

Post-operative bleeding was within standards described in literature (600-1300 ml) with a mean value of 775 ml; post-operative transfusions were indicated (1-4 units) depending on the hemograme. The variation of the Hemoglobin in the study group is shown in Figure 4

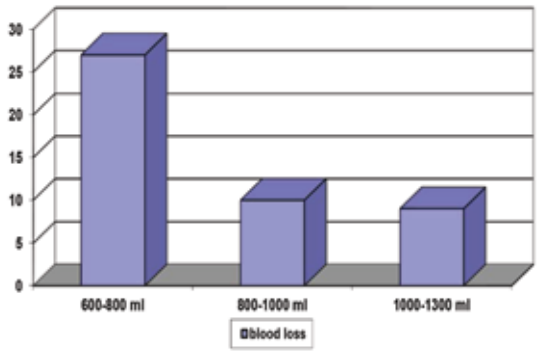

Figure 4. Post-operative blood loss

No post-operative abnormal bleeding, nor at the surgical site, neither in different organs and systems, and no major bleeding (defined as life threatening bleeding or a bleeding which required reintervention) were described.

One of the patients developed an acute allergic reaction to Cephalosporin, which had no relation to Rivaroxaban and did not interfere with its administration (Figure 5)

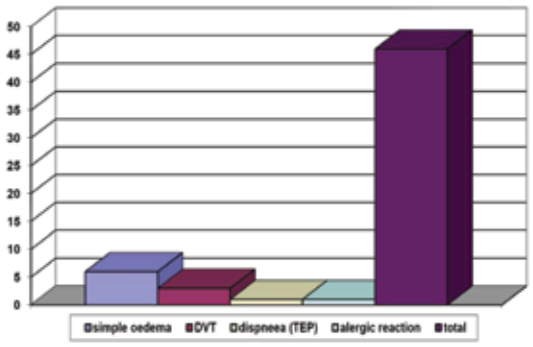

Figure 5. Clinical outcome - adverse events

Complete paraclinical evaluation (lab tests) were performed corresponding to the local standard procedures (routine post-operative tests, then second day routine tests), only repeated if the patients had post-operative anemia and needed blood transfusions. No supplementary evaluation of coagulation was necessary, none of the patients developed thrombocytopenia during these standard tests.

Liver and renal function tests were modified at 16 patients in the post-operative set; four of these patients had these tests modified the second day; the values returned to normal for all the patients at discharge. Rivaroxaban treatment was continued, we concluded that no impairment of liver or renal function appeared, nor other side effects

Discussion

The significant impact that TED after major orthopedic surgery continues to have upon mortality and morbidity makes the problem of thrombo-prophylaxis still actual, since none of the available methods managed to completely erase the risk of these complications.

Rivaroxaban, a novel oral anticoagulant has been described as having two major advantages: the oral administration and the fixed dose, no matter weight or comorbidities. For the moment, in our country, the indications for thrombo-prophylaxis with Rivaroxaban are represented by elective surgery of the hip (total hip replacement) and knee.[12]

The prospective study in this paper confirm those resulted from the RECORD studies, which show that the benefit-risk ratio for Rivaroxaban is definitely inclined to the first one.

There are certain aspects which must be discussed following presenting the results of our experience:

The compliance to long-term treatment is much better when the treatment is administered orally (such as Rivaroxaban) then injectably. This is very important especially when prolonged treatment is necessary, such as thrombo-prophylaxis after hip arthroplasty, since studies demonstrated that the risk of developing TED after this type of surgery persists for 6 weeks after surgery.[13] So it is very important for succesful thrombo-prophylaxis in hip arthroplasty including that with Rivaroxaban to respect the long-time prophylaxis rule, which, according to literature consistently reduces the incidence of thrombo-embolic events

The moment when thrombo-prophylaxis should be started (before or after surgery) has not been concluded, yet. Since none of the two methods (pre- or post-operative initiation of prophylaxis) proved to be clearly superior, the debate is still actual, especially because theoretically the patient is moving (sometimes difficult, but still moving) before arthroplasty, so at least this pro-thrombotic factor is not active, yet. Still, if pre-operative prophylaxis is intended, LMWH are to be chosen, since the indications of Rivaroxaban are restricted to post-operative thrombo-prophylaxis.

The precise moment of the first administration has to be established following the recommendations of the producer: there must be at least 8 hours after suture was finished, but in the same time hemostasis must be proven to have been achieved when Rivaroxaban is first administered, in order to allow the coagulation mechanism to achieve haemostasis. The surgeon must be sure that no abnormal bleeding occurs at the surgical site, otherwise no anti-thrombotic drug can be administered. As there might be differences between different anti-thrombotic drugs regarding the time between wound closure and first allowed administration, the rule of proven hemostasis is valid for all these drugs.[14]

Since there is a considerably difference between the designs of the studies and the timetables of the visits, the precise data referring to the incidence of different events within the study group are not to be compared to those obtained in the RECORD studies. Still, it must be underlined that within the study group there were no side events, no cases of liver and renal impairment, nor gastro-intestinal disturbances, thus suggesting that Rivaroxaban might reduce the risk of these unpleasant events .

Conclusions

Correct and complete identification of the TE risk by identifying all the thrombotic factors requires a thorough evaluation of the patient. Once TE risk being established, thrombo-prophylaxis should be started , preferably with one of the new effective anti-coagulants which were continuously improved in order to obtain efficacy, safety, specificity , tolerability and a convenient administration.

This analyses, even if performed on a small group of patients, demonstrated that conveniently orally administered Rivaroxaban demonstrated to be effective, safe and well tolerated, since no side effects were described in the study group. Until its indications will be enlarged, the properties of Rivaroxaban makes it an efficient thrombo-prophylactic agent to be used in prosthetic orthopedic surgery.

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