Prevention of Thrombus Formation After Endoprosthesis in Ambulatory Practice of Orthopedic Traumatologists

Sergey Firsov Anatolyevich

Summary
Introduction. For the first time in the Russian clinical practice, an analysis of safety and efficacy of oral anticoagulants available in the pharmaceutical market, was performed in patients after endoprosthesis of large joints, in the outpatient stage. Material and Methods. The study included 5,025 patients after total knee joint replacement, and 5,216 patients – after hip joint surgery. Results. All patients were divided into three groups based on the prescribed anticoagulant (dabigatran, rivaroxaban and apixaban). The duration of anticoagulant therapy after endoprosthesis of the hip and knee joints lasted 35 and 45 days from the time of surgery, respectively. All patients underwent ultrasonic examination of the lower extremity veins 3 and 6 months after being discharged from the hospital. In the group of the patients taking dabigatran, the incidence of clinically significant deep vein thrombosis was lower than among the patients receiving rivaroxaban and apixaban, accounting for 5% versus 7.7% and 16%, respectively. The incidence of non-fatal pulmonary thromboembolism was comparable. The occurrence of rethrombosis (recurrent deep vein thrombosis) was noted only in the rivaroxaban group. Conclusion. An assumption was put forward that extended treatment for prevention of thrombus formation after surgery of large vessels is expedient, but it requires conduct of large scale studies.

Key words: Venous Thrombosis; Pulmonary Embolism; Anticoagulants; Joint Prosthesis; Postoperative Complications; Primary Prevention; Ultrasnography, Doppler

Sažetak
Uvod. Prvi put u ruskoj kliničkoj praksi urađena je analiza bezbednosti i efikasnosti oralnih antikoagulantnih lekova, dostupnih na farmaceutskom tržištu, kod pacijenata nakon endoprotetike velikih zglobova, u ambulantnoj fazi lečenja. Materijal i metode. Studija je obuhvatila 5 025 pacijenata posle totalne zamene zgloba kolena i 5 216 pacijenata posle operacije zgloba kuka. Rezultati. Svi pacijenti su bili podeljeni u tri grupe na osnovu propisanih antikoagulantnih lekova (dabigatran, rivaroksaban i apiksaban). Antikoagulantna terapija nakon ugradnje endoproteze kuka i kola trajala je 35 i 45 dana posle operacije zgloba kuka. U grupi pacijenata koji su uzimali dabigatran, incidencija klinički značajne duboke venske tromboze bila je niža nego kod pacijenata koji su primali rivaroksaban i apiksaban (5% u odnosu na 7,7% i 16%, respektivno). Incidencija nefatalne plućne tromboembolije je slična. Pojava retromboze (rekurentne duboke venske tromboze) zabeležena je samo u grupi koja je primala rivaroksaban. Zaključak. Pretpostavka je da je produženi tretman prevencije stvaranja tromba posle operacije velikih krvnih sudova svrsishodan, ali zahteva sprovođenje studija velikih razmera.

Ključne reči: venska tromboza; plućna embolija; antikoagulant; zglobna proteza; postoperativne komplikacije; primarna prevencija; Dopler ultrasonografija

Numerous studies have shown that primary prevention significantly decreases the incidence of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) [1–5]. According to the statistical models, the number of fatal outcomes after venous thromboembolism reaches 900,000 cases a year. In the period from 1966 to 1990, 250,000 cases were reported with fatal outcome associated with venous thromboembolism per year [6].

Corresponding Author: Firsov Sergey Anatolyevich, Non-governmental Healthcare Institution “Yaroslavl Railway Clinical Hospital” 21, Suzdalskoe shosse, Yaroslavl, 150000, E-mail: serg375@yandex.ru
Endoprosthetic replacement of the knee and hip joints is associated with high risk for the development of thrombosis and thromboembolism, and without anticoagulant therapy their incidence may reach 57% and 85%, respectively [7–10]. PTE is a severe complication, and the probability of its development accounts for 28% [11, 12]. With the use of anticoagulants, the complication rate decreases dozens of times.

At present, oral anticoagulant therapy, intended for prevention of venous thromboembolic complications, is used not only during the hospital stay, but also during the outpatient treatment period [1, 4, 5, 13]. In the North America, warfarin is frequently used for prevention of venous thrombotic complications after extensive orthopedic operations during the outpatient period [14, 15]. There are a number of limitations for the use of this drug, including the narrow therapeutic index, regular control of therapy, and frequent dose adjustment [15, 16]. In Europe, low molecular heparins are predominantly used for thrombosis prevention. However, they require parenteral administration, that is not always convenient for patients, particularly if it is necessary to continue the therapy after being discharged from the hospital [11, 12, 17]. Novel oral anticoagulants, which do not require therapy control, may be administered in fixed doses and the use of which is not accompanied by the risk of drug interactions or interactions with foodstuffs, may evidently have practical advantages [7, 9, 12, 13, 18]. Nevertheless, it is necessary to determine their efficacy and safety in orthopedic practice, especially in prolonged use during the outpatient treatment [19–21].

It has earlier been shown that the efficacy and safety of prevention of thrombus formation does not significantly depend on the time of initiation of therapy [12, 13, 17]. Furthermore, these studies do not cover the outpatient period of treatment, especially long-term results, whereas complications do not frequently develop as soon as the patient is discharged from hospital [16].

The purpose of the study was to evaluate the efficacy and safety of oral anticoagulants available in the Russian pharmaceutical market in outpatients who underwent endoprosthesis of the hip and knee joints.

**Material and Methods**

The retrospective analysis included medical records of outpatients who underwent total hip and knee joint replacement in the period from 2009 - 2015 at the leading Russian clinics and who received oral anticoagulants for prevention of thrombus formation. The exclusion criteria were: any hemorrhagic diathesis, acute intracranial pathology or hemorrhagic stroke in medical history, uncontrolled arterial hypertension or myocardial infarction in the previous 3 months, exacerbated peptic ulcer in the previous 6 months, severe liver disease, and severe kidney failure.

The number of patients after total knee joint endoprosthesis (TKJEP) was 5,025, and after total hip joint endoprosthesis (THJEP) – 5,216 (Graph 1). The mean age of patients was 55.4 years; 95% confidence interval (CI), range 35 – 74 years.

All patients were divided into groups depending on the prescribed oral anticoagulant. Dabigatran etexila...
was administered in a dose of 220 mg once a day, rivaroxaban – 10 mg once a day, apixaban (used since 2013) – 2.5 mg twice a day. The therapy lasted for 35 days, from the day of surgical intervention in patients after THJEP, and for 45 days – after TKJEP. In accordance with the clinical recommendations, the use of dabigatran was initiated 4 h after the end of surgery, rivaroxaban – after 10 h, apixaban – after 12 h.

In accordance with the requirements of local clinical practice, 3 and 6 months after discharge from the hospital all patients underwent Doppler ultrasound examination of veins of the lower extremities.

The ultrasound examination was performed using different ultrasound devices according to the generally accepted technique [22]. At the time of discharge, no patients presented with DVT. In the first 3 months after the discharge, all patients were recommended to wear compression stockings.

The efficacy of the anticoagulants was evaluated by the incidence of clinically significant DVT of the lower extremities, and safety – by the incidence of DVT recurrences.

The statistical processing of the data was performed by means of the software EpiInfo 3.4.1 and SPSS 17.0 for Windows. The quantitative data are presented as mean (M) and standard deviation (SD). The nominal data are presented as relative frequencies and their 95% CI. The differences at $p<0.05$ were regarded as statistically significant.

**Results**

Among the outpatients who underwent THJEP, at the control examination 3 months after the discharge, asymptomatic DVT of the lower extremities was most rarely diagnosed in the group receiving dabigatran – in 215 (8%) cases; out of these, proximal thrombosis was found in 16 (0.7%) cases, distal thrombosis in 199 cases (7.3%) (Table 1). The highest number was found in the apixaban group, in 75 (18%) cases. Symptomatic DVT was also most rarely found in the dabigatran group, in 5% of patients, in the rivaroxaban group this adverse event developed in 7.7% of operated patients ($p<0.05$), and in the apixaban group, in 16% ($p<0.05$). Fatal PTE occurred only in the dabigatran group, however the difference with the other groups in regard to this parameter was not statistically significant. The incidence of nonfatal PTE in all three groups turned out to be comparable (Table 1). According to the data of ultrasound investigation 6 months after surgery, asymptomatic venous thrombosis was recorded with approximately equal incidence in the dabigatran and rivaroxaban groups – 1.5 and 3.3%, respectively. However, in the rivaroxaban group, 3.11% of patients presented with rethrombosis (DVT recurrence), and it was not established in the dabigatran and apixaban groups. Asymptomatic venous thrombosis was nearly 1.5 times higher in the apixaban group, though no statistically significant difference was revealed due to the small size sample (Table 2).

In patients with prevention of thrombus formation after TKJEP, a similar tendency was found 3 months later, at control examination (Table 3). Thus, in the dabigatran group, asymptomatic DVT was diagnosed in 8.5% of cases, in the rivaroxaban group – in 10.8% ($p<0.05$), and in the apixaban group – in 13%. Symptomatic DVT was statistically significantly ($p<0.01$) more rarely found in the group of patients receiving dabigatran – 4.7% versus 6.0 and 10.7% in the rivaroxaban and apixaban groups, respectively. PTE, with fatal outcome, was recorded in the dabigatran group in 2 (0.09%) cases, and in the apixaban group – in 1 (0.2%) case.

### Table 1. Incidence of thrombotic complications in patients who underwent THJEP, at control examination 3 months after discharge

<table>
<thead>
<tr>
<th>Parameter/Parametar</th>
<th>Dabigatran etexilate ($n=2646$)</th>
<th>Rivaroxaban ($n=1825$)</th>
<th>Apixaban ($n=425$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic DVT</td>
<td>215 (8%, 95% CI 7.1–8.9)</td>
<td>239* (13%, 95% CI 11.9–14.1)</td>
<td>75 (18%, 95% CI 16.8–19.2)</td>
</tr>
<tr>
<td>Proximal/Proksimalna</td>
<td>16 (0.7%, 95% CI 0.4–1.0)</td>
<td>24 (2%, 95% CI 1.7–2.3)</td>
<td>23 (6%, 95% CI 5.3–6.7)</td>
</tr>
<tr>
<td>Only distal/Samo distalna</td>
<td>199 (7.3%, 95% CI 6.6–8.0)</td>
<td>215* (11%, 95% CI 10.1–11.9)</td>
<td>52 (12%, 95% CI 11.4–12.6)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>122 (5%, 95% CI 4.1–5.9)</td>
<td>141** (7.7%, 95% CI 7.1–8.3)</td>
<td>69 (16%, 95% CI 14.9–17.1)</td>
</tr>
<tr>
<td>Symptomatic PTE</td>
<td>5 (0.1%, 95% CI 0.06–0.14)</td>
<td>2 (0.1%, 95% CI 0.07–0.13)</td>
<td>3 (0.7%, 95% CI 0.4–1.0)</td>
</tr>
<tr>
<td>Death/Smrt</td>
<td>1 (0.03%, 95% CI 0.01–0.05)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Severe VTE/fatal outcomes related to VTE</td>
<td>9/1 (0.3/0.03%,</td>
<td>12/1 (0.7/0.05%,</td>
<td>4/0 (0.9%, 95%</td>
</tr>
<tr>
<td>Teška VTE/letalni ishod uzrokovani VTE</td>
<td>95% CI 0.1–0.5</td>
<td>95% CI 0.3–0.9</td>
<td>CI 0.6–1.2</td>
</tr>
</tbody>
</table>

**Legend.** In tables 4 – 6 significance of differences compared to dabigatran group: * - $p<0.05$, ** – $p<0.01$,

**Legend.** U tabelama 4 – 6 značajnost razlika u odnosu na grupu koja je dobijala dabigatran: * - $p<0.05$, ** - $p<0.01$

DVT - duboka venska tromboza, PTE - plućna tromboembolija, VTE - venska tromboembolija
Six months after surgery, asymptomatic venous thrombosis was determined with approximately equal incidence in the dabigatran and rivaroxaban groups – 2.5 and 3.4%, respectively. However, in the rivaroxaban group, rethrombosis was also recorded (2.9% of patients), but not in other groups. In the apixaban group, asymptomatic venous thrombosis was diagnosed 2 times more frequently, though no statistically significant differences were revealed due to the small size sample (Table 4). In the group of patients taking dabigatran, 1 (0.04%) fatal outcome was reported.

**Discussion**

At present, new oral anticoagulants need to provide high efficacy, low risk of bleeding, simple usage (oral administration, no dose adjustment, and no special monitoring), safety and convenience for use in practice, not only in hospital, but also in outpatient settings [2, 3, 5, 11, 18, 23, 24].

Dabigatran etexilate, rivaroxaban and apixaban are current oral anticoagulants which are widely used in orthopedics for prevention of thromboembolic complications in patients undergoing endoprosthesis of hip and knee joints [6, 9, 19, 20, 25, 26]. These anticoagulants are considered to be effective, convenient and safe by the manufacturers and many investigators [10, 27]. Their best characteristic is that they do not require, in contrast to warfarin, constant laboratory monitoring and dose titration. In contrast to heparin, their prolonged administration does not induce thrombocytopenia [28]. Despite already proven advantages of oral anticoagulants, clinical studies evaluating their safety and efficacy in traumatology and orthopedics are still ongoing [9]. However, studies on oral anticoagulants practically do not cover the time after discharge from the hospital especially during the long follow-up period [16, 29].

In 2007, D. Warwick et al. presented data on the incidence of thromboembolic complications after discharge from hospital [16]. They showed that, on the average, thromboembolic complications developed 21.5 days after surgery, and their incidence

---

**Table 2. Incidence of thrombotic complications in patients who underwent THJEP, at control examination 6 months after discharge**

<table>
<thead>
<tr>
<th>Parameter/Parametar</th>
<th>Dabigatran etexilate (n=2596)</th>
<th>Rivaroxaban (n=1772)</th>
<th>Apixaban (n=384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic DVT</td>
<td>38 (1.5%, 95% CI 1.2–1.8)</td>
<td>59 **(3.3%, 95% CI 2.8–3.8)</td>
<td>16 (4.2%, 95% CI 3.7–4.7)</td>
</tr>
<tr>
<td>Proximal</td>
<td>6 (0.3%, 95% CI 0.16–0.44)</td>
<td>4 (0.2%, 95% CI 0.09–0.31)</td>
<td>3 (0.2%, 95% CI 0.08–0.32)</td>
</tr>
<tr>
<td>Only distal</td>
<td>32 (1.2%, 95% CI 0.8–1.6)</td>
<td>55* (out of these - 32 rethrombo-ses)</td>
<td>13 (4%, 95% CI 3.7–4.3)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>19 (0.7%, 95% CI 0.5–0.9)</td>
<td>27 (1.5%, 95% CI 1.3–1.7)</td>
<td>16 (4.2%, 95% CI 3.9–4.5)</td>
</tr>
<tr>
<td>Symptomatic PTE</td>
<td>–</td>
<td>1 (0.05%, 95% CI 0.03–0.07)</td>
<td>–</td>
</tr>
<tr>
<td>Death/Smrt</td>
<td>5/0 (0.2%, 95% CI 0.08–0.32)</td>
<td>7/0 (0.4%, 95% CI 0.2–0.6)</td>
<td>2/0 (0.5%, 95% CI 0.29–0.71)</td>
</tr>
</tbody>
</table>

**Graph 2.** Total number of thromboembolic complications after surgical interventions

**Grafikon 2. Ukupan broj tromboembolijskih komplikacija nakon hirurških intervencija**
reached 2.3% (Graph 2). They also showed that the incidence of complications after a median time since discharge from the hospital may reach 75%.

In 2008, data of the unprecedented clinical trial “ENDORSE”, which included 68.183 patients, were published [13]. This study published summarized results of prevention of thromboembolic complications in the world, including Russia. According to the presented data, in Russia, prevention was carried out only in 23.8% of cases, prevention of venous thromboembolic complications in fractures of the femoral bone was carried out in 42.9% of cases, and in extensive injuries – in 4.9%.

The fact that most patients are admitted unprepared for the previously arranged orthopedic treatment, deserves to be mentioned separately. Recently, the leading western orthopedists began giving more attention to the use of oral anticoagulants before the planned orthopedic treatment at the hospital. In 2015, M. Dietrich et al. [8] published a study including 668 patients receiving oral anticoagulants before the planned surgical intervention. It showed that such an approach greatly decreased the incidence of thromboembolic complications and mortality.

In many Russian and foreign medical institutions, even at present, prevention of thromboembolic complications is conducted by using drugs such as warfarin and aspirin. It is well known that the anticoagulation effect of warfarin significantly varies due to difference in absorption and metabolism of

### Table 3. Incidence of thrombotic complications in patients who underwent TKJEP, at control examination 3 months after discharge

<table>
<thead>
<tr>
<th>Parameter/Parametar</th>
<th>Dabigatran etexilate (n=2206)</th>
<th>Rivaroxaban (n=1897)</th>
<th>Apixaban (n=456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic DVT</td>
<td>189 (8.5%, 95% CI 8.2–8.8)</td>
<td>205** (10.8%, 95% CI 9.9–11.7)</td>
<td>59 (13%, 95% CI 12.5–13.5)</td>
</tr>
<tr>
<td>Proximal/Proksimalna</td>
<td>11 (0.6%, 95% CI 0.3–0.9)</td>
<td>13 (1.8%, 95% CI 1.5–2.1)</td>
<td>9 (4%, 95% CI 3.2–4.8)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>178 (7.9%, 95% CI 7.3–8.5)</td>
<td>192 (9%, 95% CI 8.2–9.8)</td>
<td>50 (9%, 95% CI 8.5–9.5)</td>
</tr>
<tr>
<td>Symptomatic PTE</td>
<td>104 (4.7%, 95% CI 4.2–5.2)</td>
<td>114* (6%, 95% CI 5.6–6.4)</td>
<td>49 (10.7%, 95% CI 10.3–11.1)</td>
</tr>
<tr>
<td>Death/Smrt</td>
<td>2 (0.09%, 95% CI 0.05–0.11)</td>
<td>–</td>
<td>1 (0.2%, 95% CI 0.09–0.31)</td>
</tr>
</tbody>
</table>

* DVT - duboka venska tromboza, PTE - plućna tromboembolija, VTE - venous thromboembolism/venska tromboembolija

### Table 4. Incidence of thrombotic complications in patients who underwent TKJEP, at control examination 6 months after discharge

<table>
<thead>
<tr>
<th>Parameter/Parametar</th>
<th>Dabigatran etexilate (n=2141)</th>
<th>Rivaroxaban (n=1827)</th>
<th>Apixaban (n=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic DVT</td>
<td>46 (2.5%, 95% CI 2.2–2.8)</td>
<td>63 (3.4%. 95% CI 2.9–3.9)</td>
<td>28 (6.8%, 95% CI 6.2–7.4)</td>
</tr>
<tr>
<td>Proximal/Proksimalna</td>
<td>8 (0.6%, 95% CI 0.3–0.9)</td>
<td>10 (0.5%, 95% CI 0.2–0.8)</td>
<td>6 (2.8%, 95% CI 2.5–3.1)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>38 (1.9%, 95% CI 1.5–2.3)</td>
<td>53* (out of these – 16 ret-thromboses)</td>
<td>22 (4%, 95% CI 3.7–4.3)</td>
</tr>
<tr>
<td>Symptomatic PTE</td>
<td>24 (1.1%, 95% CI 0.8–1.4)</td>
<td>31** (1.7%, 95% CI 1.3–2.1)</td>
<td>18 (4.3%, 95% CI 3.8–4.8)</td>
</tr>
<tr>
<td>Death/Smrt</td>
<td>1 (0.04%, 95% CI 0.02–0.06)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

DVT - duboka venska tromboza, PTE - plućna tromboembolija, VTE - venous thromboembolism/venska tromboembolija
the drug and its interactions with medications [15]. At the same time, in addition to its low efficacy, aspirin possesses the property of producing formation of heterotopic ossificates after endoprosthesis of the hip, that was convincingly demonstrated by R. Cohn in 2010, and G. Pavlou in 2012 [30–32].

The present study showed that the greatest efficacy in regard to the prevention of clinically significant DVT of the lower extremities in outpatient settings was demonstrated by dabigatran etexilate both after THJEP (5% versus 7.7 and 16% in the groups of rivaroxaban and apixaban, respectively, and after TKJEP (4.7% versus 6 and 10.7%, respectively). Also, patients receiving rivaroxaban presented with rethrombosis, that was not observed in the dabigatran and apixaban groups.

Conclusion

The data obtained in the present study suggest that current oral anticoagulants are efficacious and safe in prevention of thrombosis in orthopedic and trauma patients. Our 6-year experience of using these drugs and the data of international studies indicate that rivaroxaban demonstrates lower efficacy in long-term prevention of thrombosis. Dabigatran etexilate, which demonstrated the best results in long-term use in patients after hip and knee endoprosthesis, should be considered the drug with the greatest efficacy and the best safety profile.

A rather high incidence of thromboembolic complications after the use of oral anticoagulants comes under notice. In our opinion, the administration of anticoagulants should not be limited to 35 days after surgery, but continued for up to 6 months. However, this opinion requires confirmation within the framework of large scale clinical studies which should evaluate the safety and efficacy of such a long-term use of oral anticoagulants.

We believe that preoperative preparation of orthopedic patients with the use of oral anticoagulants should be a separate topic of discussion. Up to date, no significant studies on this topic have been conducted and the safety and expediency of these pharmacological preparations have not been studied.

References


2. Firsov SA, Lavin AG, Matveev RP. Российский опыт рациональной тромбопрофилактики в травматологии и ортопедии. [Russian experience in rational thromboprophylaxis in traumatology and orthopaedics]. Vestnik travmatologii i ortopedii imeni N.N. Pirovova. 2015;2:36–42. Russian.


