INTRODUCTION

Total knee arthroplasty (TKA) is an elective procedure performed on relatively healthy individuals. However, due to the inherent risk of venous thromboembolism (VTE), drugs are used for its prophylaxis. The objective of the present study was to conduct a systematic review of the literature to compare the efficacy of enoxaparin and rivaroxaban in preventing this complication and the risk of intraoperative bleeding. We reviewed the SciELO, Pubmed and Cochrane databases with the descriptors knee arthroplasty, rivaroxaban and enoxaparin through the PICO search strategy. Inclusion criteria were the articles during the study period comparing both drugs in knee arthroplasty. Relevant criteria to study eligibility were articles published since 2010 and with a sample of more than 20 patients; studies obtained in their entirety; and studies with follow-up of more than 12 months. The variables used to compare the articles were the most common postoperative complications of knee arthroplasties: venous thromboembolism and bleeding. We used the Review Man software, version 5.3, for structuring the review. In the studies analyzed, considering symptomatic venous thromboembolism, rivaroxaban resulted in higher benefits when compared to enoxaparin.

Keywords: Arthroplasty, Replacement, Knee. Venous Thromboembolism/prevention & control. Rivaroxaban. Enoxaparin.
Nonetheless, there is an important association between proximal deep vein thrombosis and pulmonary embolism, silent non-occlusive thrombi and symptomatic or fatal pulmonary embolism\textsuperscript{5,6}.

The use of anticoagulants began in 1916, with the discovery of the anticoagulant effect of the substance heparan sulfate, extracted of the liver of pork by Mclean\textsuperscript{7}. The LMWH were developed in order to reduce the limitations of warfarin and unfractionated heparin (UFH) in clinical practice and, in fact, proved to be effective and safe, besides not requiring laboratory monitoring and having longer half-life and predictable response\textsuperscript{8}.

In the last two decades, development of synthetic compounds like the LMWH and polysaccharides (fondaparinux), prompted a search for the ideal anticoagulant. These new agents should be more effective, of oral administration, simplified dosage, predictable pharmacokinetics and pharmacodynamics, and dispense with laboratory monitoring\textsuperscript{9}. Numerous clinical studies demonstrate encouraging results with agents that selectively inhibit factor Xa and thrombin. Such agents have a small molecular structure and concomitantly inhibit free plasma coagulation factors (FX and FII), but with little action when these complexes are bound to the thrombus.

Rivaroxaban is a compound derived from oxazolidione. It directly inhibits factor Xa and has a single daily dosage. Its clinical use for VTE prevention in TKA is approved in Brazil, Canada, the European Union and some countries in Asia and Africa. Currently rivaroxaban has become the most studied factor Xa inhibitor in the world, with more than 32,000 followed-up patients.

The objective of this work was to perform a literature systematic review, aiming to compare the drugs enoxaparin and rivaroxaban in the risk of intraoperative bleeding in and the prophylaxis of VTE after TKA.

**METHODS**


The relevance criteria to make the study eligible were: articles published from 2010 on and with a series of more than 20 patients; studies obtained in their entirety; studies with follow-up greater than 12 months. Inclusion criteria were...
articles in the study period, which compared both drugs in knee arthroplasty procedures. We also included studies that evaluated both hip arthroplasty (HA) and total knee arthroplasty (TKA) from which we could extract the TKA-related data.

In the first analysis, we identified 49 articles from the searched databases, and excluded nine for duplicity. In the eligibility phase (40 articles) with the complete articles, we excluded 31 articles because they did not state the inclusion criteria, totaling nine articles for the evaluation (Figure 1).

**RESULTS**

Upon evaluation of the found articles, we observed (Table 1) the following results, considering the variables of interest:

---

**Results for deep venous thrombosis**

Nieto et al.\(^{10}\) observed in their study of clinical trials that rivaroxaban compared with enoxaparin 40mg (control) showed superiority regarding venous thromboembolism events in total knee arthroplasty (RR 0.32; 95% CI 0.15-0.67).

Lassen et al.\(^{11}\), through large and randomized clinical trials, compared rivaroxaban with subcutaneous enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty (n=12,729). There were no significant differences in the incidence of adverse events, including VTE, death and prolonged hospitalization.

Gómez-Outes et al.\(^{12}\) performed a study in 16 trials with a total of 38,747 patients. Compared with enoxaparin, the risk of symptomatic VTE was
Table 1. Results of the articles analyzed concerning outcomes (bleeding, venous thromboembolism, serious adverse events and death).

<table>
<thead>
<tr>
<th>Article Details</th>
<th>Bleeding</th>
<th>Venous thromboembolism or serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levitan B et al. (2014). Benefit-risk assessment of rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty.</td>
<td>A) Major bleeding&lt;br&gt;Rivaroxaban – 75 in 10,000&lt;br&gt;Enoxaparin – 48 in 10,000</td>
<td>A) Symptomatic venous thromboembolism&lt;br&gt;Rivaroxaban – 102 cases in 10,000&lt;br&gt;Enoxaparin – 178 cases in 10,000</td>
</tr>
<tr>
<td></td>
<td>B) Minor bleeding + surgical site&lt;br&gt;Rivaroxaban – 189 in 10,000&lt;br&gt;Enoxaparin – 141 in 10,000</td>
<td>B) Mortality&lt;br&gt;Rivaroxaban – 23 cases in 10,000&lt;br&gt;Enoxaparin – 42 cases in 10,000</td>
</tr>
<tr>
<td>Li J et al. (2014). Comparison of rivaroxaban and enoxaparin on blood loss after total knee arthroplasty.</td>
<td>A) Visible blood loss&lt;br&gt;Enoxaparin greater than rivaroxaban (p=0.003)</td>
<td>Not rated.</td>
</tr>
<tr>
<td></td>
<td>B) Total blood loss&lt;br&gt;No difference between groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C) Occult blood loss&lt;br&gt;Rivaroxaban greater than enoxaparin (p=0.000)</td>
<td></td>
</tr>
<tr>
<td>Turpie AG et al. (2014). A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopedic surgery in 17,701 patients with propensity score adjustment.</td>
<td>A) Major bleeding&lt;br&gt;Rivaroxaban – 35 in 8548 cases&lt;br&gt;Enoxaparin – 27 in 7968 cases&lt;br&gt;OR weighted (95% CI) – 1.35 (0.94-1.93)</td>
<td>A) Symptomatic venous thromboembolism&lt;br&gt;Rivaroxaban (intervention) – 77 in 8548 cases&lt;br&gt;Enoxaparin (control) – 104 in 7968 cases&lt;br&gt;OR weighted (95% CI) – 0.69 (0.56-0.85)</td>
</tr>
<tr>
<td></td>
<td>B) Minor bleeding&lt;br&gt;Rivaroxaban – 365 in 8548 cases&lt;br&gt;Enoxaparin – 232 in 7968 cases&lt;br&gt;OR weighted (95% IC) - 1.52 (1.35-1.71)</td>
<td>B) Mortality&lt;br&gt;Rivaroxaban – 7 in 8548 cases&lt;br&gt;Enoxaparin – 7 in 7968 cases&lt;br&gt;OR weighted (95% IC) – 1.00 (0.53-2.00)</td>
</tr>
<tr>
<td>Sindali et al. (2013). Elective hip and knee arthroplasty and the effect of rivaroxaban and enoxaparin thromboprophylaxis on wound healing.</td>
<td>A) Minor occult bleeding&lt;br&gt;Rivaroxaban - 2%&lt;br&gt;Enoxaparin - 0%</td>
<td>A) Venous thromboembolism&lt;br&gt;Rivaroxaban – 2 in 202 (1%)&lt;br&gt;Enoxaparin – 1 in 59 (1.8%); p=0.52</td>
</tr>
<tr>
<td></td>
<td>B) Bleeding in the wound&lt;br&gt;Rivaroxaban – 5%&lt;br&gt;Enoxaparin – 1.8%&lt;br&gt;There was no statistical difference.</td>
<td></td>
</tr>
<tr>
<td>Lassen MR et al. (2012). The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme.</td>
<td>A) Postoperative bleeding&lt;br&gt;Rivaroxaban – 19 in 2746 (0.69)&lt;br&gt;Enoxaparin – 19 in 2747 (0.69)</td>
<td>A) Serious adverse events&lt;br&gt;Rivaroxaban – 224 in 2,746 (8.16)&lt;br&gt;Enoxaparin – 272 in 2,747 (9.90)</td>
</tr>
<tr>
<td>Gómez-Outes A et al. (2012). Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, systematic review, meta-analysis, and indirect treatment comparisons.</td>
<td>A) Major bleeding&lt;br&gt;Rivaroxaban – 123 in 2940&lt;br&gt;Enoxaparin – 96 in 2946&lt;br&gt;RR (95% CI) – 1.29 (0.99-1.67)</td>
<td>A) Symptomatic venous thromboembolism&lt;br&gt;Rivaroxaban – 21 in 2940&lt;br&gt;Enoxaparin – 44 in 2946&lt;br&gt;RR (95% CI) – 0.49 (0.29 to 0.83)</td>
</tr>
</tbody>
</table>

continue...
lower with rivaroxaban (relative risk of 0.49, 95% confidence interval 0.29-0.83), the same finding of Zou et al.,13, who observed a lower incidence of VTE events in the group that used rivaroxaban.

Levitan et al.14 analyzed the risks and benefits of enoxaparin and rivaroxaban in the prophylaxis of VTE in total knee arthroplasty and total hip arthroplasty. The primary analysis compared the temporal course of event rates and the differences between rivaroxaban and enoxaparin in the prophylaxis of symptomatic VTE, in addition to the causes of mortality (efficacy events). Considering death and symptomatic VTE, rivaroxaban resulted in greater benefits than harm compared with enoxaparin in patients undergoing TKA.

Sindali et al.15 evaluated 258 patients submitted to hip or knee arthroplasty. Two hundred and two individuals with a mean age of 70.7 years ±10.0, of whom 43% were men, received a daily dose of 10mg oral rivaroxaban, and 56, mean age 70.9 years ±9.8, of whom 39% were men, received a 40mg daily subcutaneous injection of enoxaparin. There were no statistically significant differences (p=0.52) in the incidence of VTE in both groups.

Turpie et al.16 observed that rivaroxaban demonstrated superior efficacy and safety profile similar to that of enoxaparin for prevention of venous thromboembolism in phase III of the RECORD program, with 17,701 patients enrolled from 252 centers in 37 countries. The incidence of symptomatic thromboembolic events three months after total knee arthroplasty surgery was 0.89% in the rivaroxaban group (n=8778) and 1.35% in the enoxaparin group (n=8635).
Results for postoperative bleeding

Lassen et al.\textsuperscript{11} presented wide-ranging clinical trials comparing rivaroxaban with subcutaneous enoxaparin for VTE prevention after TKA or HA (n=12,729). In knee arthroplasties, 2746 patients used rivaroxaban and 2747, enoxaparin, with similar rates (0.69 vs. 0.69, respectively) for the variable bleeding, including wound hematoma and local surgical bleeding. Blood loss, transfusion and wound drainage were also similar between the two groups.

Gómez-Outes et al.\textsuperscript{12} carried out a meta-analysis with 16 trials and 38,747 patients. Considering only the knee arthroplasty (2940 vs. 2946 patients), the relative risk of clinically relevant hemorrhage was equivalent in rivaroxaban and enoxaparin groups (RR 1.29, 95% CI 0.99-1.67).

Nieto et al.\textsuperscript{10} observed in their meta-analysis of randomized clinical trials that rivaroxaban showed a tendency for bleeding episodes greater than enoxaparin, but without statistical significance (RR 1.88, 95% CI 0.92-3.82).

Eriksson et al.\textsuperscript{17} compared the safety of concomitant use of drugs such as non-steroidal anti-inflammatory drugs and platelet function inhibitors, including acetylsalicylic acid, rivaroxaban, and enoxaparin in postoperative bleeding rates in total knee or hip arthroplasty, and found no differences between the groups when assessing significant bleeding events.

Sindali et al.\textsuperscript{15} demonstrated that the incidence of minor bleeding and wound complications, such as sero-sanguineous discharge, hematoma requiring surgical drainage and superficial or deep infection, were higher in the rivaroxaban-treated group (2% vs 0% and 5% vs 1.8%, respectively), results corroborated by Zou et al.\textsuperscript{13} (4.90% versus 2.67%).

Li et al.\textsuperscript{18} observed that the visible blood loss of the enoxaparin group was higher when compared to the rivaroxaban group (p=0.003). They found no significant difference in total and occult blood loss between the two groups. When analyzing occult blood loss, the group using rivaroxaban showed greater loss than the enoxaparin group.

Turpie et al.\textsuperscript{16} carried out a study in which they analyzed patients submitted to orthopedic surgeries of the hip or knee (elective arthroplasty), comparing rivaroxaban with other thromboprophylactic drugs. Patients undergoing knee arthroplasty had greater hemorrhagic events compared with enoxaparin [weighted OR 1.35 (95% CI 0.94-1.93)], with no significant difference between groups. When assessing smaller volume bleeding, rivaroxaban displayed a higher risk compared with enoxaparin [weighted OR 1.52 (95% CI 1.35-1.71)].

DISCUSSION

The development of oral active factor Xa inhibitors for VTE prevention is an important advance. The RECORD (Regulation of Coagulation in major Orthopedic surgery reducing Risk of DVT and PE) studies have demonstrated superior efficacy of such drugs compared with enoxaparin in preventing VTE, without a consequently increased risk of bleeding\textsuperscript{19,20}. As a result of these large randomized studies, the use of rivaroxaban was widespread in the worldwide clinical experience for the prevention of VTE following HA and TKA\textsuperscript{21,22}. 

Rev Col Bras Cir 46(2):e2075
The double-blinded phase III RECORD studies included more than 12,500 patients submitted to total hip and knee arthroplasty and evaluated rivaroxaban at a dose of 10mg in a single daily administration. Rivaroxaban was superior to enoxaparin, with a greater reduction in the occurrence of symptomatic VTE and death. However, the risk of bleeding is an outcome that should be considered to be a complication found and has impact on the treatment and cost\textsuperscript{23-25}. Cases of bleeding, including wound hematoma and local surgical bleeding, occurred at similar rates between groups.

Surgeons have a concern that anticoagulants can increase bleeding rates, and thus delay wound healing, predisposing to increased frequency and volume of postoperative hematomas\textsuperscript{26} and consequently infection\textsuperscript{27}. The present study, along with others, highlights potential concerns about these postoperative outcomes. The literature suggests a statistically significant increase in the number of patients that need readmission\textsuperscript{28} and reoperation due to wound complications. This increase was driven by a higher incidence of hematomas requiring drainage, antibiotic prophylaxis, and increased postoperative recovery time\textsuperscript{29}.

The postoperative complications of HA or TKA may delay recovery, prolong hospitalization, increase readmission rates and, in more severe cases, lead to long-term disability or even death\textsuperscript{30}. In this analysis of data obtained from nine studies in patients submitted to TKA, the comparison between rivaroxaban and enoxaparin for the prevention of venous thromboembolism showed variations in the incidence of complications, including bleeding and adverse events related to surgery, such as wound infection and hematoma.

In our review, rivaroxaban was superior to enoxaparin, with a greater reduction in the occurrence of symptomatic VTE and symptomatic death, corroborating data from other systematic reviews. However, the risk of bleeding was higher with rivaroxaban in some articles when compared to enoxaparin, but without statistical significance in some of them. Huang et al.\textsuperscript{31} identified advantages of rivaroxaban over enoxaparin in their meta-analysis, especially that DVT and PE rates were lower in the rivaroxaban group, though with a reduced number of articles. Gómez-Outes et al. found less bleeding with other anticoagulants, such as apixaban\textsuperscript{12}, further comparative studies with this drug being required.

Prophylaxis for VTE in orthopedic surgeries, particularly in arthroplasties, continues to cause considerable debate among professionals. On the one hand, one should avoid VTE and its repercussions and, on the other, minimize the risks of operative bleeding.

**CONCLUSION**

In the studies analyzed, considering death and symptomatic venous thromboembolism, rivaroxaban had better results, with lower adverse events than enoxaparin. Regarding the analysis of bleeding, we suggest new studies to identify the best results.
REFERENCES


Received in: 11/21/2018
Accepted for publication: 01/15/2019
Conflicts of interest: none.
Source of funding: none.

Mailing address:
Rodrigo Ribeiro Pinho Rodarte
E-mail: rrodarte@globo.com
rrprodarte@gmail.com