DOI: 10.1590/0100-6991e-20192075

Systematic review of prophylaxis for venous thromboembolism after knee arthroplasty: enoxaparin *versus* rivaroxaban.

Revisão sistemática da profilaxia para tromboembolismo venoso após artroplastia do joelho: enoxaparina versus rivaroxabana.

Rodrigo Ribeiro Pinho Rodarte[1,2]; João Antônio Matheus Guimarães[1]; José Sérgio Franco[3]; Lorran Fonseca[2]; Vilker Nascimento[2]; José Paulo Gabbi Aramburu[2]; João Mauricio Barretto[1]

A B S T R A C T

Total knee arthroplasty is an elective procedure performed on relatively healthy individuals. However, due to the inherent risk of venous thromboembolism, 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.

INTRODUCTION

Total knee arthroplasty (TKA) is an elective procedure performed in individuals with knee osteoarthrosis. However, due to the inherent risk of venous thromboembolism (VTE), one of the main complications of the procedure, several forms of prophylaxis are used. In addition to good preoperative stratification, mechanical and pharmacological methods can be used. Among the pharmacological measures, the use of aspirin, warfarin, low molecular weight heparins (LMWH), such as enoxaparin and rivaroxaban[1].

Thrombus formation is associated with the presence of the triad venous stasis, endothelial lesion and hypercoagulability. The trauma associated with TKA can result in the activation of thrombogenic factors, which present tropism for areas of vascular injury and venous stasis[2]. Blood loss associated with the surgical procedure may reduce antithrombin III levels and inhibit the endogenous fibrinolytic system, allowing thrombus formation and growth[3,4].

Most thrombi develop in the deep veins of the calf and then extend to the thigh. However, about 20% to 30% of them may originate in the ilio-femoral venous segment, unrelated to thrombi from the calf. Approximately 80% to 90% of thromboses originate in the operated limb. Most calf thrombi are small and clinically insignificant. Likewise, proximal venous thrombosis may be non-occlusive and asymptomatic, and in some cases, there will be spontaneous resolution without adverse effects.

1 - National Institute of Traumatology and Orthopedics Jamil Haddad, Division of Teaching and Research, Rio de Janeiro, RJ, Brazil. 2 - Central Military Police Hospital, Orthopedics Service, Rio de Janeiro, RJ, Brazil. 3 - Federal University of Rio de Janeiro, Faculty of Medicine, Department of Orthopedics and Traumatology, Rio de Janeiro, RJ, Brazil.

Nonetheless, there is an important association between proximal deep vein thrombosis and pulmonary embolism, silent non-occlusive thrombi and symptomatic or fatal pulmonary embolism[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[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[8].

In the last two decades, to 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[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

We searched for articles on SciELO, Pubmed and Cochrane through Cochrane databases with the keywords knee arthroplasty, rivaroxaban, and enoxaparin through the PICO search strategy. The search performed was ((("Enoxaparin" [Mesh] AND and Enoxaparin PK-10,169 and PK 10,169 and PK10,169 and PK-10169 and PK10169 and PK10169 and EMT-967 and EMT 967 and Lovenox and Clexane and EMT-966 and EMT 966 and EMT966)) AND ("Arthroplasty, Replacement, Knee" [Mesh] AND and Arthroplasties, Replacement, Knee and Arthroplasty, Knee Replacement and Knee Replacement Arthroplasties and Knee Replacement Arthroplasty and Replacement Arthroplasty, Knee and Knee Arthroplasty, Total and Arthroplasty, Total Knee and Total Knee Arthroplasty and Replacement, Total Knee and Total Knee Replacement and Knee Replacement, Total and Knee Arthroplasty and Arthroplasty, Knee and Arthroplasties, Knee Replacement and Replacement Arthroplasty, Knee and Arthroplasty, Replacement, Partial Knee and Unicompartmental Knee Arthroplasty and Arthroplasty, Unicompartmental Knee and Knee Arthroplasty, Unicompartmental and Unicondylar Knee Arthroplasty and Arthroplasty, Unicondylar Knee and Knee Arthroplasty, Unicondylar and Partial Knee Arthroplast and Arthroplasty, Partial Knee and Knee Arthroplasty, Partial and Unicondylar Knee Replacement and Knee Replacement, Unicondylarand Partial Knee Replacement and Knee Replacement, Partial and Unicompartmental Knee Replacement and Knee Replacement, Unicompartmental) AND "Rivaroxaban" [Mesh].

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

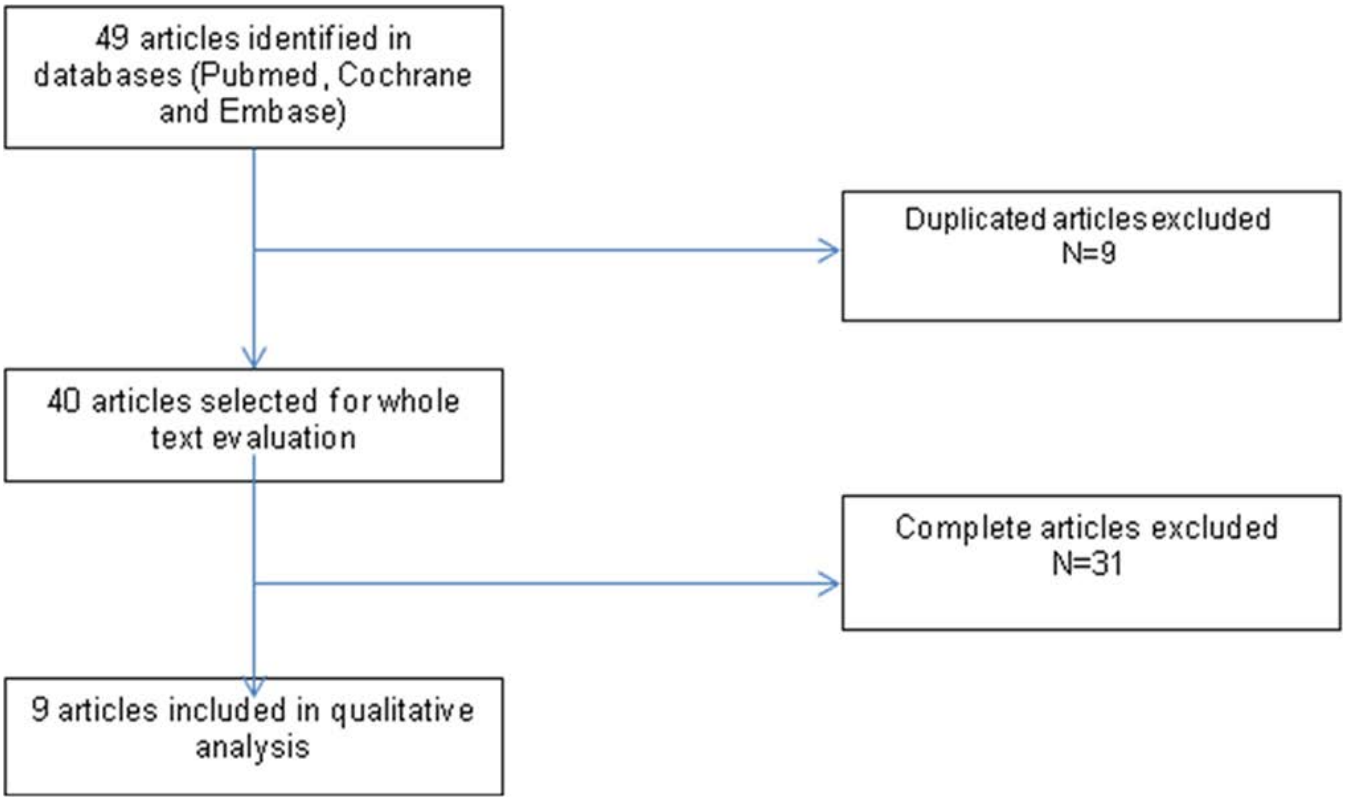

Figure 1. *Identification and selection of articles.*

Table 1. *Results of the articles analyzed concerning outcomes (bleeding, venous thromboembolism, serious adverse events and death).*

	Bleeding	Venous thromboembolism or serious adverse events
Levitan B *et al*. (2014). Benefit-risk assessment of rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty.	A) Major bleeding Rivaroxaban – 75 in 10,000 Enoxaparin – 48 in 10,000 B) Minor bleeding + surgical site Rivaroxaban – 189 in 10,000 Enoxaparin – 141 in 10,000	A) Symptomatic venous thromboembolism Rivaroxaban – 102 cases in 10,000 Enoxaparin – 178 cases in 10,000 B) Mortality Rivaroxaban – 23 cases in 10,000 Enoxaparin – 42 cases in 10,000
Li J *et al*. (2014). Comparison of rivaroxaban and enoxaparin on blood loss after total knee arthroplasty.	A) Visible blood loss Enoxaparin greater than rivaroxaban (p=0.003) B) Total blood loss No difference between groups C) Occult blood loss Rivaroxaban greater than enoxaparin (p=0.000)	Not rated.
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.	A) Major bleeding Rivaroxaban – 35 in 8548 cases Enoxaparin – 27 in 7968 cases OR weighted (95% CI) – 1.35 (0.94-1.93) B) Minor bleeding Rivaroxaban – 365 in 8548 cases Enoxaparin – 232 in 7968 cases OR weighted (95% IC) - 1.52 (1.35-1.71)	A) Symptomatic venous thromboembolism Rivaroxaban (intervention) – 77 in 8548 cases Enoxaparin (control) – 104 in 7968 cases OR weighted (95%CI) – 0 69 (0.56-0.85) B) Mortality Rivaroxaban – 7 in 8548 cases Enoxaparin – 7 in 7968 cases OR weighted (95% IC) – 1.00 (0.53-2.00)
Sindali *et al*. (2013). Elective hip and knee arthroplasty and the effect of rivaroxaban and enoxaparin thromboprophylaxis on wound healing.	A) Minor occult bleeding Rivaroxaban - 2% Enoxaparin - 0% B) Bleeding in the wound Rivaroxaban – 5% Enoxaparin – 1.8% There was no statistical difference.	A) Venous thromboembolism Rivaroxaban – 2 in 202 (1%) Enoxaparin – 1 in 59 (1.8%); p=0.52
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.	A) Postoperative bleeding Rivaroxaban – 19 in 2746 (0.69) Enoxaparin – 19 in 2747 (0.69)	A) Serious adverse events Rivaroxaban – 224 in 2,746 (8.16) Enoxaparin – 272 in 2,747 (9.90)
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.	A) Major bleeding Rivaroxaban – 123 in 2940 Enoxaparin – 96 in 2946 RR (95% CI) – 1.29 (0.99-1.67)	A) Symptomatic venous thromboembolism Rivaroxaban – 21 in 2940 Enoxaparin – 44 in 2946 RR (95% CI) – 0.49 (0.29 to 0.83)

continue...

...continue

	Bleeding	Venous thromboembolism or serious adverse events
Nieto JA *et al*. (2012). Dabigatran, Rivaroxaban and Apixaban versus Enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: Pool-analysis of phase III randomized clinical trials.	A) Major bleeding Rivaroxaban – 23 in 4955 Enoxaparin – 1 in 4971 B) Total bleeding (major and minor clinically relevant) Rivaroxaban – 160 in 4955 Enoxaparin – 124 in 4971	A) Venous thromboembolism Rivaroxaban – 34 in 4036 Enoxaparin – 99 in 4064 RR (95% CI) – 0.32 (0.15-0.67)
Eriksson BI *et al*. (2012). Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty.	A) Any bleeding Rivaroxaban + ASA (95% CI) - 1.43 (1.03-1.98) Enoxaparin + ASA (95% CI) - 1.41 (0.98-2.04)	Not rated.
Zou *et al*. (2014). Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty.	A) Hidden lesser bleeding Rivaroxaban – 1.71 (1.19 to 2.97) Enoxaparin – 1.18 (0.77 to 2.31) B) Complications in the wound Rivaroxaban – 5 cases in 102 (4.90%) Enoxaparin – 3 cases in 112 (2.67%)	A) Distal venous thromboembolism Rivaroxaban – 3 in 102 cases Enoxaparin – 14 in 112 cases B) Pulmonary thromboembolism None of the analyzed groups.

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*.[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*.[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*.[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*.[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 difference s between the groups when assessing significant bleeding events.

Sindali *et al*.[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*.[13] (4.90% *versus* 2.67%).

Li *et al*.[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*.[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 thrombo-prophylactic 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[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[21,22].

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[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[26] and consequently infection[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[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[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[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*.[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[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.

R E S U M O

A artroplastia total do joelho é um procedimento eletivo, realizado em indivíduos relativamente saudáveis. Porém, devido ao risco inerente de tromboembolismo venoso, são utilizados fármacos para sua profilaxia. O objetivo do presente trabalho foi conduzir uma revisão sistemática da literatura para comparar a eficácia da enoxaparina e da rivaroxabana na prevenção desta complicação e no risco de sangramento intraoperatório. Foi feita uma revisão no site SciELO, Pubmed e Cochrane através dos descritores, artroplastia de joelho, rivaroxabana e enoxaparina através da estratégia de busca PICO. Os critérios de inclusão foram os artigos no período estudado, que comparavam ambas as drogas em cirurgias de artroplastia do joelho. Os critérios de relevância para tornar o estudo elegível foram definidos como: somente artigos publicados a partir 2010 e com casuística com mais de 20 pacientes foram considerados; somente estudos obtidos em sua íntegra foram analisados; somente estudos com seguimento maior do que 12 meses foram considerados relevantes. As variáveis utilizadas para a comparação dos artigos foram as complicações mais comuns no pós-operatório de artroplastias do joelho: tromboembolismo venoso e sangramento. Foi utilizado o Review Man 5.3 para estruturação da revisão. Os autores observaram que nos estudos analisados, considerando tromboembolismo venoso sintomático, a rivaroxabana resultou em maiores benefícios quando comparada com a enoxaparina.

Descritores: *Artroplastia do Joelho. Tromboembolia Venosa/prevenção & controle. Rivaroxabana. Enoxaparina.*

REFERENCES

1. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: a meta-analysis. J Arthroplasty. 2017;32(2):645-52.
2. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-9.
3. Eriksson BI, Eriksson E, Gyzander E, Teger-Nilsson AC, Risberg B. Thrombosis after hip replacement. Relationship to the fibrinolytic system. Acta Orthop Scand. 1989;60(2):159-63.
4. Francis CW, Ricotta JJ, Evarts CM, Marder VJ. Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty. Clin Orthop Relat Res. 1988;(232):271-8.
5. Lieberman JR, Huo MM, Hanway J, Salvati EA, Sculco TP, Sharrock NE. The prevalence of deep venous thrombosis after total hip arthroplasty with hypotensive epidural anesthesia. J Bone Joint Surg Am. 1994;76(3):341-8.
6. Pellegrini VD Jr, Clement D, Lush-Ehmann C, Keller GS, Evarts CM. The John Charnley Award. Natural history of thromboembolic disease after total hip arthroplasty. Clin Orthop Relat Res. 1996;(333):27-40.
7. Bode C, Verheugt FW. The need for new oral anticoagulants in clinical practice: an introduction. J Cardiovasc Med (Hagerstown). 2009;10(8):593-4.
8. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98. Erratum in: N Engl J Med. 1997;337(21):1567.
9. Piccini JP, Patel MR, Mahaffey KW, Fox KA, Califf RM. Rivaroxaban, an oral direct factor Xa inhibitor. Expert Opin Investig Drugs. 2008;17(6):925-37.
10. Nieto JA, Espada NG, Merino RG, González TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res. 2012;130(2):183-91.
11. Lassen MR, Gent M, Kakkar AK, Eriksson BI, Homering M, Berkowitz SD, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. J Bone Joint Surg Br. 2012;94(11):1573-8.
12. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ. 2012;344:e3675.
13. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood Coagul Fibrinolysis. 2014;25(7):660-4.

14. Levitan B, Yuan Z, Turpie AG, Friedman RJ, Homering M, Berlin JA, et al. Benefit-risk assessment of rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total hip or knee arthroplasty. Vasc Health Risk Manag. 2014;10:157-67.
15. Sindali K, Rose B, Soueid H, Jeer P, Saran D, Shrivastava R. Elective hip and knee arthroplasty and the effect of rivaroxaban and enoxaparin thromboprophylaxis on wound healing. Eur J Orthop Surg Traumatol. 2013;23(4):481-6.
16. Turpie AG, Haas S, Kreutz R, Mantovani LG, Pattanayak CW, Holberg G, et al. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. Thromb Haemost. 2014;111(1):94-102.
17. Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thromb Res. 2012;130(2):147-51.
18. Li J, Jing J, Zhou Y, Yao Y, Zhan J. [Comparison of rivaroxaban and enoxaparin on blood loss after total knee arthroplasty]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2014;28(1):26-9. Chinese.
19. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358(26):2765-75.
20. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-80.
21. NICE. National Institute for Health and Care Excellence. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults [Internet]. London (UK): NICE; 2009 [cited 2019 Jan 12]. Available from: https://www.nice.org.uk/guidance/ta170
22. Atkins RM. NICE and venous thromboembolism. J Bone Joint Surg Br. 2010;92(5):609-10.
23. Duran A, Sengupta N, Diamantopoulos A, Forster F, Kwong L, Lees M. Cost and outcomes associated with rivaroxaban vs enoxaparin for the prevention of postsurgical venous thromboembolism from a US payer's perspective. J Med Econ. 2011;14(6):824-34.
24. Duran A, Sengupta N, Diamantopoulos A, Forster F, Kwong L, Lees M. Cost effectiveness of rivaroxaban versus enoxaparin for prevention of post-surgical venous thromboembolism from a U.S. payer's perspective. Pharmacoeconomics. 2012;30(2):87-101.
25. Kapoor A, Chuang W, Radhakrishnan N, Smith KJ, Berlowitz D, Segal JB, et al. Cost effectiveness of venous thromboembolism pharmacological prophylaxis in total hip and knee replacement: a systematic review. Pharmacoeconomics. 2010;28(7):521-38.
26. Xie J, Ma J, Huang Q, Yue C, Pei F. Comparison of enoxaparin and rivaroxaban in balance of anti-fibrinolysis and anticoagulation following primary total knee replacement: a pilot study. Med Sci Monit. 2017;23:704-11.
27. Jensen CD, Steval A, Partington PF, Reed MR, Muller SD. Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban: a retrospective cohort study. J Bone Joint Surg Br. 2011;9(1):91-5.
28. Lindquist DE, Stewart DW, Brewster A, Waldroup C, Odle BL, Burchette JE, et al. Comparison of postoperative bleeding in total hip and knee arthroplasty patients receiving rivaroxaban, enoxaparin, or aspirin for thromboprophylaxis. Clin Appl Thromb Hemost. 2018;24(8):1315-21.
29. Lotke PA. Rivaroxaban for thromboprophylaxis. N Engl J Med. 2008;359 (20):2174; author reply 2175-6.
30. Ning GZ, Kan SL, Chen LX, Shangguan L, Feng SQ, Zhou Y. Rivaroxaban for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis with trial sequential analysis of randomized controlled trials. Sci Rep. 2016;6:23726.
31. Huang HF, Li SS, Yang XT, Xie Q, Tian XB. Rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total knee arthroplasty: a meta-analysis. Medicine (Baltimore). 2018;97(48):e13465.

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

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