Thromboprophylaxis for Total Knee Arthroplasty*

Tromboprofilaxia na artroplastia total do joelho

Julio Cesar Gali[1] Danilo Bordini Camargo[1]

[1] Departament of Orthopedics, Faculty of Medical Sciences and Health, Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba, SP, Brazil

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Address for correspondence Julio Cesar Gali, MD, PhD, Departamento de Ortopedia, Faculdade de Ciências Médicas e da Saúde, Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba, SP, Brazil (e-mail: jcgali@pucsp.br).

Abstract

The authors report an update of the main methods for preventing deep vein thrombosis after total knee replacement, which are divided into mechanical and pharmacological methods. The current principal used drugs, their dosages, and the comparative risks and benefits are also reported.

Keywords
- total knee replacement
- complications
- venous thrombosis
- prevention

Resumo

Os autores descrevem uma atualização dos principais métodos de prevenção da trombose venosa profunda após artroplastia total do joelho, classificados em métodos mecânicos e farmacológicos. Reportam as principais drogas usadas, dosagem, riscos e benefícios comparativos.

Palavras-chave
- prótese total de joelho
- complicações
- trombose venosa
- prevenção

Introduction

Total knee arthroplasty (TKA) is a safe surgical procedure for pain relief and improvement of the functional limitations caused by severe arthrosis when the clinical treatment is no longer effective. However, some complications can occur. A potential complication is deep vein thrombosis (DVT). There are some risk factors for DVT: age $>$ 60 years, obesity, oral or adhesive patch contraceptive use, hormonal replacement therapy, varicose veins, inflammatory bowel disease, history of DVT or pulmonary embolism (PE), family history of thrombosis and prolonged tourniquet during arthroplasty.

Song et al[1] performed a prospective observational study with bilateral lower limb venography in 109 patients within a week after a primary, unilateral TKA. These authors reported that the postsurgical incidence of symptomatic and asymptomatic DVT was of 4.6% and 18.3% respectively.[1]

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Julio Cesar Gali 's ORCID is https://orcid.org/0000-0003-2369-6322.

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Basically, there are mechanical and pharmacological methods to prevent DVT.

Mechanical Methods

Early patient mobilization is the simplest and cheapest way to prevent thrombus formation. There are other mechanical methods to prevent DVT. Intermittent pneumatic compression reduces venous stasis, increases blood flow speed, and elevates the level of circulating fibrinolysins. Venous foot pump devices can simulate the physiological pumping action over the venous plexus when standing and walking, and, therefore, increase venous flow. Graduated compression stockings promote mild leg pressure and prevent blood accumulation.

However, mechanical compression is normally less efficient in reducing DVT than the pharmacological methods. Mechanical methods can be used in patients with high hemorrhage risk or combined with pharmacological methods.

Blanchard et al[2] evaluated post-TKA DVT occurrence in 108 patients submitted to a venography 8 to 12 days after surgery. A total of 60 patients were treated with low-molecular weight heparin (LMWH) to prevent DVT, and 48 patients were submitted to mechanical prevention by intermittent pneumatic compression of the foot. A total of 47 DVTs were diagnosed, 16 (26.7%) in the LMWH group, and 31 (64.6%) in the mechanical prophylaxis group. The difference between both groups was considered highly significant ($p < 0.001$).[2]

Lachiewicz et al,[3] in a randomized, prospective study, compared two calf compression methods as thromboembolism prophylaxis after TKA: a rapid inflation, asymmetrical compression device (RIAC) and a sequential circumferential compression device (CCD). After a primary, unilateral total arthroplasty, the incidence of thrombus was of 8.4% for the RIAC group, and of 16.8% for the CCD group ($p = 0.03$). The incidence of thrombus in bilateral TKA patients was of 4% for the RIAC group, compared with 22.7% for the CCD group ($p = 0.05$ per knee). The authors concluded that the RIAC led to a significant reduction in thromboembolism rates.[3]

He et al,[4] in a meta-analysis, demonstrated the inefficacy of continuous passive motion to prevent DVT after TKA.[4]

Pharmacological Methods

Some medical specialties attempted to create a practical clinical guide to prevent DVT. The first guide was prepared by the American College of Chest Physicians (ACCP) in 1985. This guide had two levels of recommendation. The most efficient was based on randomized clinical trials with consistent outcomes. The drugs that corresponded to these indications were warfarin, with an international normalized ratio (INR) of 2 to 3, LMWH, and fondaparinux.

On the other hand, there is a concern that an INR value of 2 to 3 can be too high for orthopedic surgeries, and that the use of drugs to reach this level, regardless of the patient risk profile, could put someone with a relative low risk of DVT in an elevated risk of bleeding.[5] Moreover, there was a very small correlation between the presence of DVT and the occurrence of PE; in addition, the role of asymptomatic DVT was questioned.[6]

In 2012, the American Academy of Orthopedic Surgeons (AAOS) published guidelines about the prevention of DVT in patients submitted to elective hip and knee arthroplasty. These patients were reportedly in risk of hemorrhage and complications associated with bleeding. In addition to the surgical procedure, the AAOS recommended the use of pharmacological agents and/or mechanical compression devices to prevent DVT in patients with no elevated risk of thromboembolism or venous bleeding. Pharmacological prophylaxis and the use of mechanical compression devices are indicated to patients with previous history of DVT; however, in individuals with a known hemorrhagic disturbance and/or active liver disease, the AAOS suggests only the use of mechanical compression devices.[7]

The drugs prescribed to prevent thrombus formation or growth are called antithrombotic agents, and they consist of antiplatelet and anticoagulation agents.

Aspirin is an efficient antiplatelet agent. In 2006, Lotke and Lonner[8] published their results with aspirin combined with early mobilization, regional anesthesia and foot pumps to prevent thromboembolic events in 3,473 patients submitted to TKA. The prevalence of non-fatal PE and proximal venous thrombosis was of 0.26% and 0.2% respectively. The authors concluded that aspirin is safer and equally efficient to other chemoprophylaxis agents in the prevention of post-TKA DVT.[8]

Callaghan et al,[9] in 2008, reported that the incidence of DVT in a population of low-risk TKA was of 2.6% with the prophylactic use of aspirin, early ambulation and foot pumps. In their opinion, prevention was exceedingly efficient.[9]

In 2010, Bozic et al[10] compared aspirin to warfarin or LMWH to prevent venous thromboembolism in TKA patients. The incidence of DVT or PE among patients treated with aspirin was of 2.3%, compared to 3.1% in patients treated with LMWH, and 4% for those treated with warfarin ($p = 0.0037$ for aspirin versus LMWH, and $p < 0.001$ for aspirin versus warfarin).[10]

Aspirin is recommended in a 325-mg dose administered twice a day. However, a recent paper reported that treatment with 81 mg twice a day is not inferior to the previously recommended dose for venous thromboembolism prophylaxis after total arthroplasty.[11]

Coumarins (warfarin) are vitamin K antagonists (oral anticoagulant agents). Warfarin use has some drawbacks: long onset of action, long half-life, INR control requirement, and the interaction between coumarins and diet.

Low-molecular weight heparins are anticoagulant agents with a high antifactor Xa activity and low anti-IIa or antithrombin activity. Liu et al[12] evaluated 2 protocols for DVT prevention with 40 mg of enoxaparin by the subcutaneous route after TKA. The treatment started 12 hours after wound closure in one group of patients, and 24 hours after in the other group, and it continued for 10 to 14 days. Both regimens yielded similar results for DVT prevention, but the group starting treatment 24 hours after surgical incision

closure presented safer outcomes regarding bleeding ($p < 0.05$).[12]

Arsoy et al[13] compared the use of LMWH with mechanical compression and aspirin after total hip or knee arthroplasty. They concluded that these agents reduced readmission rates, major complications and wound problems after primary total arthroplasties.[13]

Fondaparinux is a synthetic pentasaccharide that is a specific factor Xa inhibitor. Bauer et al,[14] in a double-blinded study, compared subcutaneous doses of 2.5 mg of fondaparinux with 30 mg of enoxaparin administered twice a day in patients submitted to major elective knee surgeries. On the 11th day, the group treated with fondaparinux presented a significantly lower incidence of venous thromboembolism (12.5%) compared with the group that was administered enoxaparin (27.8%); this corresponded to a 55.2% risk reduction ($p < 0.001$), but larger, significant bleeding was noted in patients from the fondaparinux group ($p = 0.006$).[14]

Rivaroxaban is a direct factor Xa inhibitor. In a randomized, double-blinded study, Lassen et al compared dosages of oral rivaroxaban of 10 mg once a day, 6 to 8 hours after surgery, with dosages of subcutaneous enoxaparin of 40 mg once a day, administered 12 hours before surgery, in 2,531 patients submitted to TKA. Major venous thromboembolism occurred in 1.0% of the patients treated with rivaroxaban, and in 2.6% of the patients who were administered enoxaparin (absolute risk reduction; 1.6%; $p = 0.01$). Important bleeding occurred in 0.6% of the patients treated with rivaroxaban and in 0.5% of those who were administered enoxaparin.[15]

The Record study compared rivaroxaban to enoxaparin. Bleeding at the TKA surgical site was lower during rivaroxaban use, but it was similar in total hip arthroplasties.[16]

Dabigatran is a direct thrombin inhibitor. The recommended dose is 110 mg, 1 to 4 hours after TKA; then, 110 mg, twice a day, for 10 days. In a study[17] with 1,728 patients submitted to a primary joint replacement, dabigatran use caused a 20% increase in wound bleeding compared to a 5% increase with a multimodal regimen consisting of LMWH during hospitalization and aspirin for an extended period of time ($p < 0.001$). The rate of thromboembolism for the dabigatran group was of 1.3% compared to 0.3% for the multimodal thromboprophylaxis group ($p = 0.047$).[17]

Three clinical trials, namely RE-Novate, RE-Model and RE-Mobilize, evaluated dabigatran use in both the European (40 mg/day) and American (30 mg every 12 hours) regimens in cases of major hip and knee surgeries, and their results were not inferior to those obtained with enoxaparin for DVT prevention.[18]

Apixaban is a factor Xa inhibitor. The suggested dose is 2.5 mg twice a day, starting 12 to 24 hours after surgery and continuing for 12 days (± 2) after TKA and 35 days (± 3) after total hip arthroplasty. Raskob et al[19] performed a combined analysis of two previously reported randomized, double-blinded studies that enrolled 8,464 patients and compared 2.5 mg of apixaban twice a day to 40 mg of enoxaparin once a day. Major venous thromboembolism occurred in 0.7% and 1.5% of the patients treated with apixaban and enoxaparin respectively (risk difference: apixaban minus enoxaparin = -0.8%; $p = 0.001$ for superiority). Major bleeding occurred in 0.7% and 0.8% of the patients treated with apixaban and enoxaparin respectively (risk difference: -0.02%). Major bleeding and non-major, clinically relevant bleeding occurred in 14.4% of the patients treated with apixaban, and in 4.9% of the patients treated with enoxaparin (risk difference: -0.6%). They concluded that apixaban is more efficient than enoxaparin, with no increased bleeding.[19]

A systemic, meta-analysis review and indirect treatment comparison confronted rivaroxaban, apixaban and dabigatran versus enoxaparin for DVT prophylaxis after total hip or knee arthroplasty. The relative risks and their respective 95% confidence intervals were calculated for each study individually and combined, in each anticoagulant agent. The authors reported that the relative risk of clinically relevant bleeding was higher with rivaroxaban, similar with dabigatran, and lower with apixaban. Compared to enoxaparin, the risk of symptomatic venous thromboembolism was lower with rivaroxaban and similar with dabigatran and apixaban.[20]

On the other hand, Revankar et al[21], in an economical evaluation of the use of apixaban, showed that this drug is a beneficial option for postsurgical DVT prevention compared to enoxaparin.[21]

Edoxaban is an oral, direct factor Xa inhibitor. The STAR E-3 study[22] compared 30 mg of edoxaban once a day, starting 6 to 24 hours after surgery, to subcutaneous 20 mg of enoxaparin, twice a day, starting 24 to 36 hours after surgery for 11 to 14 days after TKA in patients from Japan and Taiwan. Symptomatic pulmonary embolism and DVT or asymptomatic DVT occurred in 7.4% of the patients treated with edoxaban, and in 13.9% of those treated with enoxaparin (relative risk reduction: 46.8%), demonstrating the non-inferiority ($p < 0.001$) and superiority ($p = 0.01$) of edoxaban compared to enoxaparin. The incidence of all hemorrhagic events (major bleeding, clinically non-relevant major bleeding and minor bleeding) was of 22.3% and 18.9% in the edoxaban and enoxaparin treatment groups respectively ($p = 0.265$), suggesting that the superior efficacy of edoxaban was not associated to a higher incidence of hemorrhagic event.[22] Betrixaban is an oral direct factor Xa inhibitor. Doses of 15 mg of betrixaban administered twice a day, and 40 mg twice a day, were compared to 30 mg of enoxaparin twice a day at the Expert clinical study.[23] The incidence of DVT with 15 mg of betrixaban twice a day, 40 mg of betrixaban twice a day, and enoxaparin twice a day was of 20%, 15% and 10% respectively. There were no reports of bleeding during treatment with 15 mg of betrixaban twice a day. With 40 mg of betrixaban twice a day, bleeding occurred in 2.4% of the cases. With enoxaparin, there were 4.5% of cases of non-major, clinically relevant bleeding and 2.3% of cases of major clinically relevant bleeding. However, the authors informed that the size of the sample was relatively small; therefore, formal statistical comparisons between groups or doses were not planned.[23]

Parvizi et al,[24] in a retrospective study of 26,415 primary and review arthroplasties performed in their institution between 2000 and 2010, recommended that efforts be made to minimize PE risk during the first two weeks after the procedure, since 81% of the documented cases of symptomatic PE occurred in the first 3 postoperative days, 89% in the first postoperative week, and 94% in the first 2 postoperative weeks.[24]

There are some risk factors associated with the possibility of developing PE after TKA: the total amount of bleeding during surgery,[25] age $\geq$ 70 years, female gender, higher body mass index,[26] delayed postsurgical thromboprophylaxis,[27] and AB blood group.[28]

In summary, during TKA, the surgeon must be aware of the potential risk of DVT and PE occurrence. Early mobilization and preventive mechanical methods can be used. The risks and benefits of the pharmacological methods must be discussed with the patients. Although the goal is to prevent DVT, it is essential to avoid complications resulting from bleeding.

Conflicts of Interest

The authors have none to declare.

References

1 Song K, Xu Z, Rong Z, Yang X, Yao Y, Shen Y, et al. The incidence of venous thromboembolism following total knee arthroplasty: a prospective study by using computed tomographic pulmonary angiography in combination with bilateral lower limb venography. Blood Coagul Fibrinolysis 2016;27(3):266–9

2 Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. J Bone Joint Surg Br 1999;81(4): 654–9

3 Lachiewicz PF, Kelley SS, Haden LR. Two mechanical devices for prophylaxis of thromboembolism after total knee arthroplasty. A prospective, randomised study. J Bone Joint Surg Br 2004;86(8): 1137–41

4 He ML, Xiao ZM, Lei M, Li TS, Wu H, Liao J. Continuous passive motion for preventing venous thromboembolism after total knee arthroplasty. Cochrane Database Syst Rev 2014;(7): CD008207

5 Barrack RL. Current guidelines for total joint VTE prophylaxis: dawn of a new day. J Bone Joint Surg Br 2012;94(11, Suppl A)3–7

6 Parvizi J, Jacovides CL, Bican O, Purtill JJ, Sharkey PF, Hozack WJ, et al. Is deep vein thrombosis a good proxy for pulmonary embolus? J Arthroplasty 2010;25(6, Suppl)138–44

7 Jacobs JJ, Mont MA, Bozic KJ, Della Valle CJ, Goodman SB, Lewis CG, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Bone Joint Surg Am 2012;94(8):746–7

8 Lotke PA, Lonner JH. The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. Clin Orthop Relat Res 2006;452(452):175–80

9 Callaghan JJ, Warth LC, Hoballah JJ, Liu SS, Wells CW. Evaluation of deep venous thrombosis prophylaxis in low-risk patients undergoing total knee arthroplasty. J Arthroplasty 2008;23(6, Suppl 1):20–4

10 Bozic KJ, Vail TP, Pekow PS, Maselli JH, Lindenauer PK, Auerbach AD. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? J Arthroplasty 2010; 25(7):1053–60

11 Parvizi J, Huang R, Restrepo C, Chen AF, Austin MS, Hozack WJ, et al. Low-Dose Aspirin Is Effective Chemoprophylaxis Against Clinically Important Venous Thromboembolism Following Total Joint Arthroplasty: A Preliminary Analysis. J Bone Joint Surg Am 2017;99(2):91–8

12 Liu F, Chu X, Huang J, Tian K, Hua J, Tong P. Administration of enoxaparin 24 h after total knee arthroplasty: safer for bleeding and equally effective for deep venous thrombosis prevention. Arch Orthop Trauma Surg 2014;134(5):679–83

13 Arsoy D, Giori N, Woolson S. Mechanical Compression Reduces Readmissions and Wound Complications from Low Molecular Weight Heparin after Total Hip or Knee Arthroplasty. San Diego: AAOS Annual Meeting; 2017

14 Bauer KA, Eriksson BI, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345(18):1305–10

15 Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358(26):2776–86

16 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(10): 157–67

17 Bloch BV, Patel V, Best AJ. Thromboprophylaxis with dabigatran leads to an increased incidence of wound leakage and an increased length of stay after total joint replacement. Bone Joint J 2014;96-B(1):122–6

18 Yoshida RA, Yoshida WB, Rollo HA. Novos anticoagulantes orais para a profilaxia e tratamento do tromboembolismo venoso em cirurgias ortopédicas de grande porte. J Vasc Bras 2011;10(2): 145–53

19 Raskob GE, Gallus AS, Pineo GF, Chen D, Ramirez LM, Wright RT, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. J Bone Joint Surg Br 2012; 94(2):257–64

20 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

21 Revankar N, Patterson J, Kadambi A, Raymond V, El-Hadi W. A Canadian study of the cost-effectiveness of apixaban compared with enoxaparin for post-surgical venous thromboembolism prevention. Postgrad Med 2013;125(4):141–53

22 Fuji T, Wang CJ, Fujita S, Kawai Y, Nakamura M, Kimura T, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res 2014;134(6):1198–204

23 Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, et al; EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thromb Haemost 2009;101(1):68–76

24 Parvizi J, Huang R, Raphael IJ, Maltenfort MG, Arnold WV, Rothman RH. Timing of Symptomatic Pulmonary Embolism with Warfarin Following Arthroplasty. J Arthroplasty 2015;30(6): 1050–3

25 Miyagi J, Funabashi N, Suzuki M, Asano M, Kuriyama T, Komuro I, et al. Predictive indicators of deep venous thrombosis and pulmonary arterial thromboembolism in 54 subjects after total knee

arthroplasty using multislice computed tomography in logistic regression models. Int J Cardiol 2007;119(1):90–4
26 Bohl DD, Maltenfort MG, Huang R, Parvizi J, Lieberman JR, Della Valle CJ. Development and Validation of a Risk Stratification System for Pulmonary Embolism After Elective Primary Total Joint Arthroplasty. J Arthroplasty 2016;31(9, Suppl) 187–91
27 Plante S, Belzile EL, Fréchette D, Lefebvre J. Analysis of contributing factors influencing thromboembolic events after total knee arthroplasty. Can J Surg 2017;60(1):30–6
28 Newman JM, Abola MV, Macpherson A, Klika AK, Barsoum WK, Higuera CA. ABO Blood Group Is a Predictor for the Development of Venous Thromboembolism After Total Joint Arthroplasty. J Arthroplasty 2017;32(9S):S254–8