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Review Article

Deep Vein Thrombosis Prevention in Total Knee Arthroplasty. A Review -

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ABSTRACT

The author reported an update of main deep vein thrombosis prophylaxis and pulmonary embolism risk factors after total knee arthroplasty, divided into mechanical and pharmacological were reported. The principal currently used drugs, their dosage, comparative risks and benefits are discussed.

Keywords : Total knee arthroplasty; Complications; Venous thrombosis; Pulmonary embolism; Prevention

INTRODUCTION

Total Knee Arthroplasty (TKA) is a surgical procedure to relief pain and ameliorates impaired function caused by severe arthritis, if nonsurgical treatments are no longer helpful. TKA is generally a safe procedure however some complications may occur. One potential complication is Deep Vein Thrombosis (DVT). Song, et al. [1] did a prospective observational study using bilateral lower limb venography in 109 patients within a week after primary unilateral TKA. They reported that the incidence of symptomatic DVT and asymptomatic DVT, following the surgical procedure was 4.6 and 18.3%, respectively. There are some risk factors for DVT development: age older than 60 years, obesity, use of oral contraceptives or hormone replacement therapy, varicose veins, inflammatory bowel disease, history of DVT or Pulmonary Embolism (PE), family history of thrombosis, and prolonged tourniquet time.

Basically there are mechanical and pharmacological methods used for DVT prevention.

MECHANICAL METHODS

Early patient mobilization is the simplest and costless way to prevent thrombus formation. There are some modalities of DVT prevention with mechanical methods. Intermittent pneumatic compression is used to diminish venous stasis, enhance blood flow speed, and raising circulating fibrinolysins level'. Venous foot pumps may simulate the physiological pump action on the venous plexus that happens during weight bear and walking and thus may increase venous flow. Compression stockings promote gentle pressure to the legs for excessive blood accumulation prevention.

However, mechanical compression is usually less efficacious to demote DVT prevalence than pharmacologic methods, which can be used in patients who are at high risk of bleeding or combined to pharmacologic methods.

Blanchard, et al. [2] evaluated DVT occurrence in 108 patients after TKA, with phlebography done eight to 12 days after surgery. DVT prevention was done in 60 of them with Low Molecular Weight Heparin (LMWH), and in 48 people mechanical prophylaxis prevention was performed with continuous intermittent pneumatic compression of the foot. Forty-seven DVT were diagnosed in all patients, 16 (26.7%) in the LMWH group and 31 (64.6%) in the mechanical prophylaxis group. The difference between the two groups was considered highly significant *($p < 0.001$)*.

Lachiewicz, et al. [3] in a prospective, randomized study compared two methods of calf compression for prophylaxis of thromboembolism after TKA: a Rapid Inflation, Asymmetrical Compression (RIAC) and a Sequential Circumferential Device (SCD). After unilateral primary TKA the incidence of thrombi with was 8.4% for the RIAC group and 16.8% for the SCD group ($p = 0.03$). On the contrary the incidence of thrombi in patients with bilateral TKA, was 4% for the RIAC group compared to 22.7% for the SCD device group ($p = 0.05$ per knee). They concluded that the RIAC use significantly lower the thromboembolism rate.

He, et al. [4] in a meta-analysis study demonstrated no effectiveness of continuous passive motion therapy on preventing Venous Thromboembolic Disease (VTD) in patients after TKA.

PHARMACOLOGICAL METHODS

The first practical clinical guide to prevent DVT occurrence was done by the American College of Chest Physicians (ACCP), in 1985. This guide had two levels of recommendation. The most effective was based in randomized controlled trials with consistent results. The drugs that matched those indications were warfarin with an International Normalised Ratio (INR) of 2 to 3, low-molecular-weight heparin and fondaparinux.

On the other hand there is the concern that the INR of 2 to 3 might be high for orthopedic surgeries, and the use of drugs indicated to obtain this level regardless patients' risk profiles could place some patients with relative low risk of DVT to a hazard for bleeding [5]. Also there was a very low correlation between the presence of DVT and PE and the significance of asymptomatic DVT was questioned [6].

In 2012, the American Academy of Orthopaedic Surgeons published a guideline on preventing VTD in patients undergoing elective hip and knee arthroplasty. They reported that these patients are at risk for bleeding and bleeding-associated complications. Their recommendation was the use of pharmacologic agents and/or mechanical compressive devices for the prevention of VTD in patients who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding. For patients who have had a previous venous thromboembolism, pharmacologic prophylaxis and mechanical compressive devices are indicated. For those who also have a known bleeding disorder and/or active liver disease, they suggest the use mechanical compressive devices only [7].

Drugs prescribed to prevent thrombi formation or growing are labeled antithrombotics and they consist of antiplatelet and anticoagulants drugs.

Aspirin is an effective antiplatelet drug. In 2006, Lotke & Lonner published their outcomes with aspirin combined with early mobilization, regional anesthesia and foot pumps, for thromboembolic events prevention in 3473 consecutive patients submitted to TKA. The prevalence of nonfatal PE and proximal venous thrombosis was 0.26% and 0.2%, respectively. They concluded that aspirin is safer than and equally efficacious as other chemoprophylactic agents for DVT prevention after TKA [8].

Callaghan, et al. [9], in 2008, reported that DVT incidence in a low-risk TKA population was 2.6% with the prophylactic use of aspirin, early ambulation, and foot pumps. They considered the prevention efficacy extremely successful.

In 2010, Bozic, et al. compared aspirin to warfarin or LMWH for venous thromboembolism prevention in TKA patients. The DVT or PE occurrence among people treated with aspirin was 2.3% compared to 3.1% for LMWH group patients and 4.0% for warfarin group individuals ($P = 0.0037$ for aspirin vs LMWH and $P < .001$ for aspirin vs warfarin). Alternating logistic regression models were used to justify patients gathering within physicians and physicians within hospitals and a significance level of $P \leq .05$ to provide face validity or because of observed confounding with other variables [10].

The aspirin recommended dosage is 325 mg twice daily. However recent publication reported that 81-mg twice daily is not inferior to high-dose aspirin for venous thromboembolism prophylaxis following total joint arthroplasty [11].

Coumarins (warfarin) are antagonists to vitamin K oral anticoagulant drugs. There are some disadvantages of warfarin use: long onset of action, long half-life, INR control requirement and common interaction between coumarins and diety.

Low Molecular Weight Heparin includes several types of anticoagulant drugs that have high activity anti-factor Xa e low activity anti-IIa or antithrombin.

Liu et al. [12] evaluated two treatment protocols for DVT prevention with enoxaparin after TKA. One patients group initiated enoxaparin prescription 12 hours after wound closure, and the second group got it 24 hours after that. In both groups 40 mg enoxaparin was given subcutaneously once a day for 10-14 days. Statistical analysis using the $\chi 2$ test, Student's t test, and Wilcoxon rank-sum test showed that both regimens were similar for DVT prevention but the 24h onset group was safer for bleeding *($p < 0.05$)*.

Arsoy et al. compared LMWH to compression device with aspirin for VTD prophylaxis after total hip or knee arthroplasty. They concluded that compression device associated to aspirin decreases readmissions rates, major complications, and wound problems after primary total joint arthroplasty [13].

Fondaparinux is a factor Xa specific inhibitor synthetic pentasaccharide. In a double-blind study, Bauer et al. compared subcutaneous doses of 2.5 mg fondaparinux to 30 mg of enoxaparin twice daily in patients undergoing elective major knee surgery. The fondaparinux group had a significantly lower incidence of venous thromboembolism by day 11 (12.5 %) than the enoxaparin group (27.8%), corresponding to 55.2% reduction in risk *($P < 0.001$)* but major bleeding occurred more frequently in the fondaparinux group ($P = 0.006$) [14].

Rivaroxaban is a direct factor Xa inhibitor. In a randomized double-blind trial, Lassen et al. compared oral rivaroxaban, 10 mg once daily, received 6 to 8 hours after surgery, to subcutaneous enoxaparin, 40 mg once daily, beginning 12 hours before surgery, in 2531 patients undergoing TKA. Major venous thromboembolism occurred in 1.0% of patients in rivaroxaban group and in 2.6% of patients in enoxaparin group (absolute risk reduction, 1.6%; P=0.01). Major bleeding was seen in 0.6% of patients given rivaroxaban and 0.5% of patients given enoxaparin [15].

Rivaroxaban was compared to enoxaparin in the RECORD studies. Rivaroxaban showed less surgical-site bleeding for TKA and similarity to enoxaparin for Total Hip Arthroplasty [16].

Dabigatran is a direct thrombin inhibitor. The proposed dosage is 110 mg, one to four hours after the surgery, then 110 mg twice a day for 10 days for TKA. In a study with 1728 patients undergoing primary joint replacement the use of dabigatran led to 20% increase in post-operative wound leakage compared to 5% increase with a multimodal regimen, consisted of LMWH as an inpatient and the extended use of aspirin *($p < 0.001$)*. The thromboembolism rate in dabigatran patients group was 1.3% compared to 0.3% in patients receiving the multimodal thromboprophylaxis regimen ($p = 0.047$) [17].

Outcomes of dabigatran clinical trials studies RE-Novate, RE-Model, and RE-Mobilize using both the European regimen (40 mg/day) and the American regimen (30 mg every 12 hours) during major hip and knee surgeries did not report inferior safety and efficacy to those obtained with enoxaparin in DVT prevention [18].

Apixaban is a factor Xa inhibitor. The suggested dosage is 2.5 mg twice daily starting 12 to 24 hours after operation, continued for 12 days (± 2) after knee and 35 days (± 3) after hip arthroplasty. Raskob et al. managed a pooled analysis of two double-blind randomized studies previously reported including 8464 patients. Comparing 2.5 mg twice a day apixaban to 40 mg daily enoxaparin. The Mantel-Haenszel test was used for statistical analysis. Major venous thromboembolism occurred in 0.7% and 1.5% in the apixaban and enoxaparin patients, respectively (risk difference, apixaban minus enoxaparin = -0.8%; two-sided p = 0.001 for superiority). Major bleeding occurred in 0.7% and 0.8% in the apixaban and enoxaparin patients, respectively (risk difference -0.02%). Combined major and clinically relevant non-major bleeding happened in 14.4% of patients receiving apixaban and 4.9% of patients receiving enoxaparin (risk difference -0.6%). They concluded that apixaban was more effective than enoxaparin without increased bleeding [19].

A systematic review, meta-analysis, and indirect treatment comparisons checked rivaroxaban or dabigatran or apixaban versus enoxaparin for prophylaxis against venous thromboembolism after total hip or knee replacement. The relative risks and their respective 95% confidence intervals were calculated for each study and for the pooled studies for each of the anticoagulants. The authors reported that the relative risk of clinically relevant bleeding was higher with rivaroxaban, similar with dabigatran and lower with apixaban, and 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. in an economic evaluation of apixaban use showed that this drug is a cost-effective alternative for post-surgical venous thromboembolism prevention compared to enoxaparin [21].

Edoxaban is an oral direct factor Xa inhibitor. STARS E-3 trial compared edoxaban 30 mg once daily beginning 6 to 24 hours post surgery or enoxaparin 20 mg subcutaneously twice daily beginning 24 to 36 hours post surgery for 11 to 14 days after TKA, in patients in Japan and Taiwan. Symptomatic PE, symptomatic DVT, or asymptomatic DVT occurred in 7.4% patients receiving edoxaban and 13.9% patients receiving enoxaparin (relative risk reduction, 46.8%), demonstrating non-inferiority *($P < 0.001$)* and superiority ($P = 0.010$) of edoxaban relative to enoxaparin. The incidence of all bleeding events (major bleeding, clinically relevant non-major bleeding, and minor bleeding) was 22.3% versus 18.9% in the edoxaban and enoxaparin treatment groups, respectively ($P = 0.265$) and suggesting that the superior efficacy of edoxaban was not associated with an increased incidence of bleeding events [22].

Betrixaban is a Factor Xa (FXa) oral direct inhibitor. Betrixaban 15 mg twice a day and 40 mg twice a day were compared to enoxaparin 30 mg twice a day in the EXPERT trial. The DVT incidence for betrixaban 15 mg, betrixaban 40 mg, and enoxaparin was 20%, 15% and 10%, respectively. On the other hand bleeding report with betrixaban 15 mg was none, 2.4% for betrixaban 40 mg and 4.5% clinically significant non-major bleeds, and 2.3% clinically significant major bleeds with enoxaparin use. However the authors informed that the study had relatively small sample sizes; therefore, formal statistical comparisons between treatments groups or between doses were not planned [23].

Parvizi et al. in a retrospectively studied of 26,415 primary and revision total joint arthroplasties cases performed from 2000 to 2010 at their institution, recommended that efforts must be made to minimize PE risk during the first two weeks after the procedure, since 81% documented symptomatic PE cases occurred within three postoperative days, 89% within one postoperative week, and 94% within two postoperative weeks [24].

There are some reported risk factors associated with PE after TKA: total amount of operative bleeding, [25] age ≥ 70, female gender, higher body mass index, [26] delaying the administration of postsurgical thromboprophylaxis, [27] and in AB blood patients [28].

In summary, when performing TKA surgeons must be aware of potential DVT risks and factors associated with PE. Early mobilization and mechanical prevention methods may be used. Risk and benefit of pharmacological methods should be discussed with patients. If on the one hand, the goal is preventing DVT occurrence, conversely avoid bleeding complications is essential.

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: 266-9. https://goo.gl/zmtZQU
2. Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomized comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. J Bone Joint Surg Br. 1999; 81: 654-9. https://goo.gl/1VsqyZ
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: 1137-41. https://goo.gl/tZd3LX
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. https://goo.gl/cM92tL
5. Barrack RL. Current guidelines for total joint VTE prophylaxis: dawn of a new day. J Bone Joint Surg Br 2012; 94: 3-7. https://goo.gl/E5DeTv
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: 138-44. https://goo.gl/MZizKp
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: 746-7. https://goo.gl/F5M8tf
8. Lotke PA, Lonner JH. The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. Clin Orthop Relat Res 2006; 452: 175-80. https://goo.gl/invQqr
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: 20-4. https://goo.gl/z38QUg
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: 1053-60. https://goo.gl/qdrMto
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: 91-8. https://goo.gl/rW3Uf3
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: 679-83. https://goo.gl/NvEwik
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. AAOS Annual Meeting. San Diego, 2017. https://goo.gl/Bua3Nx
14. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001; 345: 1305-10. https://goo.gl/yAYDl0
15. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008; 358: 2776-86. https://goo.gl/wURFxI
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; 26: 157-67. https://goo.gl/WjSRst
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: 122-6. https://goo.gl/o3kaOk
18. Yoshida RA, Yoshida WB, Rollo HA. New oral anticoagulants for the prophylaxis and treatment of venous thromboembolism in large orthopedic surgeries. J Vasc Bras. 2011; 10: 145-53. https://goo.gl/ZqVZIJ
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: 257-64. https://goo.gl/E2uqJM
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: 3675. https://goo.gl/bV6TfN
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: 141-53. https://goo.gl/sD7Fxk
22. Fuji T, Wang CJ, Fujita S, Kawai Y, Nakamura M, Kimura T, et al. Edoxaban versus enoxaparin for thrombophylaxis after total knee arthoplasty: the STARS E-3 trial. Thromb Res. 2014; 134: 1198-204. https://goo.gl/pQraeE
23. Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, Sinha U, Gretler DD; 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: 68-76. https://goo.gl/5tdc6Z
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: 1050-3. https://goo.gl/UYjpHp

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: 90-4. https://goo.gl/5z0V3X

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: 187-91. https://goo.gl/ABgM0I

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: 30-6. https://goo.gl/VI5MIO

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; 2: S0883-5403(17)30181-X. https://goo.gl/QqmIms