



2018

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Recommended Citation

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Examination of Venous Thromboembolism Prophylaxis in Patients Undergoing Total Knee Arthroplasty

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Abstract

- Elective total knee arthroplasty (TKA) is the most frequently performed inpatient surgical procedure in the United States (Kurtz, Ong, Lau, Mowat, & Halpern 2007). Complications of this procedure include deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE). Various pharmacological agents exist for VTE prophylaxis. Warfarin and low-molecular-weight heparin (LMWH) were commonly used for VTE prophylaxis in the past, but with the emergence of novel anticoagulants including factor Xa inhibitors and direct thrombin inhibitors (DTIs), warfarin is used far less frequently. Aspirin is also approved for VTE prophylaxis. The purpose of this study was to determine if a superior drug or combination of drugs exist for VTE prophylaxis based on patient outcomes, cost effectiveness, and risk profile. This review of literature analyzed studies from the past 10 years that compared aspirin, warfarin, Lovenox, and the novel anticoagulants for VTE prophylaxis in post-operative TKAs. Study outcomes included VTE prevention, bleeding risk, and cost. Reversal agents were also examined. Findings of this author's literature review demonstrated that currently, no one superior medication exists for prophylaxis of VTE events in patients undergoing TKA (Cafri et al., 2017). However, current research indicates that both factor Xa inhibitors and aspirin have emerged as the medications of choice. Of the two, aspirin is commonly favored as it does not require laboratory monitoring, it is cost effective, and it is available over the counter. It also has less risk of major bleeding compared to factor Xa inhibitors.

Introduction

- Elective total knee arthroplasty (TKA) is the most frequently performed inpatient surgical procedure in the United States, with an estimated 700,000 TKAs performed in 2010 and a projected 3.48 million procedures per year by 2030 (Kurtz, Ong, Lau, Mowat, & Halpern, 2007). Well-known complications of this procedure include DVT and PE, collectively referred to as VTE. Without utilization of prophylactic measures, the reported risk of venographically documented DVT in patients undergoing TKA ranges from 41-85%. Since the implementation of VTE prophylaxis, a reduction in VTE events of 0.6-1% during hospitalization and 2-3% at three months postoperatively has been reported (Kakkar & Rushton-Smith, 2013). Various pharmacological agents exist for the purpose of VTE prophylaxis. Such agents include aspirin, clopidogrel, warfarin, LMWH, and novel anticoagulants including factor Xa inhibitors and DTIs. The American College of Chest Physicians (ACCP) and the American Academy of Orthopedic Surgeons (AAOS) initially had differing views regarding the superior VTE prophylaxis regimen for patients undergoing major orthopedic surgery, which includes TKA. However, as of 2012, the ACCP and AAOS have both approved of the sole use of aspirin as a means of VTE prophylaxis (Stewart & Freshour, 2013). The ACCP recommends use of LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban, low-dose unfractionated heparin (UFH), vitamin K antagonists, or aspirin for a minimum of ten to fourteen days postoperatively (Falck-Ytter et al., 2012). The AAOS recommends using prophylaxis but does not currently endorse a single, superior medication (AAOS, 2011).

Statement of the Problem

- Many potential pharmacologic options for VTE chemoprophylaxis exist, each with a unique profile of benefits, risks or side effects, and cost. These factors, along with patients' medical history, must be considered when determining the most suitable option for VTE chemoprophylaxis. To date, no singular "gold standard" therapy is recommended for VTE prophylaxis following TKA.

Research Question

- **Among the current pharmacologic options for VTE prophylaxis following TKA, does a superior drug or combination of drugs exist based on patient outcomes?**
- **Which of the current pharmacologic VTE prophylaxis options demonstrates the greatest cost effectiveness with the fewest risks?**

Literature Review

- An online database search of PubMed, Dynamed, Cochrane, and Science Direct were utilized to find research articles regarding outcomes of different medications for VTE prophylaxis in patients undergoing TKAs.
 - Pharmacology of medications included in this literature review were obtained from various, up to date, credible textbooks and research articles.
 - Studies were included if the patient population underwent a TKA, received VTE prophylaxis, and did not have a prior heart valve repair or preexisting condition requiring prior anticoagulation therapy.
 - Studies also had to be from within the last 10 years. Study participants were all adults.
- In a systematic review, Vincent, V. G., Phan, K., Yadin, L., & Warwick, B. (2009) examined the efficacy of aspirin in preventing VTE in patients undergoing THA or TKA
 - The overall rates of DVT and PE in the THA and TKA populations were 1.2% and 0.6%, respectively. The rate of major bleeding was 0.3%, and the pooled mortality rate was 0.2%. The researchers concluded that aspirin used both alone and in combination for thromboprophylaxis resulted in a low rate of VTE and major bleeding complications.
- Wilson, Poole, Chauhan, & Rogers, (2016) performed a systematic review of 13 total studies investigating the efficacy of aspirin for DVT prophylaxis compared to warfarin, enoxaparin, factor Xa inhibitors, and direct thrombin inhibitors following THA and TKA.
 - Wilson et al. (2016) concluded that insufficient evidence existed to establish one medication as superior and that each had a unique side effect profile to be considered on a case-by-case basis.
- Vincent et al. (2009) performed a systematic review to determine the efficacy of aspirin in preventing VTE in patients undergoing a TKA or THA.
 - The researchers concluded that aspirin used both alone and in combination for thromboprophylaxis resulted in a low rate of VTE and major bleeding complications. This study demonstrated aspirin can be used as a sole means of VTE prophylaxis in postoperative TKA patients.
- Stewart et al. (2013) evaluated the suitability of aspirin in prevention of VTE in high-risk orthopedic surgery patients. After analysis, researchers were unable to conclude whether aspirin was a safe and effective option for VTE prophylaxis in high-risk patients undergoing THA, TKA, or hip fracture surgery. They concluded that enough validation existed for practitioners to use aspirin as the sole means of VTE prophylaxis, but not enough validation existed to recommend a change to sole use of aspirin for practitioners who currently use a more potent anticoagulant.
- Neumann et al. (2012) evaluated the risks and benefits of oral direct factor Xa inhibitors versus LMWH in patients undergoing TKA or THA.
 - The factor Xa inhibitors did show a significant reduction in symptomatic DVTs compared to enoxaparin.
- Bala et al. (2017) performed a study utilizing Humana and Medicare databases from 2007 to 2015 to gather and analyze TKA cases. The purpose of this study was to determine whether differences in VTE incidence existed for patients undergoing primary TKAs depending on whether they were administered aspirin, warfarin, enoxaparin, or factor Xa inhibitors.
 - The authors concluded factor Xa inhibitors were associated with the lowest incidence of DVT and PE at 90 days. However, at two weeks and at 30 days, aspirin had the lowest DVT incidence. At six weeks, both aspirin and factor Xa inhibitors shared the lowest incidence of DVT.
- Cafri et al. (2017) evaluated the comparative safety and efficacy of aspirin, LMWH, factor Xa inhibitors, and vitamin K antagonists for VTE prophylaxis following TKA.
 - The researchers concluded that a lack of evidence existed to indicate the superiority of any agent relative to aspirin.

Discussion

- **Among the current pharmacologic options for VTE prophylaxis following TKA, does a superior drug or combination of drugs exist based on patient outcomes?**
 - Multiple medication options exist for postoperative DVT prophylaxis following TKA.
 - Each option possesses a unique mechanism of action and side effect profile; further, variable efficacy and associated cost must be considered in analyzing the utility of each option in each patient case.
 - Among the agents, aspirin and factor Xa inhibitors have demonstrated the most growth in utilization for DVT prophylaxis following TKA; they have demonstrated adequate efficacy as well. Factor Xa inhibitors are associated with an increased cost and risk of bleeding, but they also exhibit a slightly decreased risk of VTE compared to aspirin.
 - Aspirin demonstrates comparable outcomes, with only a slightly increased risk of VTE as noted above and are available for a fraction of the cost of factor Xa inhibitors. Warfarin continues to be the drug of choice in patients with mechanical heart valves requiring chemoprophylaxis.
- **Which of the current pharmacologic VTE prophylaxis options demonstrates the greatest cost effectiveness with the fewest risks?**
 - Medication cost incurred by the patient is difficult to determine due to varying insurance coverage and out of pocket expenses. A website (www.goodrx.com) was utilized to obtain average cost of each medication. The following costs do not include any insurance coverage. The cost of 365 aspirin (81 mg tablets) was \$5.70. The cost of 60 apixaban (5 mg tablets) was \$454. The cost of 30 warfarin (5 mg tablets) was \$18.25. Finally, the cost of a 30-day supply of enoxaparin (40 mg/0.4mL syringes) was \$929.65.
 - Duran et al. (2012) completed research evaluating the cost-effectiveness of rivaroxaban versus enoxaparin for VTE prophylaxis in patients undergoing THA and TKA from a United States payer's perspective.
 - Researchers utilized a decision-analytic model that was divided into the following three sub-modules according to the patient's anticoagulation: prophylaxis, post-prophylaxis, and long-term complications.
 - The researchers found that rivaroxaban was associated with a cost savings of \$465.74 per patient and prevented an average of 0.0193 symptomatic VTE events per patient. Sensitivity analysis demonstrated a cost savings ranging from \$293.01 to \$848.68.
 - Mostafavi et al. (2015) examined the cost effectiveness of aspirin compared to warfarin in TKAs. The researchers used a Markov cohort cost effectiveness analysis that compared the costs, health benefits, and the costs per quality adjusted life year (QALY) for patients 55 to 85 years of age. The results of their analysis revealed aspirin was more cost effective than warfarin in the majority of patients undergoing TKAs. In patients with a high probability of VTE and a low probability of bleeding, however, warfarin was more cost effective
- I want to give a very special thank you to Travis Wolf, PhD, Kyle Leftwich, PharmD, Professor Daryl Sieg, PA-C, Professor Russell Kauffman, PA-C, and Dawn Hackman for all of your help in writing this scholarly project.

Acknowledgements

Applicability to Clinical Practice

- Multiple medications are both safe and effective in the prevention of VTE events in patients undergoing TKA. In the past, warfarin was the most commonly utilized prophylactic agent, and it continues to be the agent of choice in patients who have previously undergone heart valve repair. However, due to its multiple potential drug interactions, frequent required laboratory monitoring of the INR, and difficulty maintaining a therapeutic INR, warfarin is being used far less frequently. Clinicians have begun favoring aspirin and factor Xa inhibitors, and both of these agents been endorsed by the AAOS and AACP as sole options for management of VTE prophylaxis in patients undergoing TKA.
- Several studies, as discussed above, have demonstrated the superiority of aspirin and factor Xa inhibitors over LMWH and warfarin in terms of efficacy of DVT prevention. Factor Xa inhibitors are costlier and demonstrate an increased bleeding risk compared to aspirin. Neither drug requires laboratory monitoring, and once daily and twice daily dosing options are available for both drugs.
- After extensive review of the literature, this author's opinion is that, in low risk patients undergoing TKA, aspirin is a safe and effective chemoprophylactic agent for DVT prevention. Aspirin has a limited risk profile, is cost effective and available over the counter, and does not require laboratory monitoring. The dosing regimen is simple and consists of one 81 mg tablet twice daily for six weeks postoperatively. Further, in the case of overdose, a reversal agent is available. Clinicians must be prudent in analyzing each patient's DVT risk preoperatively so as to choose the most superior prophylactic agent based on the patient's history and anticipated period of immobilization.

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