RESEARCH ARTICLE

The Current Status of Venous Thromboembolism Prophylaxis Following Total Joint Arthroplasty

Authors
Dustin B. Rinehart, MD; Ivy Nguyen, MD; Michael H. Huo, MD

Affiliation
Department of Orthopaedic Surgery UT Southwestern Medical Center 1801 Inwood Road Dallas, TX 75390-8883
Fax: 214-645-3300

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Corresponding author:
Michael H. Huo, MD
Email: Michael.Huo@utsouthwestern.edu

Abstract

Background: A variety of local and systemic factors contribute to the increased risk of venous thromboembolism (VTE) following total knee arthroplasty (TKA) and total hip arthroplasty (THA). The optimal regimen(s) for VTE prophylaxis are not conclusively defined at the present. This review is focused on the most current data on the outcomes of using various VTE prophylaxis following TKAs and THAs in the United State (U.S.)
Methods: A review of the literature over the past 5 years was undertaken. We in particular focused on the data comparing the efficacy and the safety of different agents.
Results: The commonly used VTE prophylaxis agents in the U.S. include: low-molecular-weight heparin, the new oral anticoagulants (factor Xa inhibitors), warfarin, and aspirin. Aspirin in particular has gained popularity over the past few years. This is principally due to several factors: less bleeding, equal efficacy, and the ease of use. Most surgeons use a "multi-modal" protocol including early mobilization, mechanical prophylaxis, and chemoprophylaxis.
Conclusion: There is no conclusive evidence with regard to what agent(s) are the most efficacious and the safest in VTE prophylaxis following TKAs and THAs. There is however general agreement between the major guidelines from the professional associations of orthopedic surgery, and from the non-orthopedic disciplines. It is important to risk-stratify each patient, and to apply the most appropriate VTE prophylaxis.

Introduction

The volume and the demand for total joint arthroplasty (total knee arthroplasty TKA, and total hip arthroplasty THA) continues to increase worldwide.[1] Many advances have evolved in the surgical techniques, the implant design and manufacturing, and the perioperative care pathways to reduce the complications and to optimize the clinical outcomes. The most optimal regimen for venous thromboembolism (VTE) prophylaxis that is both safe and efficacious however is not yet fully defined for the patients after their TKAs and THAs.

Several local and systemic factors contribute to the increased risk of VTE following total joint arthroplasties. Some of the factors in the TKA patients include: the use of tourniquet, prolonged flexion of the knee, and soft tissue retraction contributing to venous stasis. Thermal injury from the use of cement for implant fixation may result in focal areas of vascular damage.[2-4] Tissue edema and joint effusion after surgery may also contribute to venous compression and stasis. In THA patients the dislocation of the femoral head from the acetabulum results in significant limb torsion that has been demonstrated to occlude the femoral vein.[5,6] Depending on the surgical approach during THA, retractors may compress the femoral vein resulting in both venous stasis, and/or endothelial injury.[7] Postoperatively, patients have a systemic inflammatory state that promotes hypercoagulability through the activation of tissue and clotting factors.[2,8] Several studies have demonstrated a reduction in the levels of antithrombin III with concomitant inhibition of the endogenous fibrinolytic system.[9,10] Longer operative time, prolonged immobilization, and non-modifiable patient risk factors also contribute to the risk of VTE after total joint arthroplasty.[11-13] Prevention of VTE after total joint arthroplasty is critically important to reduce patient morbidity and even mortality. Moreover, the cost of treating VTE has been estimated to be greater than $30,000 in the first year after the event.[14]

Where have we been?

The use pharmacological chemoprophylaxis for the prevention of VTE following TKAs and THAs have been in a state of evolution for over half a century. Chemoprophylaxis may be effective; however, it is fraught with challenges including: hemarthrosis, hematoma formation, prolonged wound drainage, wound dehiscence leading to infection, the need for laboratory monitoring, and patient compliance. Historically, rates of asymptomatic VTE after TKAs and THAs without any thromboprophylaxis were as high as 27% and 54%, respectively.[15] Prophylaxis using unfractionated heparin began in the 1970s. The clinical complications with using unfractionated heparin included: bleeding at the surgical site with wound healing complications. Additionally, its efficacy was not optimal.[16-19] Imperiale et al. demonstrated unfractionated heparin to have the highest risk of clinically important bleeding after THAs.[20] Another popular chemoprophylaxis agent is warfarin. Both adjusted- and fixed-dose warfarin was commonly used in the 1980s and in the 1990s.[21] Warfarin was popular due to several characteristics: the mechanism of action was well-defined, it could be

administered orally, was overall effective in reducing the incidence of VTE, and the risk of significant bleeding was low as long as the level remained in the therapeutic range.[22-25] The major barrier was the labor-intensive monitoring of warfarin. In the late 1990s, low-molecular-weight heparin (LMWH) was introduced into the orthopedic surgery community. Its use expanded quickly to approximately 40% of the TKA and THA patients.[26] LMWH provided good efficacy, however bleeding at the surgical site remains a significant concern.[27]

The American College of Chest Physicians (ACCP) published its VTE prophylaxis guidelines in 2001.[28] However, their guidelines were focused on the data of various chemoprophylaxis clinical trials based upon VTE documented using venographic surveillance. Many of the patients with positive venogram were asymptomatic. Controversies remained with regard to what is the most optimal balance between the prevention of VTE versus the risks of surgical site bleeding and the complications related to the use of chemoprophylaxis. The American Academy of Orthopaedic Surgery (AAOS) introduced its VTE prophylaxis guidelines in the late 2000's. Some of the recommendations were in conflict with those outlined in the ACCP guidelines. The two groups agreed to work collaboratively over the subsequent years. The current recommendations from both the AAOS and the ACCP are now aligned in the same recommendations. The surgeon must however risk-stratify each patient and select the most efficacious and the safest prophylaxis method.[29]

Where are we now?

Over the past two decades, the chemoprophylaxis used in the U.S. included: LMWH, warfarin, factor-Xa inhibitors (apixaban and rivaroxaban), the penta-saccharide (fondaparinux), and aspirin.[30] A decade ago, the American Association of Hip and Knee Surgeons (AAHKS) conducted a survey of its membership with regard to their preferred chemoprophylaxis for VTE following hospital discharge. The survey result showed that the most commonly prescribed agent was warfarin, followed by LMWH, aspirin, and lastly the penta-saccharide (fondaparinux).[31] The survey results did not show any different surgeon preferences between the TKAs or the THAs. In the next sections, we will present the current clinical practice data over the past five years in the U.S. for VTE chemoprophylaxis following total joint arthroplasties.

Total Knee Arthroplasty

Several studies have presented data comparing different chemoprophylaxis following TKAs. Huang et al. performed a meta-analysis of randomized clinical trials on the factor-Xa inhibitors versus the LMWH. Data showed that the patients who received rivaroxaban had a lower rate of symptomatic VTE (relative risk [RR]:0.55; 95% confidence interval [CI]: 0.35-0.86; p=0.009) when compared to the LMWH group. There was no difference in the incidence of major bleeding, or in the all-cause mortality.[32] Lindquist et al. using data from a retrospective analysis reported lower bleeding complications in the patients who received aspirin than those patients who received the factor-Xa inhibitor (Odds ratio [OR]: 2.19, [CI]: 1.07-4.46).[33]

Ricket et al. supported equal efficacy of using either LMWH or the factor-Xa inhibitor, but the bleeding risk was higher with the factor Xa inhibitor (2.2% vs 6.8%, p=0.004).[34]

Warfarin has been in clinical use for nearly five decades. Huang et al. reviewed the retrospective data from a large cohort of patients. They found using multivariate analysis that warfarin use was an independent risk factor for not only clinically relevant VTE ([OR]: 5.1, [CI]: 2.1-12.5, p<0.001), but also periprosthetic joint infection ([OR]: 13.7, [CI]: 1.9-98.5, p<0.001).[35] Additionally, patient compliance and laboratory monitoring programs have also come under scrutiny with regard to improving the efficacy, and the safety profiles of using warfarin as the principal chemoprophylaxis following total joint arthroplasty.[36,37] Cho et al. reported equal efficacy with improved bleeding risks using lower dose of warfarin (lower international normalized ratio: INR= 1.5 to 2.5) over a four week course.[38]

There is increasing evidence-based data supporting the use of aspirin following total joint arthroplasty. Aspirin is inexpensive, easy for the patients to use, and requires no monitoring. Hood et al. compared the rates of VTE and bleeding complications in the TKA patients receiving aspirin to a comparator patient cohort who received other forms of chemoprophylaxis (LMWH, warfarin, factor-Xa inhibitor). Their data demonstrated that aspirin was noninferior to the other chemoprophylaxis with regard to the rates of VTE or bleeding complications.[39] Cafri et al. compared the efficacy and safety of using aspirin to using other chemoprophylaxis using large registry data analysis. Aspirin was again found to be noninferior to the other chemoprophylaxis.[30] Radzak et al. reported a significantly greater transfusion rate in the TKA patients using LMWH in comparison to aspirin (p<0.01).[40]

Total Hip Arthroplasty

Agaba et al analyzed the nationwide healthcare database to compare the rates of the efficacy and the complications in using different chemoprophylaxis following THAs. The chemoprophylaxis used included: aspirin, LMWH, warfarin, and the factor-Xa inhibitors. Their data demonstrated that the patients who received warfarin had the highest VTE rate. The highest bleeding risk was seen in the patients who received the factor-Xa inhibitor. Interestingly, the lowest risk for bleeding was in the patients who received LMWH. Data for using aspirin showed equal efficacy to using the other chemoprophylaxis agents. The data was however limited by the heterogeneity of dosing, the dosage, and the duration of use, intrinsic to any registry data analysis.[41] Bala et al analyzed the rates of VTE and the postoperative complications for each of four different thromboprophylaxis agents in their patients at the 90-day follow-up interval. They reported the best efficacy (VTE rate) with using the factor-Xa inhibitors (1.7%), and with using aspirin (1.7%). The efficacy for LMWH and warfarin was 2.6% and 3.7%, respectively at 90 days. There was no difference in the overall transfusion rates among the groups.[42]

Aspirin has gained increasing acceptance and preference as the principle VTE prophylaxis in THA patients who are risk-stratified with a standard risk profile. Parvizi et al. compared using low-dose aspirin to standard-dose aspirin after THAs. The data

demonstrated equal efficacy (0.1% versus 0.3%, p=0.919). The complication rate related to the gastrointestinal system was lower with the low-dose aspirin protocol. They however did not report any data with regard to: wound dehiscence, overall bleeding, or the need for transfusions.[43] Rondon et al. reported that aspirin was independently associated with a lower risk of death at both 30 days ([OR]:0.39, [CI]: 0.17-0.86) and 1 year ([OR]: 0.51, [CI]: 0.32-0.81).[44]

Alternatives to Chemoprophylaxis

Orthopedic surgery practice protocols have evolved over time. At present, chemoprophylaxis is no longer regarded as the "sole" method for VTE prevention. Most surgeons use a "multi-modal" approach which includes: early mobilization, graded compression stockings, and intermittent pneumatic compression devices. Given the concern of bleeding complications associated with chemoprophylaxis, the usage of the pneumatic devices has increased. Some centers utilize risk stratification, with "standard risk" patients receiving isolated mechanical thromboembolic prophylaxis and have found this to be safe and effective in TKA patients.[45] Use of outpatient pneumatic compression devices is likely to rise in conjunction with the increase in outpatient total joint arthroplasty. A systematic review by Pavon et al. found in subgroup analysis that the combination of intermittent pneumatic compression devices plus anticoagulation may provide a greater protective effect against VTE in arthroplasty patients.[46] The current recommendations from the guidelines include using a combination of chemoprophylaxis and mechanical compression following total joint arthroplasty.[47] Several studies have reported equal efficacy and lower bleeding risk in using aspirin combined with portable compression devices when compared to using LMWH.[45,49] Additional evidence has shown that patients managed with a combination of pneumatic compression devices and aspirin have superior VTE prophylaxis than patients managed with single modality pneumatic compression devices.[49]

Conclusion

The available evidence is not definitive with regard to which chemoprophylaxis is the most efficacious and the safest in patients following TKAs and THAs. There is however agreement between the two major guidelines in the recommendation for using some form of VTE prophylaxis in all patients following surgery. Aspirin is presently the most commonly used chemoprophylaxis following routine TKAs and THAs in the U.S. It is critically important to adjust the clinical use of VTE prophylaxis to each patient's risk stratification profile which includes the risks for VTE, and the risks for bleeding complications either at the surgical site, or systemically. Additional prospective, randomized trials including large cohorts of patients are needed to further define the optimal agent, the dose, the duration, and the outcomes of VTE prophylaxis following TKAs and THAs.

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