

QUESTION 4: Does the type of venous thromboembolic (VTE) prophylaxis influence the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Yes. In a majority of studies evaluating VTE prophylaxis in patients undergoing total joint arthroplasty (TJA), aspirin appears to result in a lower risk of SSI/PJI than anticoagulants (vitamin K antagonists, heparin-based products, factor Xa inhibitors and direct thrombin inhibitors).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 80%, Disagree: 10%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

The risks versus benefits of VTE prophylactic agents in patients undergoing orthopaedic procedures, particularly TJA, remain controversial. Current Academy College of Chest Physicians (ACCP) guidelines recommend agreement with American Academy of Orthopaedic Surgeons (AAOS) guidelines for VTE prophylaxis and recommend pharmacologic prophylaxis over no prophylaxis, but do not provide support for or against any specific pharmacologic agent [1]. The most recent 2012 ACCP guidelines also recommend pharmacologic prophylaxis in all patients without a high risk of bleeding, but do not specify an agent [2,3]. Current commonly-used pharmacologic agents for prophylaxis following TJA include aspirin, vitamin K antagonists (i.e., warfarin), heparin-based anticoagulants (including low molecular weight heparins (LMWH), i.e., enoxaparin or dalteparin), direct oral anticoagulants (DOACs, i.e., rivaroxaban or apixaban) and direct thrombin inhibitors (DTIs, i.e., dabigatran) [4].

Wound drainage, bleeding and hematoma formation have been associated with PJI [5,6]. Therefore, balance of thrombotic risk and bleeding risk becomes paramount in selection of the appropriate postoperative VTE prophylaxis.

A literature review was performed using the PubMed and Cochrane Database of Systematic Reviews. The Medical Subject Headings (MeSH) terms “venous thromboembolism,” “prophylaxis,” “arthroplasty” and “infection” were searched. Studies were identified to be related to VTE and arthroplasty based on their title and abstract. They were then reviewed and included if a reported outcome measure was PJI or SSI.

Low Molecular Weight Heparin

The 2012 ACCP guidelines suggest the use of LMWH for postoperative VTE prophylaxis due to extensive data supporting its efficacy and safety in medical literature [7]. However, there is conflicting evidence in the orthopaedic literature regarding the rate of complications with its use following TJA. Multiple studies in recent orthopaedic literature suggest that LMWH after TJA may result in increased SSI/PJI and wound complications. Kulshrestha et al. [8] randomized patients undergoing primary total knee arthroplasty (TKA) to receive routine LMWH prophylaxis or risk stratification with the American Society of Anaesthesiologists (ASA) physical status score for standard risk and selective use of LMWH in high risk patients. They found that patients on LMWH had almost eight times the risk of wound complications compared with patients receiving ASA. Patel et al. [6] found that LMWH, compared with ASA and warfarin, was an independent risk factor for prolonged wound drainage following primary TJA. A prospective cohort study from the Global Orthopaedic Registry (GLORY) showed a significantly higher rate of SSIs in 1,561 patients receiving LMWH prophylaxis dosing (1.6% SSI) compared with 2,194 patients receiving therapeutic warfarin with or without bridging therapy (0.6% SSI) [9]. Burnett et al. [10] studied 290 patients undergoing TJA that received LMWH for 10 days postoperatively (3.4% required return to OR for wound complications). However, multiple other studies, including the RECORD 1-4 randomized control trials (RCTs) found no difference in SSI/PJI rates in patients undergoing TJA receiving either rivaroxaban or enoxaparin [11–14].

Factor Xa Inhibitors

There is conflicting evidence in current literature regarding rates of SSI and PJI in TJA patients receiving factor Xa inhibitors compared to other pharmacologic prophylaxis. Two recent meta-analyses of RCTs found no difference in SSI/PJI rates in TJA patients receiving rivaroxaban versus enoxaparin [11,15]. Multiple other retrospective studies have also found similar rates of PJI and superficial wound infections in patients receiving rivaroxaban and enoxaparin [7,16,17]. Agaba et al. [18] performed a retrospective review of 25,966 patients undergoing total hip arthroplasty (THA) receiving a single medication for VTE prophylaxis from the Humana National Healthcare Database between 2007 and 2016. 2.12% of patients received ASA, 26.15% enoxaparin, 46.25% warfarin, 1.3% apixaban, 3.37 fondaparinux and 20.81% rivaroxaban. They found that rivaroxaban had the lowest risk of PJI [18]. However, multiple studies have also found an increased risk of early SSI requiring reoperation following TJA with use of rivaroxaban compared to enoxaparin [19,20].

Direct Thrombin Inhibitors

Evidence regarding direct thrombin inhibitors is also unclear. Multiple studies have found that the use of dabigatran following TJA leads to prolonged wound drainage and increased risk of SSI/PJI. Gill et al. [21] found a 7% rate of reoperation for wound infection with dabigatran prophylaxis following TJA compared to 1% with a protocol of dalteparin while inpatient and ASA after discharge. Aquilina et al. [22] prospectively studied a cohort of 110 patients undergoing TJA and found mean of 6.6 days of wound drainage with dabigatran versus 3.4 days with ASA. Other studies have also found longer periods of wound drainage in patients receiving dabigatran prophylaxis compared with apixaban, enoxaparin and aspirin [23,24]. Bloch et al. [24] found a 20% wound drainage rate in TJA patients following introduction of use of dabigatran prophylaxis compared to 5% when using a multimodal regimen of LMWH while inpatient and ASA as outpatient. However, the RE-NOVATE (Clinical trial examining: “dabigatran etexilate compared with enoxaparin in prevention of VTE following THA”) and RE-NOVATE 2 RCTs compare dabigatran with enoxaparin for prophylaxis following THA and found no difference in wound infection rates [25].

Warfarin

Many recent studies have shown that SSI/PJI rates in TJA patients receiving warfarin prophylaxis are significantly higher than those receiving ASA prophylaxis. Sachs et al. [26] studied 785 patients treated without any pharmacologic prophylaxis compared with 957 patients treated with warfarin postoperatively and found similar VTE rates, but twice the infection rate in the warfarin group (0.6% vs.0.3%). Huang et al. [27] performed a single institution retrospective cohort study with 25,372 TJA patients receiving warfarin titrated to an international normalized ratio (INR) of 1.8 to 2.0 versus 4,898 TJA patients receiving ASA and found a 90-day postoperative PJI rate of 1.28% in the warfarin group compared to 0.22% in the ASA group. Other studies have also found prolonged wound drainage and significantly elevated PJI rates with warfarin compared with ASA following primary TJA [28–30]. However, Deirmengian et al. [31] found no difference in 90-day SSI rates in revision TJA patients receiving ASA versus warfarin, but found that ASA was more effective for VTE prevention. Comparing warfarin to other pharmacologic anticoagulation, evidence is less clear. As discussed above, Wang et al. [9] studied patients undergoing primary TJA from the Global Orthopaedic Registry and found significantly lower rates of superficial and deep infection in patients receiving warfarin prophylaxis compared with enoxaparin. Cafri et al. [32] found no significant difference in 90-day postoperative SSI rates between groups receiving ASA 325 mg once daily, fondaparinux 2.5 mg daily, LMWH 30 mg twice daily (BID) or 40 mg daily, and warfarin (goal INR 1.5 to 3.0) in a cohort of 30,499 patients from the Kaiser Permanente Total Joint Replacement Registry.

Aspirin

As discussed above, many studies have demonstrated lower SSI/PJI rates with ASA prophylaxis compared with warfarin prophylaxis. Other studies also demonstrate lower rates of infection and wound problems with ASA versus other anticoagulants. Kulshrestha et al. [8] randomized 450 TKA cases to either routine anticoagulation with 40 mg daily enoxaparin and 450 TKA cases to risk stratification and aspirin in low risk patients or enoxaparin in elevated risk patients. In patients receiving enoxaparin, there was nearly eight times the number of wound complications. Garfinkel et al. [33] found significantly higher rates of bleeding and wound complications with rivaroxaban compared with ASA.

Conclusion

The effects of specific anticoagulants on postoperative SSI and PJI remain uncertain. Rates of SSI/PJI with aspirin prophylaxis appear to be lower than rates with anticoagulation. Nevertheless, there is little level I evidence to support differences in risk of SSI/PJI between modes of pharmacologic VTE prophylaxis. Although many RCTs have been performed to evaluate the efficacy of various pharmacologic agents in prevention of VTE and their effects on other major complications such as bleeding and death, few report on the incidence of SSI and PJI in their treatment groups. Additionally, the definitions of SSI and PJI are heterogeneous across studies, making it difficult to compare infection rates. Finally, various dosages of the different pharmacologic agents need to be studied to determine their effect on SSI/PJI rates.

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