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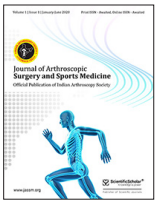

Review Article

The efficacy of aspirin as a prophylactic agent for patients recovering from total knee arthroplasties

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ABSTRACT

Guidelines regarding deep vein thrombosis (DVT) prophylaxis following total knee arthroplasties (TKAs) have had conflicting information regarding the use of aspirin as a prophylactic agent in recent years. The National Institute for Clinical Excellence refrains from listing the drug in its guidelines, while the American College of Chest Physicians advocates for the drug. Despite the conflicting guidelines, physicians have favored the drug in recent years, with more than 80% utilizing it as a prophylactic agent in TKAs. Although a consensus may have been reached by physicians regarding the use of the drug, a consensus has not been reached regarding the preferred dosage. With this in mind, a search of the PubMed database was conducted, which yielded six studies that discussed the efficacy of various dose ranges of aspirin. All studies corroborated that not only was aspirin an effective prophylactic agent but also that there was no significant difference between dosages regarding efficacies. Due to factors such as aspirin resistance and the potential of aspirin to cause gastrointestinal injuries, this literature review concludes that the dosage of aspirin given for the prophylaxis of DVT in TKAs should be considered on a patient-to-patient basis.

Keywords: Deep vein thrombosis, Aspirin, Prophylaxis, Total knee arthroplasty, Thrombus, Venous thromboembolic events

INTRODUCTION

Deep vein thrombosis (DVT) generally occurs due to the formation of a blot clot in the deep veins of the body, generally in the lower extremities.[1] A multitude of conditions can lead to the occurrence of DVT. In general, those over the age of 60 are at high risk for the ailment, while not moving for long periods can also cause DVT.[1] In the world of orthopedics, however, the manifestation of DVT generally occurs postoperatively. This is due to the fact that orthopedic surgeries often involve the cutting or scraping of bone, which can increase the risk of developing a blood clot.[2] Symptoms of DVT can be seen as leg pain, swelling, and discoloration.[2] The most serious post-operative complication, however, is the potential for DVT to cause a pulmonary embolism.[1] If the clot mentioned above present in the vein becomes loose, it has the potential to migrate through the bloodstream.[1] Eventually, the clot can settle within one's lungs, causing pulmonary embolism and possibly even death.

Aspirin has been seen as a major prophylactic agent in the treatment of DVT due to its role as an anticoagulant and antiaggregant.[3] In general, blood clots form through the accumulation and binding of platelets. With aspirin, this binding is inhibited through a series of inhibitions on the molecular level.[3] With this in mind, it can be clear to see why aspirin is a favored prophylactic agent. As such, this review aims to assess the ideal dosage of aspirin as a prophylactic agent among total knee arthroplasties (TKAs).

MATERIALS AND METHODS

A preliminary search of the PubMed database was conducted with the search terms "Aspirin" AND "DVT Prophylaxis" AND "Orthopedic Surgery" OR "Total Knee Arthroplasty" OR "Total Knee Replacement (TKR)" OR "Knee arthroscopy." With this, an initial list of 20 studies was found. Exclusion and inclusion criteria were then applied. Studies were excluded if they were not in English, did not have the efficacy of aspirin as a main outcome measure, or did not center around TKA. After the application of exclusion criteria, the list of studies was narrowed down to 6. These studies were then read through thoroughly before important themes were identified and internally coded.

DISCUSSION

A venous thrombus generally develops due to endothelial dysfunction stemming from abnormal blood flow.[4] Thrombogenesis and the aggregation of platelets begin

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to occur once this abnormal blood flow leads to hypoxia in the affected region.[5] However, the most likely predictor for the development of thrombosis is the presence of the Virchow triad, which consists of endothelial damage, venous stasis, and hypercoagulability.[4]

Orthopedic patients undergoing surgery are extremely susceptible to developing Virchow's triad.[4] Being bedridden and immobilized makes one prone to blood stasis. In addition, during the surgery itself, veins and other endothelial vascular tissue can be nicked, triggering inflammation and the aggregation of platelets.[4] Finally, the use of polymethylmethacrylate as bone cement also increases hypercoagulability.[5] As such, with procedures such as a TKA, the prophylaxis of venous thromboembolic events (VTE) and adherence to respective treatment protocols are of the utmost importance. This is especially true when one considers the fact that 60% of patients who do not receive prophylaxis during such procedures are susceptible to VTEs.[6] When given proper prophylaxis, however, this rate can fall to as low as 1.16%.[1,7]

Aspirin (acetylsalicylic acid) is an antithrombotic agent that irreversibly inhibits the activity of cyclooxygenase (COX) in platelets.[3] COX-1 and two isoenzymes catalyze the conversion of arachidonic acid to prostaglandin (PG) H2 and the production of thromboxane A2 (TXA2) and PGI2.[3] TXA2 induces vasoconstriction and aids platelet aggregation, whereas PGI2 induces vasodilatation and inhibits the aggregation of platelets.[7] This way, aspirin prevents the subendothelial deposition of platelets and the aggregation of new platelets.[7] Due to these properties, aspirin has been seen as a major agent in the prophylaxis of TKAs in recent years.[5]

Guidelines have been developed by the National Institute for Clinical Excellence (NICE), the American College of Chest Physicians (ACCP), and the American Academy of Orthopedic Surgeons (AAOS) to address the issue of prophylaxis in this high-risk population. However, according to Yeo *et al*.,[8] there are no guidelines delineating the use of prophylaxis to prevent VTE in arthroscopic surgeries. Their study aimed to identify the incidence of DVT in knee arthroplasty and knee arthroscopy patients. Their results showed that the overall incidence of DVT after arthroscopy was 0.5% as compared to the incidence after arthroplasty which was 3.1%.

In 2010, NICE recommended that all patients undergoing lower limb arthroplasty should be assessed for VTE.[9] In addition, they should be offered both mechanical and pharmacological prophylaxis from admission in orthopedic surgical patients, but this did not include aspirin.[10] It was recommended that it should last for at least 10–14 days postoperatively for surgeries involving the knee.[10]

The ACCP, on the other hand, historically recommended against aspirin but now does recommend aspirin as a prophylactic agent; however, it lists low-molecular-weight heparin (LMWH) to be considered first.[9] In addition, with the ACCP, it is recommended that prophylaxis last for 35 days.[11] Moving on, the AAOS recommends a multimodal approach but refrains from listing specific agents or the preferred length of prophylaxis, citing a lack of evidence.[6,10] Instead, they recommend a discussion between patient and physician to map out the preferred method of prophylaxis.[5]

Therefore, currently, all three guidelines do not agree with each other due to different interpretations of the available evidence. ACCP specifically recommends against aspirin in all instances, while the AAOS recommends aspirin for some patients at higher risk of adverse bleeding events.[9] According to a meta-analysis in 2016, although aspirin is a suitable therapy for the prevention of VTE and TKR, as recommended by the AAOS, the evidence available is of limited quality, and information regarding proper dosage and duration of treatment remains unclear.[9] This has led to big variations in the prescribing of prophylactic agents for VTE, as reported by Cohen *et al*.[7,12]

One major issue stemming from the prescription of aspirin is due to conflicting information regarding the potential of a relationship between clinically important VTEs and asymptomatic DVT.[9] The ACCP mentions that there is a strong relationship between asymptomatic DVT and symptomatic VTEs.[9] Meanwhile, the AAOS states that evidence regarding this relationship is lacking.[9] Many high-quality randomized control trials (RCTs) also support the notion that aspirin should not be used as a prophylactic agent.[13,14] Even when ignoring these results, only a grade B recommendation can be given for aspirin.[9]

One of the most renowned studies regarding this topic is the pulmonary embolism prevention (PEP) Trial.[5] After gathering more than 24,000 patients, the PEP trial found that aspirin use was associated with at least a 33% decrease in post-operative VTEs.[5] As such, the study concluded that aspirin was effective in the prevention of VTE for patients undergoing arthroplasty.[5] Further, corroboration of these results from future studies led to the ACCP and AAOS recommending the use of aspirin, with the former granting the highest grade of recommendation.[5]

In fact, public opinion on the matter has shifted so much that a poll conducted in 2016 from attendees of the annual meeting of the American Association of Hip and Knee Surgeons revealed that more than 80% of physicians utilize aspirin as their main prophylactic agent for hip and knee arthroplasties.[5]

There are a multitude of factors that contribute to this rise in the popularity of aspirin as a prophylactic agent, in addition to its proven efficacy. It is relatively inexpensive and well-tolerated and does not require routine blood monitoring.[15] In addition, due to the fact that it is a more "mild" agent, it has a lower likelihood of causing hematoma formation and

persistent wound drainage as compared to other agents (e.g., LMWH).[5]

With this in mind, it is clear to see that aspirin is a preferred prophylactic agent among physicians. However, a consensus remains to be reached regarding the appropriate dosage of aspirin.

In regards to the proper aspirin dosage, the initial AAOS guidelines on VTE prevention recommended using 325 mg of aspirin twice daily and graded it as 1C, citing a lack of sufficient studies on the optimal dose.[16] A meta-analysis which compared aspirin doses in cardiac literature found that the efficacy of high doses of aspirin (500–1500 mg/day) was not significantly different than medium doses (160–325 mg/day) or low doses (75–150 mg/day).[5] Lanas *et al*., Feldstein *et al*., and Azboy *et al*. have also shown that high doses of aspirin were associated with more gastrointestinal (GI) side effects.[5,17,18]

A multitude of studies have displayed aspirin efficacy at a dose of 325 mg twice daily.[11,19] Simultaneously, however, many studies have also displayed aspirin efficacy at low doses in minimizing VTEs, with the added benefit of reduced GI bleeding.[11,20,21] The plausibility behind the efficacy of doses below 75 mg/day stems from the fact that these low doses proposedly spare a platelet antiaggregant and vasodilator called prostacyclin.[11]

In a study comparing three trials spanning 3570 patients and comparing aspirin doses above and below 75 mg/day, no significant difference was found.[11] One unresolved issue in relation to dosage is the variation in patient responses to aspirin. However, doses between 30 mg and 150 mg have consistently shown to display platelet COX-1 inhibition.[5] Simultaneously, it must be considered that doses <75 mg/day have been less widely assessed than 75–150 mg/day.[17]

Parvizi *et al.* found that the majority of symptomatic VTEs (94%) occur within two weeks of an arthroplasty, with 89% occurring within the 1st week.[16] With this in mind, a sufficient regimen to prevent post-operative VTEs may be to prescribe aspirin for two weeks following surgery. However, due to the fact that the risk of VTEs is higher in patients receiving an arthroplasty, prolonged prophylaxis is justifiable, especially for high-risk patients who are less mobile.[17]

According to Adrichem *et al*.,[22], after conducting trials involving patients who had undergone knee arthroscopy, they found that anticoagulant treatment was not effective in preventing VTE. However, they do believe that an increased dosage or a longer duration of treatment could contribute to better outcomes if the treatment were to be restricted to high-risk groups.

Faour *et al*. and Shohat *et al*., both focused on the efficacy of low-dose aspirin as prophylaxis for TKA.[23,24] The former aimed to do so by retrospectively identifying patients who were given either 81 mg or 325 mg of aspirin twice daily for 4–6 weeks after successful TKA.[23] In doing so, they amassed a total of 5666 patients for analysis (1327 vs. 4339) comparing post-operative complications such as VTEs and bleeding and mortality.[23] The incidence of VTEs between the two groups was found to be 0.7% and 0.5%, respectively (P = 0.02).[23] When looking at symptomatic DVT in particular, however, Faour *et al*. found that the 81 mg group experienced an incidence of 0.3% while the 325 mg group had an incidence of 1.4% (P = 0.0009).[23] However, after accounting for confounders, it was concluded that there was no correlation between aspirin dosage and VTE incidence.[23]

Shohat *et al*., on the other hand, gathered a total of 9208 patients retrospectively, with 4413 being given 81 mg of aspirin twice daily and 4795 being given 325 mg of aspirin twice daily.[24] The two groups were then compared for VTEs found 90 days post-surgery and major bleeding events 30 days post-surgery.[24] No significant difference was found between the 81 mg group and 325 mg group regarding VTEs, with an incidence rate of 0.9% versus 1.0% (P = 0.669).[24] With these results in mind and the fact that bar one outlier, no VTEs were detected outside of the first 30 days, it was concluded that a 30-day high- or low-dosage regimen of aspirin for the prophylaxis of TKA was suitable.[24]

In contrast, Easwaran *et al*.[25] concluded that consensus could not be reached regarding the need for VTE prophylaxis for simple knee arthroscopies such as meniscectomies or anterior cruciate ligament reconstruction. There was a collective opinion that suggested that prophylaxis in this patient group should be after consideration of patient factors that deem them susceptible to thrombogenic events.

With this in mind, it is clear to see that current literature corroborates that in terms of efficacy, neither low-dose aspirin nor high-dose aspirin is inferior to the other. However, there may be other factors that must be considered on a patient-to-patient basis that may affect the dosage a physician prescribes. Evidence has risen to suggest that some patients may experience aspirin resistance.[23] With this condition, a patient may experience a greater than-normal rate of platelet production postoperatively.[23] Subsequently, this overproduction means that many platelets are left unexposed to aspirin, and a lower efficacy of the drug is seen. As such, in instances like these, it may be beneficial to utilize a higher dose of aspirin to bypass this resistance.

In contrast, however, the use of aspirin is known to cause GI ailments in certain patients, such as dyspepsia and ulcers.[23,25] This is due to the fact that in addition to being an inhibitor of platelet coagulation, aspirin also serves as an inhibitor of molecules such as PGs.[23] PGs are responsible for the stimulation of mucus and bicarbonate, which can line and protect the GI tract from damage. With PGs inhibited, the GI tract is more susceptible to lesions and sores, leading to the development of the ailments mentioned above. As such, a higher dose of aspirin may be harmful to those patients with a weak GI lining.

Taking all factors into account, there is enough evidence that aspirin is one of the most effective, inexpensive, and safest methods for VTE prophylaxis following arthroplasty. Although the optimal dose and length of prophylaxis remain unknown, the evidence is that low-dose aspirin (between 70 mg and 100 mg twice a day) for a few weeks may be sufficient for most patients.[5]

Limitations

Both Faour *et al*., and Shohat *et al*. are retrospective studies in nature.[23,24] Due to this, discrepancies between patient characteristics and irregular prescription patterns from the physicians involved may have risen. In addition to this, the retrospective nature of the study means that patient adherence to the medication could not be tracked and confirmed, thus possibly altering the results. Finally, due to the retrospective nature of these studies, the researchers were not able to control for extraneous variables, which once again may have altered their results.

Limitations of Mistry *et al*.'s study are that they only followed the patients for six weeks, as compared to other studies that followed them for three months.[7] Another limitation is that the authors did not perform the risk stratification themselves. In addition, the evidence only focused on aspirin; a comparison between aspirin and a particular anticoagulant could have been performed.

CONCLUSION

The findings of this literature review seem to corroborate data from previous pieces of literature suggesting the overall high efficacy of aspirin as a prophylactic agent for DVT in TKA. As such, we believe that the NICE, ACCP, and AAOS should all update their guidelines to account for evidence highlighting proper dosage and regimens for aspirin as a prophylactic agent. Besides this, the findings of this literature review suggest that there is no significant difference between low-dose aspirin and high-dose aspirin in terms of efficacy. Rather, doses should be determined on a patient-to-patient basis after accounting for factors such as aspirin resistance and the potential for GI complications.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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