Meta-Analysis: A Comparison of Aspirin and Rivaroxaban for Prophylaxis of Venous Thromboembolism After Hip or Knee Arthroplasty.

Md Ariful Haque

Yan an Hospital Affiliated to Kunming Medical University

Xiong Ying

Yan an Hospital Affiliated to Kunming Medical University

Sayed Abdulla Jami

Yan an Hospital Affiliated to Kunming Medical University

Ren YunFeng

Yan an Hospital Affiliated to Kunming Medical University

Siam Al Mobarak

The First Affiliated Hospital of Guangxi Medical University

Xiao Jiayu (✉ 346721374@qq.com)

Yan an Hospital Affiliated to Kunming Medical University

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Abstract

Purpose: Knee arthroplasty and hip arthroplasty (THA) patients are susceptible to post-operative venous thromboembolism(VTE). Doctors are increasingly recommending the application of different thromboprophylaxis agents such as rivaroxaban. The agents are primarily effective in preventing thromboembolism after hip and knee arthroplasty. Similarly, recent research suggests aspirin as one of the cost-effective interventions for preventing thromboembolism. Accordingly, this meta-analysis aims to compare the effectiveness of Aspirin against Rivaroxaban for the prevention or treatment of thromboembolism following knee arthroplasty and knee arthroplasty.

Methods: The researcher relied on electronic searches of about five databases. The database searches identified relevant studies used to extract meta-analyzed data and information. The databases included PubMed, Cinahl, Medicine, Cochrane Database of Systematic Reviews(CDSR), Pharma GKB, SAGE, from inception to December 2020.

Results: Different studies from the five databases we are included in this study. The studies include 2257 in the aspirin group and 2337 in the rivaroxaban group. The result revealed no significant difference between Aspirin and Rivaroxaban for the treatment of venous thromboembolism.

Conclusion: The meta-analysis result affirmed no statistically significant difference between Aspirin and Rivaroxaban in preventing venous thromboembolism, a joint arthroplasty, or hip fracture surgery. However, some health care professionals find aspirin a more effective, safe, convenient, and affordable alternative for preventing venous thromboembolism. Thus the meta-analysis recommends extensive randomized studies to confirm the stipulated outcomes.

Background And Introduction

Venous thromboembolism(VTE) is adverse from a perioperative complication that can use unintended death, especially during the perioperative period. Deep vein thrombosis(DVT) and pulmonary embolism(PE) are common complications associated with VTE occurring after joint arthroplasty [1-2]. For instance, deep vein thrombosis occurs due to prolonged bed rest and immobility, and it is seen mainly in patients who undergo hip arthroplasty [3-5]. Due to blood stasis, hypercoagulation, blood vessel injury, blood flow reduces, and this complication occurs. The abnormal activation of the patients coagulations prefers to use clinical anticoagulants such as rivaroxaban and enoxaparin To reduce VTE-related complications.

However, selecting potential cost-effective alternative prophylactic agents for preventing thrombosis after a joint arthroplasty remains a controversial clinical issue. Most of the current interventions, while effective, have adverse effects. For instance, they can increase the risk of bleeding, possibly increasing the risk of other clinical infections, extending the recovery process, and increasing hospital readmission rates. In particular, chances of possible infections and hypersensitivity are high due to the administration of untested anticoagulants, further escalating the rate of visits t hospitals. Therefore, the primary

objective of the meta-analysis is to identify the most effective intervention to prevent VTE complications. Notably, there are numerous studies in this area; the current study seeks to reinforce the existing knowledge and awareness of different prophylactic agents for treating venous thromboembolism.

Essentially with a proper treatment plan, these complications can be reduced. According to recent recommendations, the appropriate medication should be given at least 10-14 days after surgery and maximum gave up to 1 month (Russell et al.,2013) [18]. In most clinical environments, anticoagulants are still less preferred because of their adverse effects on bleeding and increased risk of thrombocytopenia [18]. Therefore, the outcome of this study will provide evidence-based clinical advice on the best intervention strategies to manage the conditions [18].

Finally, the meta-analysis will evaluate the effectiveness and safety of rivaroxaban aspirin in preventing VTE. The study outcome will further recommend other multidisciplinary care processes and changes to surgical techniques needed to promote physical therapy and ambulation. This study also encourages an increased clinical focus on aspirin, a cheap, generic antiplatelet drug, to treat VTE-related complications. Overall, the meta-analysis result will enable healthcare professionals in the modern clinical environment to make rational decisions and improve patients outcomes.

Effect Size :

The present meta-analysis study includes a large effect size with a significant difference between the effects of two medications. The study will involve six population statistic databases with 14570 patients who had undergone total hip arthroplasty or total knee arthroplasty. Aspirin was given prophylaxis compared to rivaroxaban as an antithrombotic agent given to 70% of patients.

According to a study, Piovella et al were considered to compare aspirin's inefficacy, which weighed against Rivaroxaban [7]. In the second study, the dose for the medication varied for both interventions in 2 groups [7]. One group in which rivaroxaban and the other group give the intervention for the drug is administered with aspirin [7]. The participants in both groups were not blind to the study, and the control group is the patient group administered with rivaroxaban [7]. The case groups are the patient group that was given aspirin after surgical procedures [7].

Saltybaeva et al. show that the incidence of venous thromboembolism in the group administered with aspirin and the group administered with rivaroxaban group 6.9% for aspirin and 5.7% for Rivaroxaban (P=0.83) [8].

Methods

Literature search strategy: The study relied on electronic database searches to give evidence-based data and information on the clinical topic. The researcher attained higher efficacy search outcomes using PubMed, Cinahl, Medicine, Cochrane Database of Systematic Reviews(CDSR), Pharma GKB, and SAGE to December 2020. The search strategy was based upon advanced search in databases using multiple

keywords connected using operators such as AND, OR, NOT. The search strategy was maximized by combining keywords such as Rivaroxaban AND Aspirin OR total knee arthroplasty OR total hip arthroplasty OR knee replacement OR hip replacement to search for MeSH fields. The comprehensive list of references was retrieved manually for further identification of relevant articles.

Study inclusion and exclusion criteria :

The eligible studies for meta-analysis were based on different conditions. For instance, patients receiving Rivaroxaban and Aspirin after joint arthroplasty or hip fracture surgery were eligible for inclusion in this study. Another criteria for inclusion was the presence of VTE-related complications such as bleeding events. Such complications would help the researcher ascertain the effectiveness of Rivaroxaban and Aspirin in treating thrombosis. The final inclusion criteria were studies published in English.

Therefore eligible research studies for the meta-analysis study were based upon a particular population size in which interventions were based upon changes in aspirin in one population, and rivaroxaban was given to another study group. This was a case-control study combination for chemoprophylaxis done after total knee arthroplasty or total hip arthroplasty. The different exclusion and inclusion criteria were set up. The inclusion criteria were set up if the studies reported primary vein thromboembolism outcomes and secondary outcomes of surgical interventions such as bleeding or wound complications.

In essence, this vein thromboembolism includes deep vein thrombosis and pulmonary embolism. The VT was diagnosed by clinical methods or by the patient's signs and symptoms. The severity of bleeding was analyzed, and the tissue-specific bleeding was analyzed as internal bleeding; thus, the reoperation possibilities were also explored. In addition to this, the quantitative study data was taken up from the most recent studies. The publications mainly were from peer-reviewed articles, and the English language was the inclusion criteria, case reports, laboratory studies, repeated publication, animal experiments, reviews, editorials, and expert opinions.

Data Extraction and Critical Appraisal :

The study relied on independent reviewers and disparate to facilitate study search, selection, abstraction, and quality assessment. The data extracted from relevant search studies was investigated by reviewing the data from the population health databases. The inclusion criteria were narrowed in terms of the study year: the country where the analysis was performed, the total number of patients who underwent TKA and THA. Similarly, bleeding was observed in some of the participants. Thus the number of patients who received rivaroxaban or aspirin was controlled and highly monitored. The studies were further studied for primary outcomes of venous thromboembolism. The secondary results were based upon the severity of bleeding as well as wound complications and clotting. The risk for bias in the considered studies was analyzed by the Cochrane collaboration tool.

Assessing the quality of the selected research studies:

The researcher conducted an independent review of the research studies to ascertain their methodological quality. The study relied on the Cochrane risk of bias criteria to verify the reliability. The researcher graded each study item as either low risk, high risk, or no clear risk. The assessment criteria also included the assessment of the outcome data and other related biases.

Outcomes :

The expected primary efficacy of the study outcome is the possibility of the adjusted symptomatic venous thromboembolism. The prevention of bleeding and other related clinical complications associated with the condition is also a significant outcome of the efficacy of the proposed intervention measures. Finally, the secondary outcome measure is the reduction of VTE-related mortality rates.

Statistical Analysis :

The statistical analysis of the outcomes majorly analyzed the relevance of the study. The weighted mean difference and standard deviation were used along with relative risk(RR). The heterogeneity was an essential consideration in the population demographics, and thus the random-effects model was used in this study design. The analysis for sensitivity was also performed. All statistical analysis was performed using review manager 5.3 software (Cochrane collaboration, software update, oxford, united kingdom).

The analysis includes electronic searches of various research databases carried out on patients who underwent total hip or knee replacements. All the studies have been carried out institutionally following ethics and with the consent of patients. The medical history of patients, age, and other parameters like socioeconomic status have been standardized. Various population groups have been taken into consideration to minimize bias.

According to an article published in the New England journal of medicine, out of 3424 patients who underwent total hip arthroplasty or total knee arthroplasty(Anderson et al., 2018), venous thromboembolism occurred in 0.64% of patients who received aspirin as prophylaxis as compared to 0.70% of the patients who received rivaroxaban as an antithrombotic agent [6].

Another research article was published in the international research journal of pharmaceutical and biosciences based on a study carried out from February 2019 till May 2019 on 204 patients(Kumaravel et al., 2019) [9]. The effect of Aspirin versus Rivaroxaban undergoing total knee replacement, the effectiveness of aspirin has weighed against rivaroxaban [10]. In the post-operative period, deep vein thrombosis symptoms were observed in the patients divided into groups receiving Aspirin 150 mg daily versus patients who received Rivaroxaban 10 mg daily from 1-14 post-operative days. In the aspirin group, deep vein thrombosis was found in 4.615% of patients in the aspirin group, whereas 6.154% of patients suffered DVT rivaroxaban group. Blood loss events like hematoma formation and significant bleeding occurred in 3.07% in the aspirin group compared to 4.61 % in the rivaroxaban group [9].

SAGE journals published an article comparing primary outcomes(Deep vein thrombosis/ pulmonary embolism) and secondary outcomes(bleeding and wound complications) in the follow-up of prophylaxis

by Aspirin and Rivaroxaban following TKA and THA [10]. The aspirin dosage ranged from 81mg daily, and that for rivaroxaban was 10mg daily [10]. The study is based on 4594 patients, out of which 2257 were in the aspirin group, and 2337 were in the rivaroxaban group [10]. The patients whose mean age was 62.7 to 71.2 years were followed up in the post-operative phase up to 90 days [10]. No significant difference was found in the DWT rate in the aspirin and rivaroxaban groups. No difference in major bleeding was found either [10].

According to Chung et al. 268 Korean patients from May 2011 to November 2013 undergoing total knee replacement were carried out. Divided into groups that received 100mg aspirin and the others who received 10 mg rivaroxaban were followed up postoperatively [11]. The incidence of overall venous thromboembolism was not significant. However, it was significantly lower in the group having rivaroxaban (10%) for chemoprophylaxis than aspirin (38.2%). The mean amount of bleeding was similar among both groups [10].

In the study conducted by the American college of cardiology(Aspirin for VTE prophylaxis after hip and knee surgery), the authors performed a systematic review and compared aspirin for venous thromboembolism prophylaxis in patients undergoing total hip replacement or total knee replacement. In 6060, patients were involved in randomized clinical trials, relative risk(RR) for deep vein thrombosis in 1.04 patients, and pulmonary embolism in 1.01 patients [14]. The study concluded that aspirin did not differ significantly from other coagulation therapies to prevent or control post-operative venous thromboembolism [14].

Jichao Lu al. Medicine (Baltimore) studied the efficacy of rivaroxaban to prevent DVT and PE after total hip replacement or total knee arthroplasty in thirteen RCTs, which were included in the study [15]. It showed that the overall rate of venous thromboembolism events, deep vein thrombosis, and death was 1%, 6%, <1%, and 1%, which showed that rivaroxaban was proven to have a superior effect in THA patients [15].

Results

Quality of Studies :

Out of 2337 identified articles, the total number of participants was 14570, the effect size was large, but no gender bias was done. In addition to this, the baseline age of participants was 65 ± 5 years. The risk rate of venous thromboembolism after the total hip arthroplasty and total knee arthroplasty was 1.12(95% CI, 0.72-1.82) for aspirin in comparison to other anticoagulants as warfarin. The findings for the venous thromboembolism were divided into two subcategories, which are deep vein thrombosis(DVT) and pulmonary embolism. Thus risk rate for DVT is 1.02; 95% CI, 0.72-1.64 and PE risk rate is 1.01; 95% CI, 0.68-1.45

Discussion

The secondary outcomes, such as severe internal bleeding and the risk of hemolysis, increase by several folds accounting up to 3 times. In addition to this, the chances of wound hematoma and wound sepsis did not differ in statistical results for patients who received Aspirin and Rivaroxaban. Also, there is no significant statistical difference in the potential risk of VTE, DVT, and PE between administration of Aspirin and Rivaroxaban after THA OR TKA.

The risk for venous thromboembolism does not vary statistically for aspirin administration and (RR, 0.76;95% CI, 0.41-1.61) and Rivaroxaban (RR, 1.57;95% CI, 0.57-4.23). Thus the quality of evidence had a diverse range with good quality to the average rate. Still, no significant statistical difference was seen for aspirin and rivaroxaban administration after total knee arthroplasty and total hip arthroplasty.

In a study based on 390 patients reported by Qiang Huang 2019 et al., all the patients are initially given where subcutaneous were divided into two groups [16]. In essence, about 198 patients were subjected to a 100mg dose of aspirin once daily, whereas 192 were given 10 mg of rivaroxaban daily for 16 days and followed for the next 90 days [16]. The incidence of venous thromboembolism was 6.6% in the aspirin group and slightly less at 5.7 % in the rivaroxaban group. Major bleeding occurred in 2 patients of the aspirin group, while only one patient reported in the rivaroxaban group [16]. There was no incidence of pulmonary embolism in the rivaroxaban group than one reported case in the aspirin group [16]. Due to no significant differences in the follow-up of complications, aspirin was considered to be a safe and cheap alternative [16].

Another study by Zou and others conducted on 324 patients from 2011 to 2013 compared the safety and efficacy of Aspirin, Rivaroxaban, and low molecular weight heparin(LMWH) prevention of Deep vein thrombosis [12]. It was reported that DVT was least reported in the group where oral rivaroxaban was administered at 10 mg daily postoperatively for 14 days. Still, at the same time, post-operative blood loss and wound complications were observed more in this group [12]. There was no significant difference in the incidence of DVT in groups with aspirin at 100 mg daily and those with subcutaneous LMWH at a dose of 0.4 ml daily in the post-operative period [12].

Jose Luiz Colleoni et al., compared the efficacy and safety of Aspirin and Rivaroxaban to prevent venous thromboembolism after total knee arthroplasty in 32 patients [13]. Group A received 300mg of aspirin, and group B received 10 mg of rivaroxaban daily for 14 days postoperatively and was followed up daily for four weeks [13]. No observable differences were found in both groups. Hence both Aspirin and Rivaroxaban were equally effective for preventing venous thromboembolism after total knee arthroplasty [13].

Prolonged follow-up of 1107 patients who had completed 6 to 12 months of anticoagulation therapy with either rivaroxaban 20mg or 10 mg once daily. Aspirin 100mg once daily showed that recurrent venous thromboembolism was reported 1.9% in the group given Rivaroxaban 20mg daily, 1.6% in the group reported rivaroxaban 10 mg daily, and 5.0 % in the aspirin group. Major bleeding was reported less in the groups managed with rivaroxaban than the aspirin group, which projects a favorable benefit-risk profile in the rivaroxaban group.

Clinical Efficacy :

Asymptomatic patients are more prone to recurrence of DVT, whether the clinical outcomes reveal the lower efficacy of DVT recurrence after surgical interventions for knee or hip arthroplasty. Clinical efficacy of the literature reviews and randomized trials for comparing Aspirin and Rivaroxaban reveals 3.6 % chances for recurrence in patients with provoked patients. However, the possibilities for replication are 5.6 % (Jeffrey et al.,2017) in patients with unprovoked DVT even after taking aspirin instead of rivaroxaban[17]. It was evident that anticoagulants such as rivaroxaban alone can lessen the recurrence incident by 70% in unprovoked and provoked DVT patients[17].

Rivaroxaban is also known as low molecular weight heparin. If replaced with aspirin for up to 1 year in DVT patients, preventing lethargic or no lethargic episodes recurrent venous thromboembolism, without the rise in the risk of hemolysis was the 20 mg dose for lethargic patients and 10 mg dose for no lethargic patients. Prevention of recurrent pulmonary embolism is essential because the case fatality rate at 30 days is at least twice as high with pulmonary embolism as deep vein thrombosis. Pulmonary embolism, which is a complication of DVT, must be prevented with a combination of Aspirin and Rivaroxaban as the mortality rate for pulmonary embolism is twice in 30 days as with severe DVT[12].

Analysis :

Both Aspirin and Rivaroxaban effectively prevent post-operative complications of THA, and TKA are used regularly. The action of aspirin is not limited to arterial circulation. It also has antithrombotic effects on venous thromboembolism. It acetylates fibrinogen, and fibrin inhibits the activation of thrombin mediated factor. It has been shown that aspirin reduces proximal and distal deep vein thrombosis and minimizes fetal and non-fetal PEs. Besides, it is an inexpensive mild, well-tolerated, widely available, and effective antithrombotic agent with a well-established side effect profile. Even in mild dosage, aspirin catalyzes the platelet COX irreversibly. This further interferes with the aggregation of platelets and increased bleeding time. Even in a single dosage, it irreversibly inhibits the formation of TXA₂, which is for 8 -11 days. Proteins can not be formed by platelets, which means the cyclooxygenase enzyme can be reformed. In mild dosage, i.e., 40 mg daily of aspirin is sufficient to inhibit the platelet aggregation. Results show that aspirin may be the right choice for chemoprophylaxis due to its lower cost and similar prophylactic profile to Rivaroxaban (Bozic et al., 2010)

In clinical trials such as pulmonary embolism prevention, aspirin was majorly taken by patients who underwent hip or knee arthroplasty and showed better results from deep vein thrombosis or pulmonary embolism. In contrast, no statistical evidence was observed for aspirin and rivaroxaban administration for TKA and THA. The mean difference deviation and the risk rates were near the baseline. According to the American Association of orthopedic surgery, in 2012 suggests aspirin is the prophylactic drug for thrombophlebitis.

Conclusion

The pharmacodynamics and pharmacokinetics action for aspirin for blood thinning and decreased platelet aggregation was equivalent to the directorial administration of rivaroxaban for its anticoagulation. When aspirin was administered in a small amount, it irreversibly catalyzes the platelet enzymes and promotes the formation of thromboxane A₂, thus promoting vasoconstriction. Therefore both medications prevent the VTE resurgence at the same levels. Still, some additional benefits of aspirin are that it is safer and has lesser side effects than rivaroxaban, and it is cheaper than rivaroxaban for prolonged duration prophylaxis. There was no bias in the study for both groups of medication administration and no significant differences in mean difference and standard deviation. The patient's characters were similar, and both had undergone surgical interventions for DVT and PE, I e., similar operative characteristics. Thus the cohort study had a pooled data of 6. Thus improving the efficacy of results.

The limitation occurred in terms of heterogeneity for study protocol for dosage difference. It does not address the efficacy of chemoprophylaxis regimens for high-risk populations. It is more vulnerable to such diseases as patients with cancer or a family history of these diseases.

Declarations

Ethical Approved : Approved by Yan'an Hospital Affiliated to Kunming Medical University Ethical Committee.

Declarations: Not applicable

Funding: Not applicable yet

Conflicts of interest/Competing interests: The authors declare that they have no competing interests.

Data availability: The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions: MAH, XJ & SAJ, Substantial contributions to conception and design. All authors: Data acquisition, data analysis and interpretation. All authors: Drafting the article or critically revising it for important intellectual content. All authors: Final approval of the version to be published. RYF & XY: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Shows the PRISMA flow chart for meta-analysis of Aspirin Versus Rivaroxaban for venous thromboembolism prophylaxis after TKR or THA.

1. (Stephen et al., 2019)

2. (Colleoni et al., 2017)

3. (Mistry et al., 2017)

4. Qiang Huang et al. 2019

5. (Kumaravel et al., 2019)

6. (Anderson et al., 2018)

Figure 2

Shows the forest plot of venous thromboembolism.

Supplementary Files

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