Cohort Study

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Comparison of low-dose (162 mg) and high-dose (650 mg) Aspirin prophylaxis following total joint arthroplasty: a prospective cohort study

Seyyed Hossein Shafiei, MD[a], Mohammad Rastegar, MD[a], Peyman Mirghaderi[b,c], Babak Siavashi, MD[a], Seyed Mohammad Javad Mortazavi, MD[b,*]

Background: Since Aspirin's adverse effects are dose-dependent, and evidence supporting the use of low-dose (LD) Aspirin in preventing venous thromboembolism (VTE) after total hip arthroplasty (THA) is weak, the authors do not know what the minimal effective dosage of Aspirin is to prevent VTE. This study aimed to compare the rates of 90-day symptomatic VTE following THA and total knee arthroplasty in healthy patients taking LD Aspirin vs. high-dose (HD) Aspirin for 6 weeks postoperatively.

Materials and methods: A prospective cohort of patients with THA and total knee arthroplasty was conducted at two tertiary centres. Symptomatic VTE within 90 days of index arthroplasty was the primary outcome; gastrointestinal bleeding (GIB) and mortality were secondary outcomes.

Results: The final analysis included 312 consecutive patients: 158 in the LD group and 154 in the HD group. Two groups were similar regarding preoperative data, including sex, age, BMI, smoking, diabetes mellitus, Hgb and platelet count, and type of surgery. The LD group had one deep vein thrombosis (0.6%), and the HD group had two (1.3%) ($P = 0.62$). Neither group had PTE. Therefore, VTE rates are the same as deep vein thrombosis rates and similar between the groups (0.6% vs. 1.3%, $P = 0.62$) Regarding GIB due to anticoagulant therapy, no patient in the LD group reported GIB, whereas two (1.3%) patients in the HD group reported GIB within 90 days of arthroplasty. GIB rates did not differ significantly between groups ($P = 0.24$). Considering VTE + GIB combined, the HD groups showed a higher rate of complications ($N = 4$, 2.6%) than the LD groups ($N = 1$, 0.6%) but not statistically significant ($P = 0.21$).

Conclusions: Prophylactic administration of Aspirin with low doses (81 mg BID) and high doses (325 mg BID) for six weeks is equally effective at reducing VTE in total joint arthroplasty patients and had similar adverse effects.

Level of Evidence: Therapeutic Level II

Keywords: Aspirin, gastrointestinal bleeding, high-dose, low-dose, total Joint arthroplasty, venous thromboembolism

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common and effective treatments for end-stage degenerative joint disease, including osteoarthritis [1]. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is one of the leading causes of preventable morbidity, mortality, and healthcare expenditures[2]. As a result of the prolonged surgery and reduced mobility postoperatively, all patients undergoing total joint arthroplasty (TJA) are at risk for VTE. Thus, anticoagulation is administered up to 5–6 weeks after surgery to reduce VTE risk[3]. Among people who are anticoagulated, rates of VTE are variable following THA and TKA: up to 5% for DVT and 2% for PTE[4].

Various anticoagulants can be used to prevent VTE, including simple oral agents (Aspirin), injectable anticoagulants (low molecular weight heparin), and novel oral anticoagulants (dabigatran and rivaroxaban). In the search for ideal chemoprophylaxis, a number of challenges are still being addressed, such as bleeding and wound-related issues, administration route, titration, and blood monitoring[5,6]. Aspirin is a cheap oral drug that does not require blood testing and is well-tolerated and safe[7]. A large body of evidence supports Aspirin's efficacy in preventing postoperative VTE[2,4,8–11]. Nevertheless, using Aspirin as the sole prophylactic antithrombotic agent in orthopaedic patients has remained controversial despite decades of successful and safe

HIGHLIGHTS

- Aspirin with low doses (162 mg) and high doses (650 mg) is equally effective.
- Both doses showed similar adverse effects.
- 90-day mortality and gastrointestinal bleeding were similar between the two groups.

[a]Orthopedic Surgery Research Centre, Sina University Hospital, [b]Joint Reconstruction Research Center and [c]Surgical Research Society (SRS), Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

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*Corresponding author. Address: Imam Khomeini Hospital, End of Keshavarz Blvd, Keshavarz Blvd, Tehran, 1419733141, Iran, Tel: +9821-6658-1586, fax: +9821-6658-1586. E-mail address: smjmort@yahoo.com (S. M. J. Mortazavi).

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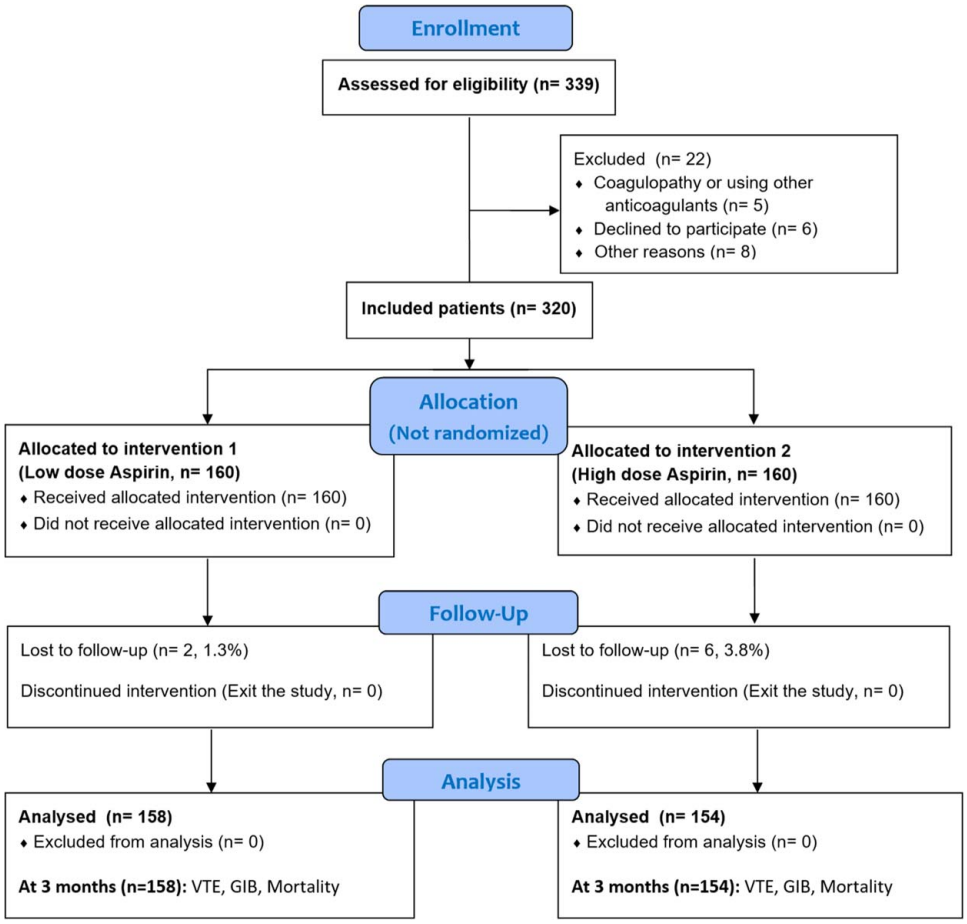

Figure 1. Flow diagram of patients' enrolment and study assessments. GIB, gastrointestinal bleeding; VTE, venous thromboembolism.

use. The majority of studies included "standard risk" patients, and the controversy is more prominent among other patient populations[12]. Over the past decades, PTE rates after TJA have not decreased markedly[13], and potent anticoagulants contribute only to a lower incidence of asymptomatic VTE[14–16]. Since PTE persists as an essential complication, the role of potent anticoagulants has been debated[17,18]. Administrating potent anticoagulants can increase the risk of bleeding, wound complications, and hospitalization days, compared to a simple Aspirin[19–21].

The American College of Chest Physicians (ACCP) and American Association of Orthopedic Surgeons (AAOS) have recommended Aspirin alone as a single agent for the prophylaxis of VTE after joint replacement surgery and a dose of 325 mg BID for six weeks following surgery[22,23]. On the other hand, 77% of the participants in the International Consensus Meeting (ICM) 2022 agreed that low-dose (LD) Aspirin is the most effective and safest prophylaxis for VTE[24]. It was unclear until recently what was the optimal dose of Aspirin for VTE prevention[25]. Few studies suggest that twice-daily (BID) LD Aspirin (81 mg), compared with high-dose (HD) Aspirin (325 mg) for 4-6 weeks, does not differ regarding VTE events after TJA[9,25–27]. The minimal effective dosage of Aspirin in preventing VTE is unknown since the adverse effects are dose-dependent, and the evidence supporting the use of LD Aspirin in preventing VTE after THA is weak.

To this end, our incentive to conduct this study was due to the paucity of evidence derived from prospective cohort studies on its topic. This study compared the 90-day symptomatic VTE rates among healthy patients following THAs and TKAs with 81 mg BID of Aspirin vs. 325 mg BID of Aspirin for 6 weeks postoperatively. We aimed to secondarily investigate differences in the rate of complications between the two dosing regimens, including 90-day gastrointestinal bleeding events and mortality. We hypothesized that a LD Aspirin would be as effective as a HD Aspirin in preventing VTE and be associated with fewer gastrointestinal bleeding (GIB) events.

Methods

Study design and ethics statement

This study was reported in accordance with STROCSS criteria[28]. A prospective cohort study of patients with TJA was performed in two tertiary centres of our Medical University between January 2020 and January 2022. The patients were given Aspirin in two different doses to prevent VTE for 6 weeks: 325 mg BID or 81 mg BID. Our university institutional review board (IRB) has approved the study's protocol and declared it ethically acceptable (Approval ID: IR.TUMS.MEDICINE.REC.1399.293). The participants voluntarily signed informed consent forms and participated in the study.

Table 1
Patients' demographic and data

Variable (Mean ± SD or *n* %)	Low dose (*N* = 158)	High dose (*N* = 154)	*P*
Preoperative data			
Male sex	53 (33.5)	58 (37.7)	0.45
Age (year)	53.3 ± 18.4	55.0 ± 18.9	0.43
Body mass index (Kg.m^{-2})	27.0 ± 4.3	26.9 ± 4.3	0.72
Smoke	36 (22.8)	22 (14.3)	0.06
Diabetes mellitus	24 (15.2)	21 (13.3)	0.46
Platelet count (per microlitre)	252.5 ± 90.0	255.2 ± 85.7	0.79
Type of surgery			0.16
Primary (281. 90.1%)	146 (92.4)	135 (87.7)	
Revision (31, 9.9%)	12 (7.6)	19 (12.3)	
Joint			0.22
Knee (64, 20.5%)	28 (17.7)	36 (23.4)	
Hip (248, 79.5%)	130 (82.3)	118 (76.6)	
Operation data			
Anaesthesia			0.32
Spinal	69 (43.7)	76 (49.4)	
General	89 (56.3)	78 (50.6)	
Length of stay (day)	4.6 ± 3.4	4.9 ± 2.6	0.07
THA approach (248, 100%)			< 0.001*
Direct anterior	98 (75.4)	58 (49.2)	
Lateral	32 (24.6)	60 (50.8)	
Type of prosthesis			0.87
Cemented	62 (39.2)	59 (38.3)	
Cementless	96 (60.8)	95 (61.7)	

THA, total hip arthroplasty.
*Indicates significant *P* value.

Participants, inclusion, and exclusion criteria

Our study involved 320 consecutive adult patients in two orthopaedic clinics who were being treated with TKA or THA [Figure 1].

Inclusion criteria

Primary or revision TKA and TJA
Intended to participate and sign a consent
American Society of Anesthesiologists (ASA) score of I–III

Exclusion criteria

Medical history of DVT or PTE
Any coagulopathy (factor V Leiden, antithrombin III deficiencies, Glanzman thrombasthenia, etc.)
Using other medications that interfere with the study outcome (Rivaroxaban, Plavix, Warfarin, etc.)
Active malignancy
A different form of VTE chemoprophylaxis was given rather than Aspirin, Aspirin allergy, or intolerance
No intention of participating or illiterate for successful completion of the follow-up and the forms.
Major comorbidities such as heart failure or renal failure
Unicompartmental knee replacement

Interventions and study protocol

TKA cases were treated using standard conventional PS (posterior stabilizer) TKA. The same surgeon with a fellowship in adult reconstruction performed all TKA procedures using a medial parapatellar approach and a standard midline incision. All of the patients received cemented posterior stabilized prostheses (NexGen LPS-Flex) by Zimmer Biomet (Warsaw). All participants received the same preoperative and postoperative care according to the same protocol. We applied a tourniquet (250 mmHg) and did not employ suction drains. Aspirin (325 or 81 mg/BID) was used postoperatively as a VTE chemoprophylaxis (begin on POD 1). The pain management protocol includes Celecoxib (400 mg) + Pregabalin (75 mg) + Acetaminophen (1g) + Omeprazole (40 mg), taken orally one hour before surgery for all patients. The patients received 2.0 g of injection cephazolin as antibiotic prophylaxis. Patients received 1.5 g of IV tranexamic acid before surgery. Following the closure of the articular capsule, a cocktail was injected intra-articularly, consisting of normal saline (90 mL) + ketorolac (60 mg) + Marcaine (4 mL, 0.5%) + Lidocaine (5 mL, 2.0%) + 3 mg tranexamic acid. During the postoperative period, the following analgesics were administered: celecoxib (400 mg), omeprazole (20 mg), pregabalin (75 mg), acetaminophen (2g), and oxycodone (PRN, maximum 15 mg per day). Patients were mobilized by a walker within 6–8 h of surgery, and range-of-motion exercises were begun. We allowed patients to walk partial weight-bearing using crutches for 4–6 weeks. Brace was not used on any patients. There were no compression devices applied to the patients' calves after surgery.

The THA surgery was performed by three surgeons with fellowships in adult reconstruction either using the direct anterior approach or lateral approach. The bearing surface in all surgeries was metal on a highly cross-linked polyethylene. Fitmore stems (Zimmer, Inc.) and CORAIL implants (DePuy Orthopaedics, Inc.) were used for the femoral component. Hemispherical porous-coated Trilogy cups (Zimmer, Inc.) and porous-coated Pinnacle cups (DePuy Orthopaedics, Inc.) were used for the acetabular component. 2D templating was performed on all patients before surgery using mediCAD software[29]. The perioperative care was the same for TKA patients described above, except THA patients did not receive cocktail injections and oxycodone.

Outcome measures and data collection

The study's primary outcome was symptomatic VTE (DVT and PTE) within 90 days of index arthroplasty. In addition, the secondary outcomes were GIB and mortality within 90 days. The routine follow-up for TJA patients at our centre consists of 1 week, 3 weeks, 6 weeks, 3 months, 6 months, 12 months after surgery, and then annually. Clinical manifestations of DVT, such as pain, warmth, redness, swelling, and tenderness in the lower

Table 2
Study results (90 days follow-up)

Variable (Mean ± SD or *n* %)	Low dose (*N* = 158)	High dose (*N* = 154)	*P*
VTE	1 (0.6)	2 (1.3)	0.62
DVT	1 (0.6)	2 (1.3)	0.62
PTE	0	0	—
GIB	0	2 (1.3)	0.24
Mortality	0	0	—
Total VTE/bleeding complications	1 (0.6)	4 (2.6)	0.21

DVT, deep vein thrombosis; GIB, gastrointestinal bleeding; PTE, pulmonary thromboembolism; VTE, venous thromboembolic.

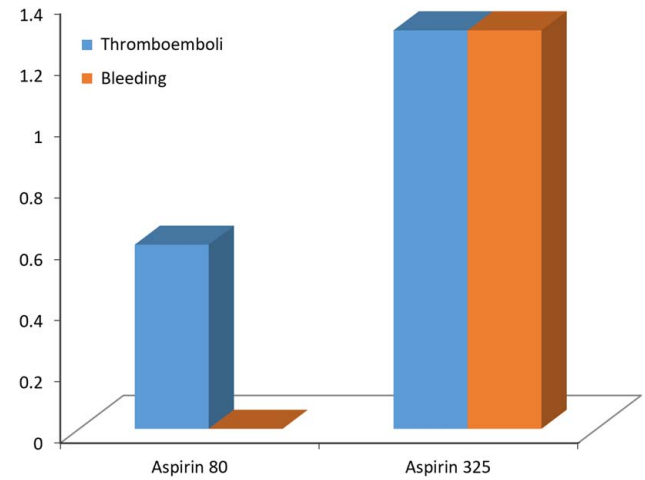

Figure 2. Thromboembolic and haemorrhagic complications in two groups of aspirin.

limb, positive Homans sign, and different leg circumferences, were used to screen DVT. PTE was also screened by clinical symptoms like dyspnoea and chest pain. Colour Doppler ultrasound confirmed DVT suspicion, and lung ventilation/perfusion scan or computed tomography-angiography confirmed PTE suspicion. Our orthopaedic resident (PGY-3) conducted the physical examination and VTE screening blinded to the study groups. GIB was defined as bleeding from the upper gastrointestinal tract confirmed by endoscopy.

Hospital length of stay, type of anaesthesia, cemented or cementless prosthesis, and platelet counts before surgery were compiled by the surgeon using the checklist. Blood loss during the surgery is measured by measuring the blood loss directly in volume units. In addition, the patient's demographics, history of VTE, and comorbidities were recorded. Finally, all parameters were compared between the two groups under prophylactic Aspirin doses of 81 mg and 325 mg.

Statistical analysis

Data were analyzed by SPSS 23.0 (IBM SPSS Inc.). Normality was determined by the Shapiro-Wilk test. Using Student's *t*-tests, Mann–Whitney tests, and Analysis of Variance (ANOVA), a comparison of continuous variables by their normality was performed. The nominal variables were also compared using the χ^2 and Fisher exact tests. The repeated measures ANOVA test was used to compare the group scores across time. *P* values of less than 0.05 were considered significant.

Results

The final analysis included 312 consecutive patients: 158 in the LD group (81 mg Aspirin BID) and 154 in the HD group (325 mg Aspirin BID) [Figure 1]. Two groups were similar regarding preoperative data and demographics, including sex, age, BMI, smoking, diabetes mellitus, and platelet count, and type of surgery [Table 1]. In terms of surgical information, the two groups were similar, aside from the THA approach. In the LD groups, direct anterior approach was predominant (75.4%), while in the HD groups, a more lateral approach was prevalent (50.8%, $P < 0.001$).

The LD group had one DVT (0.6%), and the HD group had two (1.3%) ($P = 0.62$) [Table 2]. Neither group had PTE. Therefore, VTE rates are the same as DVT rates and similar between the groups (0.6% vs. 1.3%, $P = 0.62$) [Figure 2].

Regarding GIB due to anticoagulant therapy, no patient in the LD group reported GIB, whereas two (1.3%) patients in the HD group reported GIB within 90 days of arthroplasty. GIB rates did not differ significantly between groups ($P = 0.24$). Considering VTE + GIB combined, the HD groups showed a higher rate of complications ($N = 4$, 2.6%) than the LD groups ($N = 1$, 0.6%) but not statistically significant (0.21). During the study period, no death occurred.

Details on the five patients who had VTE or GIB within 90 days following their arthroplasty are provided in [Table 3].

Discussion

The main finding of this study was that the administration of both LD (81 mg BID) and HD (325 mg BID) Aspirin for 6 weeks was effective and safe for patients undergoing joint replacement surgery. LD Aspirin not only was not inferior to HD, but also demonstrated an insignificantly lower risk of VTE and GIB. Thus, we considered it reasonable to take LD Aspirin (81 mg BID) into account for the routine practice of TJA. It is important to note that our study is not the first to compare VTE rates between different dosages of Aspirin after TJA. Therefore, we should consider the findings of our study within the context of other published findings.

Patients undergoing arthroplasty surgery have a well-established risk of developing VTE and subsequent PTE that can be fatal[7,30,31]. In more recent ACCP guidelines from 2012, Aspirin was recommended as an appropriate method of VTE prophylaxis after TJA[22]. To choose the best anticoagulant and dosage, it is essential to balance agent efficacy and side effects caused by drugs with higher risk profiles[6]. The network meta-analysis by Tarabichi and colleagues of all levels of evidence studies[24] showed that the lowest risk of VTE development was seen with LD Aspirin (100 mg). There was no significant difference between low molecular weight heparin and rivaroxaban when compared to LD Aspirin in their risk of causing VTE [Odds ratio (OR), 95% CI = 1.11 (0.33, 3.76) and 1.38 (0.55, 3.45)]. In contrast, VTE is more likely to occur when HD Aspirin (325 mg) is taken [OR = 7.9 (2.60, 24.05)] followed by heparin (OR = 5.94 (2.28, 15.47)) as compared to LD Aspirin. Furthermore, when the risk of bleeding events was assessed in all studies, LD Aspirin (81 mg) had the lowest risk estimate. In sum, they found that LD Aspirin effectively reduced the risk of VTE compared with other medications and caused fewer bleeding incidents[5,24,32–35]. Despite previous research findings, recent literature now disproves the notion that HD Aspirin (325 mg BID) offers greater protection against cardiovascular and cerebrovascular issues than LD Aspirin (75–100 mg BID)[36–38]. In the Pulmonary Embolism Prevention (PEP) study in 2001, LD Aspirin (80 mg BID) significantly lowered the incidence of DVT and PTE in patients undergoing TJA by at least one-third of place controls[39]. Still, the AAOS guidelines recommend that HD Aspirin (325 mg BID) be used to prevent VTE following TJA[40].

Table 3

Information of patients with VTE or GIB

Sex	Age	BMI	Smoke	Comorbidity	Type of surgery	Anaesthesia	Condition	Aspirin dose	Treatment
Male	79	33	Yes	DM	Primary THA	General	DVT	81 BID	Conservative
Female	69	30	Yes	—	Primary TKA	Spinal	DVT	325 BID	Conservative
Female	73	27	Yes	DM	Primary THA	Spinal	DVT	325 BID	Conservative
Male	64	23	Yes	—	Primary THA	Spinal	GIB	325 BID	Conservative
Male	51	27	No	—	Primary THA	General	GIB	325 BID	Conservative

DM, Diabetes mellitus; DVT, deep vein thrombosis; GIB, gastrointestinal bleeding; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolism.

There has been evidence that if taken at doses between 30 and 150 mg, Aspirin inhibits the activity of the platelet COX-1 enzyme[36]. Several studies directly compare the LD and HD Aspirin as chemoprophylaxis for VTE after TJA[9,25–27,41–46]. Uvodich and colleagues. compared 90-day incidence of symptomatic VTE on 3512 patients treated with either LD (81 mg BID) or HD (325 mg BID) Aspirin 4–6 weeks after surgery. Neither group showed a difference in symptomatic VTE incidence (0% vs. 0.1%, $P = 0.79$), GIB events (no cases), and mortality (0.3% vs. 0.1%, $P = 0.24$)[25]. According to Parvizi *et al.*[27], their prospective cross-over study on 4651 primary TJA did not reveal any differences in VTE between LD and HD groups (0.1% vs. 0.3%, $P = 0.35$). The rates of GIB and ulceration (0.3% vs. 0.4%, $P = 0.66$), as well as acute periprosthetic joint infection (PJI) (0.2% vs. 0.5%, $P = 0.28$), were modestly higher in the HD group, but statistically not significant[27]. To the best of our knowledge, their study was the only prospective study in the literature search. In the setting of revision surgery, Tang and colleagues' study on revision TKA and revision THA patients demonstrated non-inferiority of LD Aspirin vs. HD Aspirin[43,45]. Only one study found a significant difference in favour of LD Aspirin, that of Merkow *et al.*[44]. On HD Aspirin (325 mg BID), 133 VTE cases were reported among the 9413 TKA compared with 8 cases among the 3453 TKA on HD Aspirin (81 mg BID) (1.41% vs. 0.23%, $P < 0.001$)[44]. The only systematic review comparing the low and HD Aspirin found that in patients receiving LD or HD Aspirin, there were no significant differences in the rates of symptomatic PTE (0.33% vs. 0.65%, $P = 0.16$), symptomatic DVT (0.52 vs. 0.99%, $P = 0.23$), 90-day mortality (0.33 vs. 21%, $P = 19$), or major bleeding (54% vs. 29%, $P = 38$)[26].

LD Aspirin also showed comparable effects to HD when assessing for other conditions, such as heterotopic ossification (HO) development[41]. Van Nest and colleagues revealed that Aspirin-treated patients were less prone to develop HO following THA (34.8% vs. 45.5%) and HO following TKA (13.4% vs. 18.4%) compared with non-Aspirin VTE prophylaxis. When comparing low and HD Aspirin, HO formation was lower in LD Aspirin patients (81 mg) vs. HD Aspirin patients (325 mg), although not significantly[41]. It could show that LD Aspirin is not only sufficient for VTE prophylaxis but is also sufficient to prevent HO. Our study's results align with the existing literature on LD Aspirin compared with regular-dose Aspirin in the control of VTE after TJA. For otherwise healthy patients, we recommend using LD Aspirin during TJA[47].

Our study faced several limitations. First, our sample size is not that large to provide a strong and valid conclusion and is underpowered. Because the sample size was small and only a few patients experienced VTE, it was not possible to identify risk factors and conduct a multivariate analysis. Second, we did not consider wound complications such as dehiscence and infection. Our primary outcome was VTE events; previous studies showed no difference in wound conditions between the different dosages of Aspirin[27]. Furthermore, our patient sample is inhomogeneous in some respects, and primary TJAs differ significantly from their revision counterparts. Lastly, the study was not randomized, because of which it suffers from selection bias.

Conclusions

According to this prospective comparative study, prophylactic administration of Aspirin with low doses (81 mg BID) and high doses (325 mg BID) for 6 weeks is equally effective at reducing VTE in TJA patients. In addition, 90-day mortality and GIB were similar between groups. Therefore, lower doses are recommended for safety reasons. To confirm these findings, more large-scale randomized clinical trials are needed in the future.

Ethical approval

The study was reviewed and approved by Institutional Review Board of Tehran University of Medical Sciences. (Approval ID: IR.TUMS.MEDICINE.REC.1399.293).

Consent

All the patients obtained informed consent to publish this study and accompanying data. On request, a copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author contribution

S.H.S. contributed to the study conception and design, performed surgeries, and revised the manuscript. P.M. analyzed the data and wrote the first draft of the manuscript and revised it. M.R. contributed to the study design, data collection, and draw figures. B.S. contributed to the study conception and design, performed surgeries, and revised the manuscript. S.M.J.M. supervised the study, performed the surgeries, and edited the final text. All authors commented on previous versions of the manuscript and revised it. All authors read and approved the final manuscript."

Conflicts of interest disclosure

The authors report no declarations of interest.

Research registration unique identifying number (UIN)

NA.

Guarantor

Seyed Mohammad Javad Mortazavi.

Availability of data and material

The data that support the findings of this study are available from the corresponding author, S.H.S., upon reasonable request.

Provenance and peer review

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