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Low-Dose Aspirin for Venous Thromboembolism Prophylaxis is Associated With Lower Rates of Periprosthetic Joint Infection After Total Joint Arthroplasty

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Running Title: Low Dose Aspirin for VTE Lowers PJI Rate

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ABSTRACT

Background: Aspirin as a venous thromboembolism (VTE) prophylactic agent has been shown to have anti-staphylococcal and anti-biofilm roles. Optimal acetylsalicylic acid (ASA) dosage would facilitate antimicrobial effects while avoiding over-aggressive inhibition of platelet antimicrobial function. Our purpose was to determine periprosthetic joint infection (PJI) rate after total joint arthroplasty (TJA) in patients receiving low-dose ASA (81 mg bid), in comparison to high-dose ASA (325mg bid).

Methods: We conducted a retrospective cohort study between 2008 and 2020. Eligible patients were older than 18 years, undergoing primary TJA, both total knee arthroplasty (TKA) and total hip arthroplasty (THA), had a minimum 30-day follow-up, and received a full course ASA as VTE prophylaxis. Patients' records were reviewed for PJI, according to Musculoskeletal Infection Society (MSIS) criteria. Patients were excluded if they underwent revision arthroplasty, had a history of coagulopathy, or an ASA regimen that was not completed. In total, 15,825 patients identified, 8,761 patients received low-dose ASA and 7,064 received high-dose.

Results: The high-dose cohort had a higher PJI rate (0.35 vs. 0.10%, p = 0.001). This relationship was maintained when comparing subgroups comprising TKA (0.32 vs. 0.06%, p = 0.019) or THA (0.38 vs. 0.14%, p = 0.035), and accounting for potentially confounding demographic and surgical variables (Odds Ratio 2.59, 95% Confidence Interval 1.15 - 6.40, p = 0.028).

Discussion: Comparing low-dose to high-dose ASA as VTE prophylactic agent, low-dose ASA had a lower PJI rate. This may be attributable to a balance of anti-infective properties of ASA and anti-platelet effects.

Keywords: Aspirin; Venous Thromboembolism Prophylaxis; Dosing; Total Joint Arthroplasty; Periprosthetic Joint Infection

INTRODUCTION

Periprosthetic joint infection (PJI) remains a serious postoperative complication associated with significant morbidity, mortality, and healthcare costs [1,2]. Given the rapidly increasing number of total joint arthroplasties (TJAs), the burden of PJI is expected to increase, with current data suggesting an incidence of PJI following TJA ranging from 1 to 4.6% [3]. Post-operatively, a robust immune response is critical to prevent the adherence of bacteria and the development of biofilm [4,5]. Peri-operative modifications of the host immune response can facilitate the prevention of PJI development. Interestingly, aspirin (ASA), which is routinely administered post-operatively as a venous thromboembolism event (VTE) prophylaxis, has a potential anti-staphylococcal and anti-biofilm role [5–10].

In recent years, the orthopaedic communities have accepted the antiplatelet agent ASA as the primary VTE prophylactic method following total joint arthroplasty [11–17]. ASA has some distinct benefits, including widespread availability, ease of oral administration, and low cost. Furthermore, the risk of postoperative hematomata , wound drainages, extended hospital stays, and infectious complications can be decreased by less aggressive anticoagulation therapies like ASA following TJA [17–23]. It has been demonstrated that ASA has a direct antibacterial effect, with potent anti-staphylococcal synergy with concomitant antibiotic administration [24]. In a mouse model of implant-associated infection, ASA has a dose-dependent effect on reducing infectious burden in the moderate dosing range, however, this effect was lost when using high-dose ASA (7mg/kg bid) [10]. As platelets have potent anti-microbial properties and platelet deficiency is strongly linked to PJI severity in a pre-clinical model [25], an optimal ASA dose would facilitate anti-microbial effects, while avoiding over-aggressive inhibition of platelet anti-microbial function. While some studies suggest that using ASA as a VTE prophylaxis method

reduces PJI risk following TJA [4,16], there is no study to evaluate if ASA dose after joint arthroplasty will affect the rate of PJI.

Our study aimed to determine the rate of PJI after total knee arthroplasty (TKA) and total hip arthroplasty (THA) in patients receiving low-dose ASA (defined as 81mg bid) in comparison to those receiving high-dose ASA (defined as 325mg bid). We hypothesized that using 81mg bid of ASA (162mg total daily dose) will be more effective than 325mg bid (650mg total daily dose) at reducing PJI following TJA, without increasing the risk of postoperative wound complications.

MATERIALS and METHODS

Study Design and Population

We conducted a retrospective cohort study of patients undergoing primary TJA. According to an institutional database, 36,332 TJA entries were registered between January 4th, 2008 and October 30th, 2020. Eligible patients were older than 18 years, undergoing primary TJA, and received a full course of ASA post-operatively as VTE prophylactic agent. We had a minimum follow-up of 30 days after surgery for 18,901 patients before 2015, and a minimum of 90 days in 17,431 patients after 2015, when a nurse navigation program was initiated at our institution.

We reviewed patients' records for PJI, which was defined according to the Musculoskeletal Infection Society (MSIS) criteria [26]. Entries were excluded if patients were anticoagulated for revision arthroplasty, had a previous history of VTE or coagulopathy, the ASA regimen was not completed, or the ASA dosage was not specified. The cohort was further stratified based on low- and high-dose ASA. At our institution, high-dose ASA was initially the preferred dose for VTE prophylaxis, but more recent trends in management favor low-dose ASA. The review of the electronic medical records included demographic characteristics, comorbidities, surgical variables, post-operative complications, VTE prophylaxes, clinical and laboratory data.

In total, 15,825 patients were identified for inclusion in the analysis. 8,761 patients received VTE prophylaxis with low-dose ASA (81mg bid), and 7,064 patients received high-dose ASA (325mg bid). Demographic characteristics are summarized in Table 1. More patients in the low-dose ASA cohort had a history of diabetes mellitus (DM) (7.1 vs. 2.5%, $p < 0.001$), and had Tranexamic acid (TXA) use during the surgery (82.9 vs. 51.3%, $p < 0.001$). Patients in the high-dose cohort were more likely to undergo TKA (48.1 vs. 41.3%, $p < 0.001$), undergo THA through a lateral approach (60.7 vs. 39.5% $p < 0.001$), have bilateral surgery (7.4 vs. 2.0%, $p < 0.001$),

receive a general anesthetic (3.9 vs. 2.9%, $p < 0.001$), and have tourniquet usage during the surgery (69.9 vs. 29.8%, $p < 0.001$). Also, high-dose cohort patients had more blood loss (128 vs. 103 mL, $p < 0.001$) and transfusion rates (4.0 vs. 1.9%, $p < 0.001$) (See Table 1). In the combined cohort, there were no statistically significant differences in rates of post-operative myocardial infarction (MI), cerebrovascular accident (CVA), gastrointestinal (GI) ulceration, or GI hemorrhage (See Table 2).

Study Definitions

According to the MSIS guidelines [26], PJI was confirmed with the presence of one of the major criteria or, if necessary, based on the score obtained in the presence of minor criteria. A complete ASA regimen was defined whenever the VTE prophylactic agent was used for at least two weeks after discharge. Low-dose ASA was defined as when patients completed 81mg bid, and high-dose ASA for patients using 325mg bid.

Statistical Analyses

Parametric continuous data were presented as means with ranges and p-values were calculated by performing t-tests. Nonparametric continuous data were also presented as means and p-values were calculated by performing Mann-Whitney tests. Categorical data were presented as number counts and percentages (%). Chi-Square or Fisher's Exact tests were used to calculate p-values for categorical data. Primary total knee arthroplasty (TKA) and total hip arthroplasty (THA) cases were examined separately in secondary analyses. Logistic regression analyses were performed considering ASA dose as the main variable of interest and adjusted logistic regression analyses were performed for demographic and surgical co-variates (including age, sex, Body mass

index (BMI), Charlson comorbidity index (CCI) [27], operative time, operated joint, and TXA use), with odds ratio (OR) calculated. P-values less than 0.05 were deemed significant. Receiver operating characteristic (ROC) curves were used to assess the accuracy and trade-off between sensitivity and specificity for the development of PJI in patients undergoing primary TJA. Based on these values, the Youden's index was measured to identify an optimal platelet count cutoff and area under the curve (AUC) for predicting the development of PJI. All statistical analyses were performed using R Studio (Version 3.6.3, Vienna, Austria).

RESULTS

Patients receiving high-dose ASA had a higher percentage of PJI vs. patients receiving low-dose ASA (0.35 vs. 0.10%, p = 0.001). This relationship was maintained when assessing primary TKA (0.32 vs. 0.06%, p = 0.019), and primary THA (0.38 vs. 0.14%, p = 0.035) (See Table 2). Regression analyses adjusted for demographic and surgical variables, comparing rates of PJI in high- to low-dose ASA cohorts (with low-dose as reference), revealed an OR of 2.59 (95% CI 1.15 - 6.40, p = 0.028) (See Table 3). Age, sex, CCI, operative time, and type of joint did not influence the rate of PJI in this cohort (p = 0.667, 0.115, 0.692, 0.135, and 0.215 respectively). However, BMI and TXA use analysis revealed an OR of 1.10 and 0.46 (95% CI 1.03 - 1.17, p = 0.003 and 0.21 - 0.97, p = 0.045) respectively (See Table 3). Regression analyses for TKA and THA were performed separately and included in the Supplementary Material, Tables 1 to 4.

Primary TKA

TKA regression analysis comparing rates of PJI in high-to low-dose ASA cohorts (with low-dose as reference), revealed an OR of 5.88 (95% CI 1.58 – 37.99, p = 0.021), (See Supplement Table 1)

Primary THA

THA regression analyses comparing rates of PJI in high-to low-dose ASA cohorts (with low-dose as reference), revealed an OR of 2.81 (95% CI 1.17 – 7.43, p = 0.026), (See Supplementary Table 3).

Receiver operating characteristic/Area under the curve (ROC/AUC) analysis of platelet count as a variable for the development of PJI in both cohorts did not reveal good prediction models. AUC for low-dose ASA was 0.64 (Cutoff 286.00×10^9/L, 95% CI 0.44 - 0.84), and AUC for high-dose ASA was 0.47 (Cutoff 271.00×10^9/L, 95% CI 0.35 - 0.60) (See Table 4 and Figure 1). Furthermore, logistic regression analyses revealed no association between platelet count and development of PJI (OR 1.00, 95% CI 0.99 - 1.00, p = 0.631) (See Table 5).

DISCUSSION

Using a large institutional database, we performed a retrospective cohort study assessing the relationship between ASA dose and incidence of PJI in patients undergoing primary TJA. When comparing low- to high-dose ASA as VTE prophylaxis in this study, low-dose ASA had a lower rate of PJI. This relationship was maintained when comparing subgroups comprising TKA or THA solely, and accounting for potentially confounding demographic and surgical variables. Further, the rate of DM, which is a known risk factor for PJI, was higher in the low-dose ASA group [26]. While a higher dose of ASA may theoretically be associated with higher renal and GI complications rates, our analysis showed no increased risk.

There is no current consensus on the optimal dose of ASA for VTE prophylaxis following primary TJA [28]. Choice of prophylaxis depends on patient-specific risk factors and shared decision-making between provider and patient. However, our study suggests a potential benefit to prescribing ASA at 81mg bid over 325mg bid following TJA. At low doses, aspirin primarily inhibits COX-1 and is sufficient to prevent thrombosis. At high doses, Aspirin leads to both COX-1 and COX-2 inhibition, while also producing more anti-inflammatory and analgesic effects [28]. Further, there are putative anti-infective properties of ASA that appear to involve effects on both bacteria and platelets. Previous animal and clinical studies have examined the relationship between bacteria, platelets, and antiplatelet agents in the development of staphylococcal endocarditis [30,31]. Yeaman theorized that there is a balance of ASA ability to prevent bacterial aggregation to platelets while not completely inhibiting platelet activation and degranulation in this context [32]. While the ROC curve in our study did not reveal an adequate platelet cutoff value that would predict PJI, platelets themselves are increasingly recognized as essential contributors to antibacterial defense [31,32]. Furthermore, a recent study assessing

thrombocytopenia in a mouse model of staphylococcal orthopaedic implant infection revealed platelet deficiency as a risk factor for infection burden [25]. ASA direct anti-microbial effect has been best described in the context of staphylococcus species, which may contribute to the reduction of PJI seen in our study [34]. It has been shown that ASA can affect the pathogenicity of staphylococcus and have a synergistic effect with antibiotics [6]. However, ASA has also been shown to chelate iron and increase biofilm formation *in vitro* [35]. Therefore, we theorized that an optimal dose of ASA might exist to balance these protective effects while providing sufficient thromboprophylaxis.

The primary strength of this study is the large cohort of patients undergoing TJA that completed a course of defined high- and low-dose ASA for DVT prophylaxis. Furthermore, a robust statistical analysis included both unadjusted and adjusted logistic regression assessing for demographic and surgical variables as confounders. Also, our findings were maintained upon assessment of TKA and THA separately.

The retrospective and observational nature of this study inherently limits the strength of the conclusions drawn. At our institution, low-dose ASA is also a more contemporary intervention, which may introduce confounders that are unaccounted for in our study (including factors such as antibiotic selection, blood transfusion thresholds and other peri-operative protocols). The effect size using absolute risk reduction was also small at 0.25% but clinically significant given the volume of TJA. It is important to note that the effect in this study identifies a correlation and causality is not definitely delineated. The specific microbiology of each infection was also not included in this study. Furthermore, although our findings were maintained upon assessment of TKA and THA separately, few occurrences of PJI in each joint limit the reliability and precision of the estimates and increase the chance of overfitting the model. Also, the incidence

of PJI at our center was lower than the reported national average (0.21 vs. 2.0 to 2.4%) [1]. However, while external validity remains an important consideration, we would not expect the variable of lower PJI rate to affect overall treatment effect in cohorts with a higher baseline PJI rate.

Future analysis could investigate if ASA versus other common VTE prophylactic agents, such as low-molecular-weight heparin (LMWH) or warfarin, results in a decrease specifically in staphylococcal infection. The effect of ASA dose on PJI microbiology could also be expanded to include revision arthroplasty populations. Basic science and animal models are also needed to understand further the mechanisms underlying this small but relatively important difference.

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Table 1. Demographic and surgical variables for all primary total joint arthroplasty cases.

Demographic	*ASA 81mg bid (8,761)*	*ASA 325mg bid (7,064)*	*p-value*
Age in years (range)	64 (12 – 101)	63 (16 – 96)	0.183
Women (%)	4,749 (54.2%)	3,763 (53.3%)	0.264
BMI in Kg/m^2 (range)	29.6 (10.52 – 73.82)	29.7 (9.31 – 54.66)	0.528
Diabetes mellitus (%)	**562 (7.1)**	**178 (2.5)**	**<0.001**
PVD (%)	102 (1.3%)	101 (1.4%)	0.472
Renal disease (%)	156 (2.0%)	110 (1.6%)	0.072
Operated joint			**<0.001**
Knee (%)	**3,620 (41.3%)**	**3,398 (48.1%)**	
Hip (%)	**5,141 (58.7%)**	**3,666 (51.9%)**	
Hip Approach			**<0.001**
Direct Anterior (%)	**3,112 (60.5%)**	**1,442 (39.3%)**	
Lateral (%)	**2,029 (39.5%)**	**2,224 (60.7%)**	
Bilateral surgery (%)	**174 (2.0%)**	**521 (7.4%)**	**<0.001**
Anesthesia			**<0.001**
General (%)	**247 (2.9%)**	**277 (3.9%)**	
Spinal (%)	**8,369 (97.1%)**	**6,752 (96.1%)**	
Tourniquet use			**<0.001**
No (%)	**2,542 (70.2%)**	**1,024 (30.1%)**	
Yes (%)	**1,078 (29.8%)**	**2,374 (69.9%)**	
Tourniquet time in minutes (range)	88.6 (49 – 175)	82.4 (38 – 180)	0.767
TXA use			**<0.001**
No (%)	**1,497 (17.1%)**	**3,443 (48.7%)**	
Yes (%)	**7,264 (82.9%)**	**3,621 (51.3%)**	
EBL in mL (range)	**103 (0 – 5200)**	**128 (0 – 5000)**	**<0.001**

Blood Transfusion			**<0.001**
No (%)	**8,596 (98.1)**	**6,784 (96.0%)**	
Yes (%)	**165 (1.9%)**	**280 (4.0%)**	

ASA=Aspirin; mg=Milligrams; bid=*"bis in die"* twice a day; BMI=Body mass index; Kg/m^2=Kilogram/square meter; PVD=Peripheral vascular disease; TXA=Tranexamic acid; EBL=Estimated Blood Loss; mL=Milliliter.

Table 2. Post-Operative Complications.

Complications	***ASA 81mg bid (8,761)***	***ASA 325mg bid (7,064)***	***p-value***
PJI			
Total (%)	**9 (0.1%)**	**25 (0.4%)**	**0.001**
Knee	**2 (0.1%)**	**11 (0.3%)**	**0.019**
Hip	**7 (0.1%)**	**14 (0.4%)**	**0.035**
Acute MI (%)	3 (0.0%)	9 (0.1%)	0.114
CVA (%)	5 (0.1%)	11 (0.2%)	0.159
GI ulcer (%)	2 (0.0%)	1 (0.0%)	1.000
GI hemorrhage (%)	4 (0.1%)	3 (0.1%)	1.000

ASA=Aspirin; mg=Milligrams; bid=*"bis in die"* twice a day; PJI=Periprosthetic joint infection; MI=Myocardial infarction; CVA=Cerebrovascular accident; GI=Gastrointestinal.

Table 3. Logistic regression looking at periprosthetic joint infection as primary outcome adjusting for demographic and surgical variables.

Predictor	***Estimate***	***OR (95% CI)***	***p-value***
ASA Dose			
81mg bid	Reference		

325mg bid	**0.951**	**2.59 (1.15 – 6.40)**	**0.028**
Age	0.008	1.01 (0.97 –1.05)	0.667
Sex			
Women	Reference		
Men	0.586	1.80 (0.88 – 3.83)	0.115
BMI (Kg/m^2)	**0.095**	**1.10 (1.03 – 1.17)**	**0.003**
CCI	0.074	1.08 (0.70 – 1.48)	0.692
Operative time	0.005	1.01 (1.00 – 1.01)	0.135
Operated joint			
Knee	Reference		
Hip	0.464	1.59 (0.77 – 3.39)	0.215
TXA use	**-0.772**	**0.46 (0.21 – 0.97)**	**0.045**

*Number of observations: 14,528

OR=Odds ratio; CI=Confidence interval; ASA=Aspirin; mg=Milligrams*;* bid=*"bis in die"* twice a day; BMI=Body mass index; Kg/m^2=Kilogram/square meter; CCI=Charlson comorbidity index; TJA=Total joint arthroplasty; TXA=Tranexamic acid.

Table 4. ROC/AUC analysis assessing for platelet cutoff value as predictor of PJI in patients undergoing primary total joint arthroplasty.

Platelet Count	***Cutoff Value***	***Sensitivity***	***Specificity***	***AUC***	***95% CI***
ASA 81mg bid	286.00×10^9/L	0.78	0.68	0.64	0.44 – 0.84
ASA 325mg bid	271.00×10^9/L	0.40	0.68	0.47	0.35 – 0.60

ROC/AUC=Receiver operating characteristic/Area under the curve; PJI=Periprosthetic joint infection; CI=Confidence interval; ASA=Aspirin; mg=Milligrams*;* bid=*"bis in die"* twice a day.

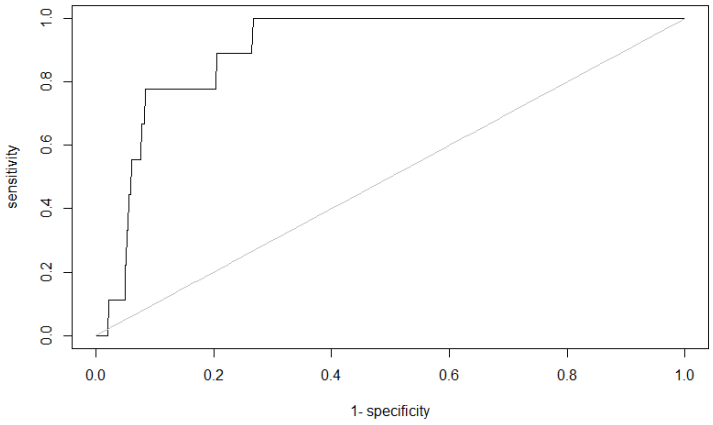
Table 5. Logistic regression looking at periprosthetic joint infection as primary outcome adjusting for PLT.

Predictors	***Estimate***	***OR (95% CI)***	***p-value***
ASA Dose			
81mg bid	Reference		
325mg bid	0.253	1.29 (0.62 – 2.92)	0.516
PLT	-0.001	1.00 (0.99 – 1.00)	0.631

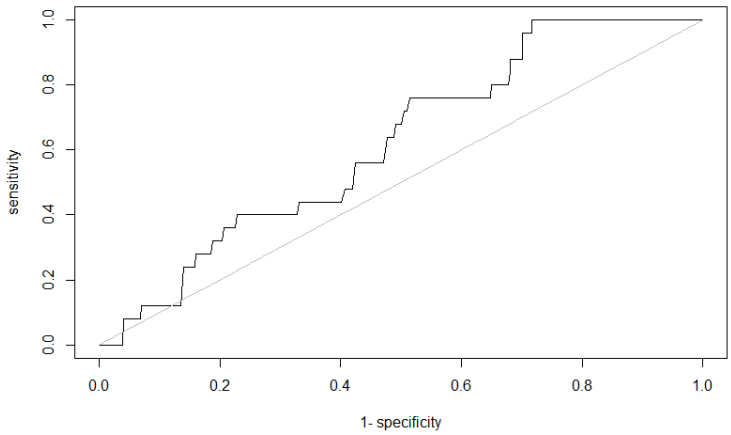
PLT=Platelets; OR=Odds ratio; CI=Confidence interval; ASA=Aspirin; mg=Milligrams; bid=*"bis in die"* twice a day.

Figure 1. ROC curve assessing for a cutoff value for platelet counts as a predictor of periprosthetic joint infection.

A) AUC for low-dose ASA (81mg, bid): 0.639 (Cutoff 286.00×10^9/L, 95% CI 0.44 - 0.84).



B) AUC for high-dose ASA (325mg, bid): 0.473 (Cutoff 271.00×10^9/L, 95% CI 0.35 - 0.60).



ROC=Receiver operating characteristic; AUC=Area under the curve; ASA=Aspirin; mg=Milligrams; bid= *"bis in die"* twice a day; CI=Confidence interval.

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