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Perioperative clopidogrel (Plavix) continuation in shoulder arthroplasty: approach cautiously

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Background: While the effect of clopidogrel on outcomes in elective hip and knee arthroplasty has been well described, there is a paucity of data regarding elective shoulder arthroplasty.

Methods: Fifty-eight patients were identified who underwent primary anatomic total shoulder arthroplasty (TSA) or reverse shoulder arthroplasty while prescribed clopidogrel. There were 33 (57%) reverse shoulder arthroplasties and 25 (43%) TSAs performed. Patients were separated into two groups based upon their use of clopidogrel in the preoperative period. Twenty patients (35%; group 1) continued clopidogrel through surgery, and 38 patients (65%; group 2) did not. The mean age was 74 years, and the mean follow-up was 42 months.

Results: Both groups demonstrated substantial improvements in pain and motion: visual analog scale pain improved by 7 points ($P < .001$), elevation by 71° ($P < .001$), external rotation by 29° ($P < .001$), and internal rotation by 1.7 points ($P < .001$), with no significant difference between groups. At the final follow-up, the mean American Shoulder and Elbow Surgeons score was 77 in group 1 and 86 in group 2 ($P = .067$, minimum clinically important difference = 9). Estimated blood loss was 176 mL in group 1 and 127 in group 2 ($P = .02$). There was one transfusion in group 1 (5%) and 0 in group 2 ($P = .16$). The 90-day complication rates were 3/20 (15%) in group 1 and 0/37 in group 2 (hazard ratio = 13, $P = .14$). There was no statistically significant difference between groups for 30-day adverse cardiac events (2.6% and 0%, respectively, $P = .46$).

Conclusion: For the patients who continued clopidogrel preoperatively, estimated blood loss was significantly higher and trended toward a lower American Shoulder and Elbow Surgeons score (with differences meeting the minimum clinically important difference) and a higher 90-day complication rate. Perioperative continuation of clopidogrel in shoulder arthroplasty should be approached cautiously.

The reported risk of perioperative bleeding associated with shoulder arthroplasty has varied over time. While most studies demonstrate a low rate of bleeding complications and transfusions,[8,16] a study by Gruson et al found a 43% rate of blood transfusion after shoulder arthroplasty.[12] Furthermore, postoperative bleeding can lead to hematoma formation, which has been associated with an increased risk of positive cultures and subsequent deep infection.[9] Tranexamic acid (TXA) use is one strategy that many surgeons use to minimize intraoperative blood loss, and multiple authors have found this medication to have substantial benefit, with no added risk for patients with a history of venous thromboembolism.[1,7,21]

Another common measure taken to mitigate the risk of complications from excessive bleeding is to instruct patients who usually take antiplatelet medications to discontinue these medications prior to shoulder arthroplasty.[3,4,10] However, this instruction does not come without some potential risk. In addition to aspirin, one of the most common medications in this class is clopidogrel (Plavix), which is typically prescribed to patients to prevent thrombosis of a recently placed cardiac stent.[5] Premature discontinuation of clopidogrel after stent placement has been correlated with an increased risk of coronary stent thrombosis.[13] Moreover, there are some patients who remain on lifelong clopidogrel after cardiac or vascular events. Additionally, patients

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undergoing noncardiac surgery relatively soon after stent placement are at a higher risk of major adverse cardiac events (ACEs) occurring postoperatively.[15,17] This highlights the importance of adherence to antiplatelet therapy.

Given the uncertainty about bleeding risk, the decision of whether or not to hold clopidogrel in the preoperative period is often left to the discretion of the orthopedic surgeon. Thus, it is important that orthopedic surgeons are able to make a recommendation about the continuation of clopidogrel just prior to shoulder arthroplasty. For hip and knee arthroplasty procedures, perioperative clopidogrel continuation has been associated with more frequent postoperative blood transfusions but no difference in the ACE rate.[14] To our knowledge, no studies exist that provide information regarding the surgical complications and outcomes of patients undergoing shoulder arthroplasty based on continuation or cessation of clopidogrel. The purpose of this study was to evaluate the effect of preoperative clopidogrel use on the clinical outcomes, estimated blood loss (EBL), transfusion and ACE rates, and complications of shoulder arthroplasty. We hypothesized that patients who continued clopidogrel preoperatively would have more surgical complications and possibly worse outcomes after shoulder arthroplasty than patients who held clopidogrel.

Methods

After obtaining institutional review board approval, a retrospective review of our institutional Total Joint Registry Database was performed. Patients aged ≥18 years who underwent primary anatomic total shoulder arthroplasty (TSA) or reverse shoulder arthroplasty (RSA) for any indication at a single institution between 2008 and 2018 and had been prescribed clopidogrel were included. We then performed a review of the electronic medical records (EMRs) for each patient identified, collecting demographics (gender, age, date of surgery, body mass index, and follow-up), anticoagulation details, operative information, and postoperative outcomes. EBL, transfusions, complications (including infections and postoperative bleeding), and reoperations were recorded.

Anticoagulation data were gathered by manual review of the EMR. Clinical notes were searched using terms “clopidogrel” and “Plavix”. Indication for clopidogrel, concurrent anticoagulation, date of the last preoperative dose, and date of the first postoperative dose were obtained from the EMR. Patients were separated into two groups based upon their continuation or cessation of clopidogrel in the preoperative period. Patients were categorized as group 1 (clopidogrel continued) if their last dose was <5 days before their surgical date and categorized as group 2 (clopidogrel held) if their last dose was ≥5 days before their surgical date. This 5-day time point is the standardized practice at our institution as established as part of our periprocedural anticoagulation protocol. The decision to continue or hold clopidogrel was individualized as a combined decision between orthopedic surgeons and cardiovascular physicians. Each patient was evaluated at the latest follow-up with several metrics: visual analog scale (VAS) for pain, active range of motion, and American Shoulder and Elbow Surgeons (ASES) score. Active internal rotation was graded using the “IR score” (0-7 scale).[18] Outcome measures included incidence of the postoperative ACE and complications, EBL, reoperations, motion, and pain.

Data are reported using standard summary statistics, including means and standard deviations for continuous variables and counts and percentages for categorical data.

The associations of continuing clopidogrel vs. holding were analyzed using univariate logistic regression; odds ratios were reported with 95% confidence intervals. Preoperative range of motion measurements and VAS pain scores were compared to their corresponding postoperative values, overall and separately by clopidogrel continued preoperatively or not using paired t-tests. Rates of survivorship free of surgical complications and reoperations were calculated using the Kaplan-Meier method, and rates were reported with 95% confidence intervals. Estimates were generated for the overall cohort as well as separately by whether clopidogrel was continued or held preoperatively. All statistical tests were two-sided, and P values less than 0.05 were considered statistically significant. The analysis was conducted using SAS, version 9.4M6 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

There were 20 patients in group 1 (clopidogrel continued) with a mean age of 73 years old. There were 38 patients in group 2 (clopidogrel held) with a mean age of 74 years old (intergroup comparison $P = .95$). Group 1 included 60% male patients, and group 2 included 55% male ($P = .73$). The mean body mass index in both groups was 30 kg/m^2. Fifty-five percent of patients in group 1 were taking concurrent anticoagulants other than clopidogrel at the time of surgery, in comparison to 47% of patients in group 2 ($P = .58$). The indications for surgery were similar between groups as 55% of the patients in both groups had osteoarthritis as their primary indication; cuff tear arthropathy was the primary surgical indication for 30% of group 1 patients and 37% of group 2 patients ($P = .66$) [Table I]. Reverse total shoulder arthroplasty was performed in 6 patients for other indications: three patients in group 1: malunion (n = 2) and acute fracture (n = 1) and 3 patients in group 2: acute fracture (n = 1), nonunion (n = 1), and rheumatoid arthritis (n = 1).

Surgical characteristics

Seventy percent of patients in group 1 underwent RSA with the remaining 30% undergoing TSA. In group 2, 50% of patients underwent RSA and 50% underwent TSA (intergroup comparison $P = .14$). TXA was administered in 10% of group 1 patients and 5% of group 2 patients ($P = .50$). The mean EBL in group 1 (clopidogrel continued) was 176 mL and significantly more than the mean of 127 mL in group 2 (clopidogrel held) ($P = .018$) [Fig. 1]. The surgical time was 78 minutes in group 1 compared to 84 minutes in group 2 ($P = .37$).

Complications and reoperations

One of 19 (5%) patients in group 1 underwent postoperative allogenic blood transfusion compared to 0 of 38 patients in group 2 ($P = .16$); this patient was treated with RSA and had an EBL of 350 ml in the setting of acute fracture management. The 30-day ACE rate was 0 of 20 patients in group 1 (clopidogrel continued) compared to 1 of 37 (3%) patients in group 2 (clopidogrel held), and this difference did not reach statistical significance ($P = .46$). The 30- and 90-day overall surgical complication rates were 15% for group 1 compared to 0% for group 2 ($P = .14$). The 90-day surgical complications for group 1 included the following: surgical-site hematoma not requiring reoperation (1), acute blood loss anemia requiring postoperative transfusion (1), and periprosthetic fracture after a fall (1). At 1 year, the surgical complication rate remained 15% for group 1 and was 5% for group 2 ($P = .21$) [Fig. 2]. Group 1 had a 95% survivorship free of any reoperation at 90 days compared to 100% in group 2. At 5 years, the survivorship of group 1 remained 95% while group 2 decreased slightly to 97% [Fig. 3].

Table I
Preoperative and intraoperative characteristics comparing groups 1 and 2.

	Clopidogrel continued preoperatively?		
	No (group 2); n = 38 patients	Yes (group 1); n = 20 patients	*P* value between groups
BMI, mean (SD)			0.9348
Kg/m^2	30.3 (6.54)	29.7 (6.10)	
Age, mean (SD)			0.9478
Years	73.9 (6.43)	73.2 (8.49)	
Gender, n (%)			0.7292
Male	21 (55.3%)	12 (60.0%)	
Female	17 (44.7%)	8 (40.0%)	
Concurrent anticoagulants, n (5)			0.5806
Yes	18 (47.4%)	11 (55.0%)	
No	20 (52.6%)	9 (45.0%)	
Indication for surgery, n (%)			0.6645
Osteoarthritis	21 (55.3%)	11 (55.0%)	
Cuff arthropathy	14 (36.8%)	6 (30.0%)	
Other	3 (7.9%)	3 (15.0%)	
Arthroplasty type, n (%)			0.1438
RSA	19 (50.0%)	14 (70.0%)	
TSA	19 (50.0%)	6 (30.0%)	
TXA administered, n (%)			0.4986
Yes	2 (5.3%)	2 (10.0%)	
No	36 (94.7%)	18 (90.0%)	
Surgery duration, mean (SD)			0.3661
Minutes	84.3 (20.97)	78.0 (15.00)	
EBL, mean (SD)			0.018*
mL	127.3 (77.51)	176.3 (83.15)	

BMI, body mass index; *SD*, standard deviation; *RSA*, reverse shoulder arthroplasty; *TSA*, total shoulder arthroplasty; *TXA*, tranexamic acid; *EBL*, estimated blood loss.
*Statistically significant.

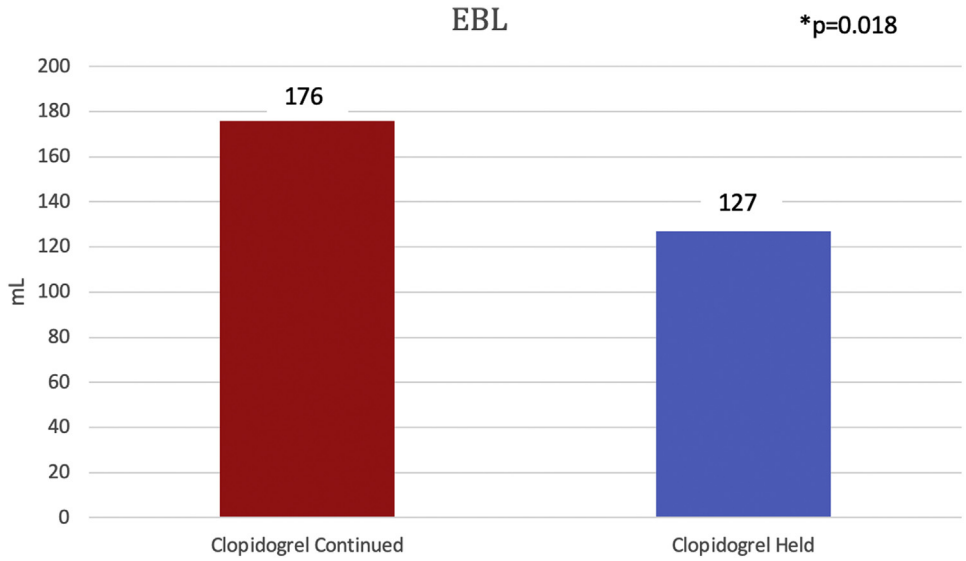

Figure 1 EBL comparison between groups 1 (clopidogrel continued) and 2 (clopidogrel held). *Statistically significant. *EBL*, estimated blood loss.

Clinical outcomes

The mean follow-up for group 1 was 39 months (standard deviation [SD] = 21) and 44 months (SD 20) for group 2. For group 1, VAS pain scores improved from 7.3 preoperatively to 1.1 postoperatively ($P < .0001$), active forward elevation improved from 74° to 141° ($P < .0001$), active external rotation improved from 19° to 49° ($P < .0001$), active internal rotation improved from 2.7 to 4.5 points ($P = .0002$), and the mean postoperative ASES score was 77. For group 2, VAS pain scores improved from 7.7 preoperatively to 0.8 postoperatively ($P < .0001$), active forward elevation improved from 76° to 149° ($P < .0001$), active external rotation improved from 22° to 51° ($P < .0001$), active internal rotation improved from 3.2 to 4.8 points ($P < .0001$), and the mean postoperative ASES score was 86. There was no significant difference in the improvement in VAS pain from preoperative to postoperative periods when comparing between groups 1 and 2 (6.2 [group 1] vs. 6.9 [group 2]; $P = .16$). There were also no significant differences between groups 1 and 2 when comparing preoperative to postoperative active forward elevation improvements (67° [group 1] vs. 73° [group 2]; $P = .44$), active external rotation improvements (30° [group 1] vs. 28° [group 2]; $P = .64$), and active internal rotation improvements (1.8 points [group 1] vs. 1.7 points [group 2]; $P = .95$) [Table II]. Interestingly, the difference in postoperative ASES scores between

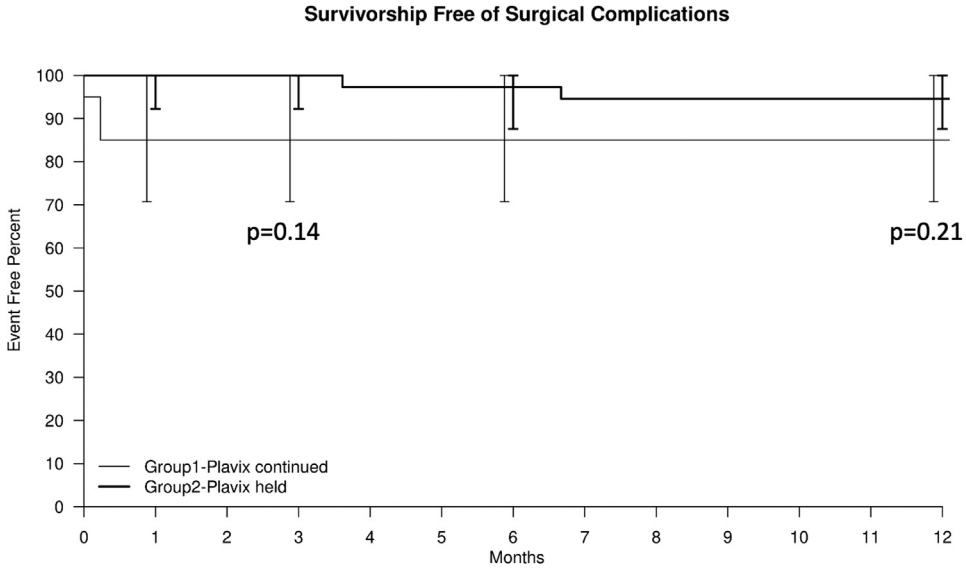

Figure 2 Kaplan-Meier plot of 1-year survivorship free of surgical complications comparing groups 1 and 2.

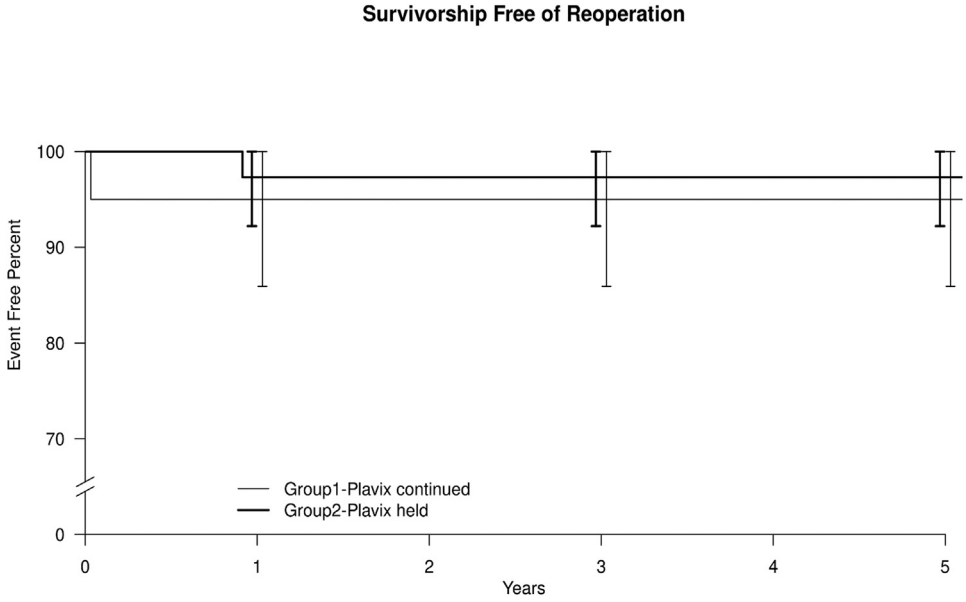

Figure 3 Kaplan-Meier plot of 5-year survivorship free of reoperation for groups 1 and 2.

groups met the minimum clinically important difference for shoulder arthroplasty[22] [Fig. 4]: the patients who held clopidogrel preoperatively had a superior outcome (ASES = 86; SD = 17) vs. patients who did not (ASES = 77; SD = 13) [$P = .067$]. After subgroup analysis by arthroplasty type, there was a significant difference between RSA in group 1 (ASES = 73; SD = 16) and RSA in group 2 (ASES = 89; SD = 17) [$P = .047$], but no significant difference between TSA in group 1 (ASES = 86; SD = 18) and TSA in group 2 (ASES = 84; SD = 11) [$P = .82$].

Discussion

There are no current guidelines regarding perioperative management of clopidogrel for shoulder arthroplasty. Some patients who undergo shoulder arthroplasty are prescribed clopidogrel, most commonly as prophylaxis for stent thrombosis after cardiac intervention. As premature cessation of clopidogrel after stent placement is associated with thrombosis,[13] it is critical that surgeons are able to give objective rationale for their recommendation to hold clopidogrel in the perioperative period if they choose to do so. Our study found that shoulder arthroplasty patients who continued clopidogrel in the preoperative period had significantly higher EBL and trended toward an inferior ASES score and a higher 90-day complication rate than similar patients who held clopidogrel preoperatively. These findings should be considered by surgeons when making the decision whether or not to recommend clopidogrel cessation for their patients before shoulder arthroplasty.

The statistically significant increase in EBL for the clopidogrel-continued group when compared to the clopidogrel-held group validates part of our hypothesis, and the suspected rationale is logical: platelet inhibition is directly proportional to EBL. While the

Table II
Postoperative results for groups 1 and 2.

Group	Outcome	Pre-Op mean (SD)	Post-Op mean (SD)	*P* value (preoperative vs. postoperative)	Post-Op improvement (95% CI)	*P* value (improvement; group 1 vs. group 2)
Clopidogrel continued (group 1)	Forward elevation	74.4 (38.5)	141.1 (40.4)	<.0001*	66.7 (47.8-85.5)	.44
Clopidogrel held (group 2)	Forward elevation	75.7 (36.6)	148.9 (32.0)	<.0001*	73.2 (60.1, 86.3)	
Clopidogrel continued	External rotation	18.7 (15.9)	48.7 (18.9)	<.0001*	30.0 (18.6-41.3)	.64
Clopidogrel held	External rotation	22.3 (18.4)	50.6 (28.0)	<.0001*	28.3 (18.1-38.4)	
Clopidogrel continued	Internal rotation	2.71 (0.85)	4.53 (1.42)	.0002*	1.82 (1.01, 2.64)	.95
Clopidogrel held	Internal rotation	3.16 (1.37)	4.84 (1.30)	<.0001*	1.69 (1.11, 2.26)	
Clopidogrel continued	VAS pain	7.32 (1.16)	1.11 (1.41)	<.0001*	−6.21 (−7.04, −5.38)	.16
Clopidogrel held	VAS pain	7.71 (1.31)	0.82 (1.24)	<.0001*	−6.88 (−7.55, −6.22)	

CI, confidence interval; *VAS*, visual analog scale.
*Statistically significant.

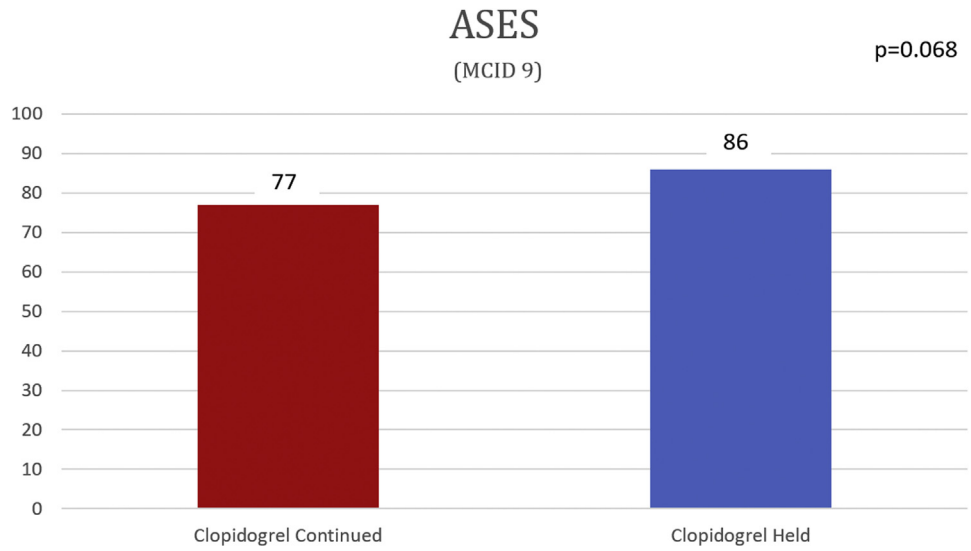

Figure 4 Comparison of the mean ASES score between groups 1 and 2. *ASES*, American Shoulder and Elbow Surgeons; *MCID*, minimum clinically important difference.

EBL difference between groups was only 49 mL, our findings were limited to intraoperative blood loss only. We would assume this intergroup difference in bleeding would continue in the immediate postoperative period and can extrapolate this intraoperative difference to be much larger if blood loss for the entire perioperative period was able to be measured. The 30- and 90-day complication rates for patients who continued clopidogrel were 15% (3/20 patients) compared to 0% for patients who held clopidogrel. Two of the three complications that occurred in the clopidogrel-continued group were related to bleeding, and the other was due to trauma. All three of these complications occurred no later than 9 days postoperatively. Compared to Jovy et al's 2.5% 30-day complication rate they found after analyzing 5801 shoulder arthroplasties from the NSQIP database,[16] 15% for our patients who continued clopidogrel is quite high for an elective surgery. It is also important to understand the impact of the complications that did occur. Clopidogrel-continued patients had a 95% survivorship free of any reoperation at 90 days compared to 100% in the patients who held clopidogrel. While absolutely lower in patients who held clopidogrel, this is only a slight difference, and statistical analysis was not able to be performed owing to the infrequency of reoperations in either group. This is in contrast to the results of Cancienne et al[6] who reviewed 684 shoulder arthroplasty patients taking therapeutic postoperative anticoagulation and found them to have increased rates of wound complications and revision surgery within 1 year postoperatively when compared to postoperative shoulder arthroplasty patients not taking anticoagulants. An important difference between the Cancienne et al study and ours is that the medications used for anticoagulation in their study included warfarin, enoxaparin, rivaroxaban, fondaparinux, apixaban, and dabigatran. These medications are a different class than clopidogrel, and some consider them to confer a stronger anticoagulant effect. One explanation for our results could be that patients who continued clopidogrel have more frequent early postoperative complications owing to significantly increased EBL, but overall their rate of reoperations is no different than patients who held clopidogrel because the magnitude of bleeding-related complications they sustain does not confer a poor prognosis.

Similar to how a surgeon considers surgical complications when deciding how to manage clopidogrel in the perioperative shoulder arthroplasty period, he or she must also take into account the incidence of postoperative ACEs in this patient population. In our study, the patients who continued clopidogrel had a 0% 30-day ACE incidence compared to 3% of patients who held clopidogrel. This was not statistically significant, and the incidence for both groups is comparable to other studies that examined the ACE rate after shoulder arthroplasty. Singh et al reviewed 3480 patients who underwent shoulder arthroplasty and found a 2.6% incidence of 90-day ACEs[20] while Chalmers et al found a 0% incidence in their series of 127 patients.[8] Lovy et al analyzed 5801 shoulder arthroplasty patients and found a 0.6% incidence of 30-day ACEs and/or death.[16] Our data suggest that holding

clopidogrel for shoulder arthroplasty is relatively safe in regard to ACEs.

Both groups of patients (clopidogrel held and clopidogrel continued) in our study experienced significant improvements in VAS pain, forward elevation, external rotation, and internal rotation at the final follow-up. For the patients who continued clopidogrel, the mean improvements in forward elevation (67°) and external rotation (30°) are similar to other studies for RSA and TSA[2,11,19] which examined general cohorts of shoulder arthroplasty patients. There were no significant differences between clopidogrel-held and clopidogrel-continued patients for preoperative to postoperative improvement of VAS pain, forward elevation, external rotation, and internal rotation. However, patients who held clopidogrel had a mean ASES score of 86 at the final follow-up in comparison to patients who continued clopidogrel who had a mean score of 77. While this difference was not statistically significant ($P = .067$), the difference in the absolute ASES score between the two groups did meet the accepted value for minimum clinically important difference for shoulder arthroplasty.[22] In the study by Simovitch et al of 1183 shoulder arthroplasties with a minimum 2-year follow-up, they found a mean postoperative ASES score of 87 for TSA and 84 for RSA. This suggests that while the VAS pain and range of motion postoperative outcomes for our clopidogrel-continued patients are comparable to a cohort of shoulder arthroplasty patients not prescribed clopidogrel, the ASES score is lower, and this difference should be emphasized as it is an accurate and reliable functional outcome measure.

This study does have limitations that merit discussion. Similar to other retrospective reviews, there is a selection bias present as the patients in our study were not randomized to either hold or continue clopidogrel prior to their shoulder arthroplasty being performed. There is a possibility that patients in the clopidogrel-continued group were more medically frail than the patients in the other group, thus possibly confounding our results. However, we believe the design of our study did lend itself to minimizing confounders as best as possible because our control group was internal and consisted of patients who were prescribed clopidogrel but held the medication preoperatively. With respect to medical comorbidities and long-term effects of anticoagulation, this was the closest cohort we could have used to match with the patients who continued clopidogrel preoperatively. Furthermore, the higher percentage of RSA in the clopidogrel-continued group may provide a confounding factor in EBL differences between groups. Our study was also limited by including outcomes from multiple surgeons at one institution, and while they all use a similar surgical approach, technique, and postoperative protocol, there are small differences between them that do exist such as implant preference. However, the inclusion of data from multiple surgeons does serve to increase the generalizability of our results, although they should be interpreted with the caveat that these procedures were performed at a high-volume academic referral center. The use of TXA in our study (7% of patients) is likely lower than the current rate of use for shoulder arthroplasty procedures. Our low utilization rate reflects the fact that TXA was not commonly used perioperatively for patients at high risk for thrombosis until recently. Our data for bleeding-related complications could be affected by the lack of TXA use. Finally, we had a relatively small sample size with 20 patients who continued clopidogrel preoperatively and 38 patients who held clopidogrel. The trends seen for an inferior ASES score and a higher 90-day complication rate in clopidogrel-continued patients certainly may have been statistically significant if our sample size was larger. However, there are no data available to our knowledge regarding clopidogrel use and shoulder arthroplasty. Therefore, our results should be considered with these limitations in mind.

Conclusion

Clopidogrel use had no statistical effect on outcomes for pain or range of motion between these different patient groups. Additionally, there were no significant differences in postoperative ACEs or transfusion rates between groups. However, for the patients who continued clopidogrel preoperatively, EBL was significantly higher, and there were trends toward an inferior ASES score and a higher 90-day complication rate. Patients undergoing shoulder arthroplasty should be counseled about the increased risks of continuing clopidogrel preoperatively, and surgeons should approach this situation cautiously.

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