The Effect of Continued Low Dose Aspirin Therapy in Patients Undergoing Percutaneous Nephrolithotomy

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Abbreviations and Acronyms

CMI = case mix index

CT = computerized tomography

PCNL = percutaneous nephrolithotomy

S.T.O.N.E. = size, topography (stone location), obstruction, number of stones and evaluation of HU

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Purpose: Aspirin is often stopped prior to percutaneous nephrolithotomy due to concern about the surgical bleeding risk. There is evidence that discontinuing aspirin perioperatively increases thromboembolic events and continuing it may be safe. We assessed the effect of continuing low dose aspirin through percutaneous nephrolithotomy and its effect on surgical and safety outcomes.

Materials and Methods: We retrospectively reviewed the records of 285 consecutive percutaneous nephrolithotomies performed between 2012 and 2015 at our institution. We compared outcomes and complications in patients who continued 81 mg aspirin daily to those in patients not receiving aspirin.

Results: A total of 67 patients (24.5%) were maintained on low dose aspirin and 207 (75.5%) were not on aspirin. The aspirin group was older (66 vs 52 years), included more tobacco users (58.2% vs 31.4%) and had a higher ASA® (American Society of Anesthesiologists®) score (2.9 vs 2.5, all $p < 0.001$). There was no difference in mean S.T.O.N.E. (size, topography [stone location], obstruction, number of stones and evaluation of HU) score (7.6 vs 7.7, $p = 0.71$) or blood loss (44 vs 54 ml, $p = 0.151$). There was no difference in residual stone fragment size, including 0 to 2 mm in 65.3% vs 61.4% of aspirin vs no aspirin cases, 3 to 4 mm in 19.4% vs 16.2% and greater than 4 mm in 15.3% vs 22.4% ($p = 0.407$). Length of stay and the change in hemoglobin, hematocrit and creatinine were similar. There was no difference in the readmission rate (14.9% vs 12.6%, $p = 0.618$) or the total complication rate (34.4% vs 26.6%, $p = 0.221$). There was also no difference in the number of major complications (10.4% vs 5.8%, $p = 0.193$), bleeding complications (3.0% vs 2.9%, $p = 0.971$) and the transfusion rate (1.5% vs 1.0%, $p = 0.57$).

Conclusions: Percutaneous nephrolithotomy appears effective and safe in patients who continue low dose aspirin perioperatively.

Key Words: kidney; nephrolithiasis; nephrostomy, percutaneous; aspirin; complications

Percutaneous nephrolithotomy is commonly performed to treat large, complex renal calculi and stones otherwise not amenable to other minimally invasive options. This procedure is considered the gold standard for large renal stones and it is recommended in guidelines to treat urinary lithiasis.[1–3] Although it is efficacious, this procedure is not without risk. Commonly cited procedure related risks include bleeding with a potential risk of blood transfusion, infection and less commonly

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transgression of the thoracic cavity resulting in pneumothorax, hemothorax or hydrothorax, which may require chest tube drainage.[4]

Many surgical candidates for PCNL have associated medical comorbidities, which further add to the overall procedure related risk. Cardiovascular disease, which has specifically been associated with urinary lithiasis, comprises 1 such associated medical risk.[5,6] Patients with known cardiovascular disease who are determined to be at some increased degree of risk for adverse cardiovascular events are often given antiplatelet agents to mitigate the development of such events.[7] Due to the highly vascularized nature of the renal parenchyma historically such agents have often been discontinued for percutaneous renal procedures due to concern for an increased risk of bleeding and a potential need for blood transfusion.

In fact, in a 2014 ICUD (International Consultation on Urological Diseases)/AUA (American Urological Association) review paper Culkin et al recommended that "oral anticoagulant and antiplatelet medications should be discontinued prior to PCNL."[8] However, the evidence on which this recommendation was based did not specifically track thromboembolic events and is of low quality. The investigators additionally acknowledged that at the time of writing no study had yet been done to evaluate the continuation of low dose aspirin during PCNL. This concern for increased perioperative bleeding must be balanced against the risk of cardiovascular events, which may be associated with withdrawal of antiplatelet agents, and the known medical conditions of the patient.[9,10]

Recent reports describe PCNL during continued aspirin therapy in patients who require such therapy and demonstrate that PCNL may be safely performed in this patient group.[11–14] Based on these early reports we changed our PCNL protocol in 2012 to enable patients to continue low dose aspirin therapy throughout the entire course of the treatment episode. Our tertiary care institution is a large stone treatment referral center where PCNL is frequently performed and it also has a high associated CMI.[15] As such, a relatively high proportion of our referred patients regularly receive antiplatelet agents, including low dose aspirin, for related medical comorbidities and associated risk factors.

Based on our early positive experience performing PCNL in patients continuing on aspirin we hypothesized that continuing aspirin therapy through the PCNL perioperative period likely would not adversely affect surgical or safety outcomes. The current study was designed to retrospectively assess that question. To our knowledge we report the largest cohort to date of patients undergoing PCNL while continuing low dose aspirin therapy.

MATERIALS AND METHODS

After receiving institutional review board approval we retrospectively reviewed the charts of all patients who underwent PCNL performed by a single surgeon at our institution between February 2012 and December 2015. February 2012 was the date at which we revised our preoperative protocol for PCNL to include aspirin continuation in patients who were on low dose aspirin (81 mg once daily). Aspirin treatment was done for primary or secondary prevention of cardiovascular events as directed by the primary physician. Aspirin was not held or started by our team in any patient.

The continuation of aspirin therapy was coordinated with our preoperative and perioperative anesthesia services. Compliance was verified during the medication history update, which is part of our standardized preoperative check-in process. Aspirin therapy was continued on postoperative day 1 in all patients who were receiving it preoperatively. Patients on aspirin at a dose higher than 81 mg once daily, another blood thinner such as clopidogrel or warfarin, or any drug from the novel oral anticoagulant class were excluded from analysis.

The parameters collected were patient demographic information, including age, gender, body mass index, smoking history, comorbidities and ASA (American Society of Anesthesiologists) score, stone related parameters using the S.T.O.N.E. score,[16] operative details, including operative time, estimated blood loss, the number of tracts and the tract dilation method, and postoperative details, including residual stone size and changes in hemoglobin in gm/dl, percent hematocrit and creatinine as well as the 30-day complication and readmission rates. For patients on low dose aspirin we recorded whether the indication was for primary or secondary prevention of cardiovascular events.

Complications were recorded and classified based on the modified Clavien-Dindo system. Major complications were defined as Clavien-Dindo grade IIIa or higher. Bleeding complications were deemed to be significant according to the judgement of the primary surgeon and included the need for transfusion or angioembolization.

Our technique of traditional prone PCNL has been described previously.[17] It involves percutaneous access by an interventional radiologist at the time of the procedure, tract dilation to 30Fr with a balloon catheter or an Amplatz rigid dilation kit, stone removal by rigid and flexible nephroscopy using an ultrasonic lithotripter and holmium laser lithotripsy as necessary, and the creation of multiple tracts as necessary. Ureteral stent and 16Fr to 18Fr nephrostomy tube placement is done at the conclusion of the case. Flexible nephroscopy is used liberally to avoid applying excessive torque with the rigid scope and minimize the necessity of multiple tract creation. Antegrade ureteroscopy is routinely performed to clear the ureter.

Chest x-rays are routinely obtained in the recovery room to rule out pneumothorax, hemothorax and hydrothorax. We check complete blood counts and metabolic panels immediately postoperatively as well as on each postoperative day in the hospital. All patients undergo noncontrast CT postoperatively, most commonly on postoperative day 1. The total residual stone burden after

primary procedure was scored as 0 to 2, 3 to 4 and greater than 4 mm based on postoperative CT. Patients with a residual stone burden were offered second look nephroscopy or ureteroscopy to clear the remaining stone burden. All patients were treated with bilateral sequential compression devices and subcutaneous low dose unfractionated heparin prophylaxis postoperatively.

Statistical analysis was performed with SPSS®, version 23 using the Student t-test for continuous variables and the chi-square or Fisher exact test for categorical variables when comparing the aspirin group vs the group not on aspirin.

RESULTS

At our institution 285 consecutive patients underwent PCNL during the study period. Of these patients 67 (24.5%) were maintained on low dose aspirin therapy at the time of PCNL, including 40 (59.7%) and 27 (40.3%) for primary and secondary prevention, respectively. Table 1 lists medical comorbidities in the aspirin group.

Table 2 shows demographics in the cohort of patients on and not on aspirin therapy at PCNL. The aspirin group was older (mean age 66 vs 52, $p < 0.001$), had a higher ASA score (2.9 vs 2.5) and was more likely to have a smoking history (58.2% vs 31.4%, each $p < 0.001$). Mean S.T.O.N.E. scores were similar in the groups (7.6 vs 7.7, $p = 0.86$). There was no difference in body mass index or gender between the groups.

Table 2 also shows operative details between the cohorts. Mean operative time was shorter in the group with vs without aspirin (163 vs 190 minutes, $p = 0.005$). Mean blood loss did not differ in the aspirin vs no aspirin group (44 vs 54 ml, $p = 0.11$). There was no difference in the number of tracts or the tract dilation method between the groups. However, a difference was seen in the access location with upper pole access in more patients on aspirin (51.4% vs 40.8%, $p = 0.024$).

Table 3 shows postoperative outcomes, including residual stone size and changes in laboratory values. There was no difference in residual stone size between the groups, including 0 to 2 mm in 65.3% vs 61.4% of aspirin vs no aspirin cases, 2 to 4 mm in 19.4% vs 16.2% and greater than 4 mm in 15.3% vs 22.4% ($p = 0.407$). There was no difference in the proportion of patients requiring a second procedure. There was also no difference in length of stay. Similar changes were seem in the 2 groups in mean hemoglobin, hematocrit and creatinine.

There was no difference in the 30-day readmission rate in the aspirin vs the no aspirin group (14.9% vs 12.6%, $p = 0.618$), and the rates of total complications (34.4% vs 26.6%, $p = 0.221$) and major complications (Clavien 3 or greater 10.4% vs 5.8%, $p = 0.193$) were also similar. There was no difference in bleeding complications. The transfusion rate was similar in the aspirin and no aspirin groups (1.5% vs 1%, $p = 0.57$). In 1 patient in the aspirin group a nonfatal postoperative myocardial infarction was managed medically. No patients in either group required angioembolization for bleeding. Table 3 lists all major and bleeding complication data.

Table 1. *Indications and comorbidities in patients on low dose aspirin therapy at PCNL*

Aspirin Indication	No. Pts (%)
Prevention:	
Primary	40 (59.7)
Secondary	27 (40.3)
Coronary artery disease:	22 (32.3)
Coronary stent	8 (11.8)
Coronary artery bypass graft	6 (8.8)
Cerebral vascular accident	7 (10.3)
Atrial fibrillation	5 (7.4)
Peripheral vascular disease	9 (13.2)
Hypertension	48 (70.6)
Hyperlipidemia	33 (48.5)
Diabetes mellitus	20 (29.4)

Table 2. *Demographic and operative details in patients receiving and not receiving 81 mg aspirin at PCNL*

	Aspirin	No Aspirin	p Value
No. pts (%)	67 (24.5)	207 (75.5)	—
Mean ± SD age	66 ± 10	52 ± 15	<0.001
No. male (%)	37 (55.2)	100 (48.3)	0.325
No. Caucasian (%)	52 (77.6)	163 (78.7)	0.845
Mean ± SD ASA score	2.9 ± 0.4	2.5 ± 0.6	<0.001
No. current or former smoking history (%)	39 (58.2)	65 (31.4)	<0.001
Mean ± SD body mass index (kg/m^2)	32.1 ± 9	30.3 ± 9	0.151
Mean ± SD S.T.O.N.E. score	7.6 ± 4	7.7 ± 3.8	0.86
No. renal units	72	228	—
Mean ± SD stone size (mm)	37 ± 16	40 ± 19	0.198
Mean ± SD PCNL S.T.O.N.E. score	7.6 ± 2	7.7 ± 2	0.712
No. synchronous bilat PCNLs (%.)	5 (7.5)	21 (10.1)	0.551
Mean ± SD operative time (mins)	163 ± 62	190 ± 67	0.005
Mean ± SD estimated blood loss (ml)	44 ± 45	54 ± 48	0.11
No. tracts (%):			0.383
Single	70 (97.2)	216 (94.7)	
Multiple	2 (2.8)	12 (5.3)	
No. access site (%):			0.024
Upper pole	37 (51.4)	93 (40.8)	
Mid pole	16 (22.2)	30 (13.2)	
Lower pole	17 (23.6)	93 (40.8)	
Multiple	2 (2.8)	12 (5.3)	
No. tract dilation method (%):*			0.428
Amplatz	7 (9.7)	36 (15.8)	
Balloon	53 (73.6)	159 (69.7)	
Balloon + Amplatz	12 (16.7)	33 (14.5)	

* All tracts were 30Fr.

DISCUSSION

PCNL has been traditionally considered a high bleeding risk procedure due to the highly vascular nature of the kidney. Early series showed

Table 3. *Postoperative outcomes, and 30-day readmission and complication rates in patients receiving and not receiving 81 mg aspirin at PCNL*

	Aspirin	No Aspirin	p Value
Postop details			
No. mm residual stone size after 1 procedure (%):			0.407
Less than 2	47 (65.3)	140 (61.4)	
2–4	14 (19.4)	37 (16.2)	
Greater than 4	11 (15.3)	51 (22.4)	
No. requiring 2nd procedure (%)	31 (46.3)	106 (51.2)	0.609
Mean ± SD hemoglobin change:			
Hemoglobin (gm/dl)	−0.99 ± 1.1	−0.94 ± 0.96	0.744
% Hematocrit	−2.9 ± 3.8	−2.8 ± 3.1	0.849
Serum creatinine (mg/dl)	0.06 ± 0.22	0.03 ± 0.18	0.271
Mean ± SD length of stay (days)	3.2 ± 2.7	3.2 ± 3.8	0.924
Readmissions + complications			
No. readmissions (%)	10 (14.9)	26 (12.6)	0.618
No. pts with complications (%)	23 (34.4)	55 (26.6)	0.221
No. major complications (%):*	7 (10.4)	12 (5.8)	0.193
Sepsis	2 (3.0)	6 (2.9)	
Pleural effusion requiring drainage	3 (4.5)	4 (1.9)	
Malpositioned nephrostomy tube requiring replacement	1 (1.5)	2 (1.0)	
Myocardial infarction	1 (1.5)	0	
No. bleeding complications (%):	2 (3.0)	6 (2.9)	1
Significant gross hematuria	1 (1.5)	4 (1.9)	
Postop blood loss anemia	1 (1.5)	1 (0.5)	
Retroperitoneal hematoma	0	1 (0.5)	
No. pts needing transfusion (%)	1 (1.5)	2 (1.0)	0.57
No. postop thrombotic events (%)	1 (1.5)	0	0.245

* Clavien IIIa or greater.

postoperative blood transfusion rates between 12% and 23%.[18,19] However, the transfusion rate in the large, contemporary Percutaneous Nephrolithotomy Global Study was significantly lower at only 5.7%.[2] Based on this concern for high bleeding risk most investigators who have examined PCNL and its complications have excluded anticoagulated patients or have had patients stop anticoagulation prior to the procedure.[20] Therefore, the bleeding risk that may be attributable to antiplatelet or anticoagulant medications has not been well evaluated in the literature to date.

To our knowledge this report represents the largest study of patients undergoing PCNL while continuing low dose aspirin therapy, representing 67 patients (24.5%) in our series. A previous study demonstrating the safety of PCNL while continuing aspirin therapy was limited by a smaller number of patients (15 or 5.2%) who similarly continued aspirin therapy periprocedurally.[13,14] Our high proportion of patients who receive aspirin on a continuous basis is attributable to the CMI of our hospital, which is in the 97th percentile among American hospitals.[15] The CMI is a measure that serves as a surrogate for patient clinical complexity. Additionally, based on the finding in the previous study of the safety of continuing aspirin perioperatively prior to PCNL we were able to accrue high numbers in our study by systematically not stopping aspirin since 2012 in any patient treated with PCNL.

Our patients who continue to receive low dose aspirin through the surgical period tend to be older, have more comorbidities and be more likely to use tobacco at baseline. Despite these characteristics they experience no greater likelihood of surgical complications than those who are not on aspirin and the perioperative outcomes are the same. The major complications, bleeding complications and transfusion rates in our 2 groups compare favorably to those in much larger, multicenter PCNL studies which did not include patients on aspirin.[2]

Sepsis and pleural effusion requiring drainage comprised most major complications in each group. One patient in the aspirin group experienced a nonfatal myocardial infarction. The most common bleeding complication was gross hematuria. In 1 patient in the aspirin group clot retention developed, requiring a visit to the emergency department for evacuation. Two of the 4 patients in the nonaspirin group telephoned us to report persistent hematuria approximately 1 week postoperatively but ultimately they required no intervention. Only 1 patient in the nonaspirin group experienced hematuria significant enough to require blood transfusion. In 1 patient in the nonaspirin group an asymptomatic retroperitoneal hematoma found on postoperative CT was treated conservatively.

Interestingly operative time was shorter in patients on aspirin than in those not on aspirin despite no differences in preoperative stone volume or stone complexity. This could potentially be related to the higher proportion of upper pole access in the aspirin group. It is feasible that factors not specifically recorded at surgery, such as the ease of stone fragmentation, could have affected operative time. It is also worth noting that while estimated blood loss did not reach significance, it was lower in the aspirin group. This could be an artifact due to the sample size or the inherent difficulty of measuring blood loss during PCNL, or it could possibly be secondary to the shorter observed operative time.

Our findings are similar to those in studies of aspirin continuation through other types of renal surgical procedures. Two large series of aspirin therapy continuation through partial nephrectomy were recently published, of which neither identified a significant difference in major or bleeding complications, or the transfusion rate associated with aspirin continuation.[21,22] Another recent study of major complication and bleeding complication rates in patients who continued vs stopped aspirin around

the time of percutaneous renal biopsy revealed no significant difference between the 2 groups.[23]

Furthermore, a growing body of evidence shows that aspirin cessation, for which the most common reason is an elective surgical procedure,[24] leads to an increase in thrombotic and ischemic adverse events in the perioperative period. This phenomenon has been termed the aspirin withdrawal syndrome.[25] In a large systematic review of the records of more than 50,000 patients who received aspirin and who were at risk for coronary artery disease a threefold increase in the risk of adverse events was found in those who were nonadherent with the aspirin regimen or who were instructed by physicians to stop aspirin.[26] The mean elapsed interval was 10.6 days between drug cessation and the thrombotic event. Other smaller series and systematic reviews have also shown a significantly increased risk of cardiac, vascular and cerebrovascular thrombotic events following aspirin cessation.[27–29] The only randomized, controlled trial comparing daily low dose aspirin to placebo in surgical patients at high risk for coronary artery disease demonstrated that aspirin continuation through surgery and the perioperative period conferred a 7.2% absolute risk reduction of major adverse cardiac events with a number needed to treat of 14 patients.[30] Therefore, the protective benefits of perioperative aspirin continuation appear to outweigh the negligible risk of increased bleeding complications based on the available evidence in the literature.

Because our study was not designed to assess the risks of stopping aspirin in the PCNL population, it cannot provide insight in that regard. However, it demonstrates that continuing aspirin therapy in patients who already receive it does not have an adverse effect on surgical or safety outcomes compared to those outcomes in patients who are not on aspirin at baseline.

Limitations of our study include its single center, retrospective, nonrandomized, nonblinded design and the related inherent susceptibility toward bias. It is possible that some adverse events could have been missed during the 30-day followup. Further, one must consider that surgeon experience, the patient population, specific surgeon preferences and aspects of the technique may influence the outcome of this particular procedure. Multi-institutional studies may prove beneficial to corroborate these findings and further determine whether other patient factors or operative techniques influence outcomes aside from aspirin status.

CONCLUSIONS

In patients undergoing PCNL performed by an experienced surgeon continuing low dose aspirin therapy during the perioperative period appeared safe and surgical outcomes appeared to be similar to outcomes in patients not on aspirin therapy. Larger, prospective studies should be done to confirm and validate these findings.

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EDITORIAL COMMENT

The unfortunate reality is many patients requiring surgery have significant comorbidities. For established cardiovascular disease perioperative cessation of aspirin may increase thromboembolic complications (reference 25 in article). In the current study Otto et al found that continued low dose aspirin did not adversely affect bleeding or outcomes following standard percutaneous nephrolithotomy. They report similarly low transfusion rates in patients on continued aspirin and those not on therapy although each group additionally received heparin prophylaxis. This may provide some reassurance to experienced urologists who treat patients deemed at high risk for thrombosis or those on dual antiplatelet therapy in whom clopidogrel, ticagrelor or prasugrel is held but aspirin is recommended to be continued.[1]

However, it remains unclear whether these results would translate to patients on high dose aspirin. Current guidelines differ on defining the therapeutic dose based on patient risk, although most agree that bleeding complications increase at higher aspirin doses. The ongoing prospective, randomized ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness) Trial should help better determine the ideal aspirin dose to decrease ischemic events and minimize bleeding.[2]

As more unhealthy patients present for care increased recognition of comorbidities, comprehensive risk stratification and further refinement in surgical technique will be necessary to balance optimal surgical outcomes with undesired complications.

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