Arthroplasty Today 9 (2021) 61–64

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original research

The Association Between Clopidogrel and Gastrointestinal Bleeding After Primary Total Joint Arthroplasty

David Kugelman, MD, Greg Teo, MD, Michael Doran, MD, Daniel Buchalter, MD, William J. Long, MD, FRCSC *

Investigation Conducted at New York University Langone Orthopaedic Hospital, New York, NY, USA

ARTICLE INFO

Article history:
Received 23 October 2020
Received in revised form
10 March 2021
Accepted 3 April 2021
Available online xxx

Keywords:
Total joint arthroplasty
Total knee arthroplasty
Total hip arthroplasty
Complications following arthroplasty
Gastrointestinal bleeding

ABSTRACT

Background: Anticoagulation after total joint arthroplasty has been demonstrated to reduce venous thromboembolism. However, anticoagulation can lead to adverse bleeding events. The purpose of this study was to assess if an association exists between specific anticoagulation modalities, such as clopidogrel, and postoperative gastrointestinal (GI) bleeding.

Methods: A prospective cohort of Medicare patients undergoing total joint arthroplasty from 2017 to 2019 (3535 patients) was retrospectively reviewed. The baseline characteristics and anticoagulation methods were compared between the "GI bleed" cohort and the "non-GI bleed cohort." Independent t-tests were conducted for continuous variables, while chi-squared analysis was conducted for dichotomous variables.

Results: Thirteen patients (0.42%) sustained a postoperative complication of a GI bleed. The mean age for patients sustaining a GI bleed was 69.23 years compared with 72.30 years for the non-GI bleed cohort ($P = .11$). Six patients who sustained a GI bleed (46%) were on an anticoagulation therapy other than aspirin, and this trended toward significance ($P = .09$). Five patients who sustained a GI bleed (38%) were on clopidogrel ($P < .01$). Seven percent of patients on clopidogrel sustained a postoperative GI bleed ($P < .01$). None of the patients who sustained a postoperative GI bleed had a history of peptic ulcer disease.

Conclusion: Patients on clopidogrel in the acute perioperative period demonstrated a strong association with the complication of postoperative GI bleeding. Arthroplasty surgeons should be aware of this association to educate and monitor patients on clopidogrel therapy and to work as part of interdisciplinary teams to assess the risks vs benefits of perioperative clopidogrel.

Introduction

Total joint arthroplasty (TJA) is one of the most commonly performed and fastest growing orthopedic procedures in the United States [1]. Currently, over one million total knee and total hip arthroplasties (TKA and THA) are performed in the United States on an annual basis [1]. As the population continues to age, there are estimates that by 2030, a nearly 600% increase in the number of TKAs and 200% increase in the number of THAs can be expected [1].

Improvements in surgical technique and peri-operative protocols have contributed to an improvement in morbidity and mortality after TJA. However, complications after TJA are prevalent and still exist [2,3]. As the life expectancy in the United States continues to increase, TJA will be performed in older patients who may be subject to increased complications after these procedures [4–7]. One rare, yet potentially fatal, complication after TJA is gastrointestinal (GI) bleeding [3].

As an individual ages, comorbidities increase, as seen in the Medicare patient population of those older than 65 years [7–11]. In order to treat cardiac embolic events and other venous thromboembolic events, high-risk patients are often placed on oral anticoagulation [11]. However, anticoagulation therapy does not come without dangers, which include hemorrhagic complications, such as GI bleeding.

This research was considered IRB exempt as part of the quality improvement initiative at our institution.

* Corresponding author. Department of Orthopaedics, New York University Langone Orthopaedic Hospital, 14th floor, 301 East 17 St, Manhattan New York 10003, USA.

E-mail address: doctor_long@hotmail.com

https://doi.org/10.1016/j.artd.2021.04.005

Table 1
Demographics in patients undergoing TJA who sustained a postoperative gastrointestinal bleed and those who did not.

Patient demographics/characteristics	Gastrointestinal bleed cohort (n = 13)	Nongastrointestinal bleed cohort (n = 3056)	*P* value
Age (mean)	69.23 y	72.30 y	.36
BMI (mean)	33.17	29.49	.69
Gender	7 males, 6 females	1016 males, 2040 females	.11
Ethnicity	Caucasian = 10 African American = 3	Caucasian = 2480 African American = 232 Hispanic = 244 Other/refused to answer = 100	.23
American Association of Anesthesiologists (ASA) score	1 = 0 2 = 5 3 = 7 4 = 1	1 = 67 2 = 1483 3 = 1421 4 = 85	.61

Clopidogrel is an anticoagulant used in patients with cardiovascular, cerebrovascular, and peripheral vascular diseases [12]. Patients who undergo stenting procedures receive a postoperative dual antiplatelet protocol, which generally includes aspirin in addition to clopidogrel. The American Heart Association and American College of Cardiology recommend dual antiplatelet therapy for at least 1 year after stent placemen [12]. However, no specific guidelines exist with respect to clopidogrel discontinuation, with many patients remaining on the medication for life [12].

Clopidogrel has been associated with increased blood transfusions and major blood loss when continued during the perioperative period [13,14]. This has led to recommendations for discontinuation of the drug before elective surgery, when deemed safe by the patient's cardiologist. However, little is known about hemorrhagic complications with respect to the timing of restarting clopidogrel in the acute perioperative period after TJA. The purpose of this study is to assess if a difference in GI bleeding occurs between patients that were restarted on clopidogrel in the early postoperative period and those that were not, after elective TJA.

Material and methods

After institutional review board approval, a retrospective review of prospectively collected data of Medicare patients undergoing TJA at our institution from 2017 to September 2019 was analyzed. Demographic data were collected for each patient, which included age, medical history, body mass index (BMI), and American Association of Anesthesiologists (ASA) score. Inpatient medication dispensing was collected, with specific focus on the anticoagulation medication patients received postoperatively. A chart review was performed assessing postoperative complications, including GI bleeding. Medicare patients enrolled in Bundled Payments for Care Improvement (BPCI) are monitored for 90-day complications, even if the complication and readmission are managed at another institution. This makes our GI bleeding rate accurate to monitor postoperative symptomatic complications, even if they were readmitted or seen elsewhere. Patients who underwent arthroplasty for a hip fracture, those who had a unicompartmental knee replacement, and those who had incomplete data were excluded from the analysis.

All statistical analyses were performed using SPSS software (IBM SPSS). Statistical tests were performed, using chi-squared analysis for categorical variables and students t-tests for continuous variables. Results were statistically significant if the P value < .05.

Results

A total of 3070 patients were included in the final analysis. Of which, 1549 patients underwent TKA, while 1507 patients underwent THA. Peptic ulcer disease was documented for 18 patients (0.59%). A postoperative complication of a GI bleed occurred in 13 patients (0.42%). No patients with a history of peptic ulcer disease sustained a postoperative GI bleed.

The average age of the cohort was 72.2 years. The average BMI of the cohort was 29.5. With respect to gender, 1023 patients were male (33.4%) while 2046 patients were female (66.6%). With respect to ethnicity, 2490 patients were Caucasian (79.2%), 235 patients were of African American ethnicity (7.7%), 244 patients were of Hispanic ethnicity (7.9%), 74 patients were of Asian ethnicity (2.4%), and 100 patients identified as "other" or refused to document their ethnicity (3.3%). No significant differences were demonstrated between patients sustaining a postoperative GI bleed and those who did not have this complication with respect to age, gender, BMI, ASA, or ethnicity (Table 1).

Table 2
Anticoagulation history and time-point at which postoperative gastrointestinal bleed occurred.

	Acute postoperative anticoagulation	Procedure	POD gastrointestinal bleed occurred
Patient 1	Aspirin 81 mg BID	TKA	POD#10
Patient 2	Enoxaparin 30 mg/0.3 ml, q12	TKA	POD#7
Patient 3	Aspirin 81 mg BID, clopidogrel 75 mg restarted POD1	THA	POD#37
Patient 4	Aspirin 81 mg BID	TKA	POD#92
Patient 5	Aspirin 81 mg BID	THA	POD#40, POD#50
Patient 6	Aspirin 81 mg BID	THA	POD#99
Patient 7	Aspirin 81 mg BID, clopidogrel 75 mg restarted POD1	THA	POD#38
Patient 8	Aspirin 81 mg BID, clopidogrel 75 mg restarted POD1	THA	POD#41
Patient 9	Aspirin 81 mg BID	THA	POD#53
Patient 10	Aspirin 81 mg BID	THA	POD#89
Patient 11	Aspirin 81 mg BID	THA	POD#76
Patient 12	Aspirin 81 mg BID, clopidogrel 75 mg restarted POD1	THA	POD#88
Patient 13	Aspirin 81 mg BID, clopidogrel 75 mg restarted POD1	TKA	POD#121
		TKA = 4, THA = 9	Mean = 64.7 d

BID, twice daily; POD, postoperative day.

Most patients (2268 patients, 73.9%) were on only aspirin postoperatively. The remaining 801 patients (26.1%) were on a postoperative anticoagulation medication other than single antiplatelet therapy with aspirin. These other anticoagulants included clopidogrel, heparin, enoxaparin, apixaban, rivaroxaban, dabigatran, fondaparinux, cilastozel, ticragelor, and warfarin. A nonstatistically significant trend was demonstrated between patients who were prescribed nonaspirin chemoprophylaxis and sustaining a GI bleed ($P = .09$). Clopidogrel was restarted on 70 patients (2.3%) in the acute hospital setting postoperatively. The postoperative complication of a GI bleed ($P < .01$) was demonstrated in 5 patients on clopidogrel (7.1% of those on the drug). Patients on clopidogrel accounted for 38% of GI bleeds ($P < .01$).

Perioperative anticoagulation history for patients sustaining a GI bleed and the time point at which the complication occurred are listed in Table 2. Aspirin was prescribed to 12 patients (92%) who sustained a GI bleed—these patients were all prescribed 81 mg bid. All patients sustaining a GI bleed received both toradol and a nonsteroidal anti-inflammatory drug (NSAID) during their hospital stay. Celecoxib was given to 6 of these patients (46%), meloxicam was given to 5 patients (38%), and 2 patients (15%) were on both celecoxib and meloxicam during their hospitalization. All patients who sustained a GI bleed received at least 3 NSAIDs during their hospital stay, and 2 patients (15%) were prescribed 4 NSAIDs. GI protective medications such as protonix or famotidine were prescribed to 11 of the patients (84.6%) who sustained a GI bleed. There was no documentation on why 2 patients (15%) did not receive perioperative GI prophylaxis. All patients receiving clopidogrel who sustained a GI bleed had a history of a cardiac stent, anywhere between 2 and 15 years before their TJA (mean = 11.2 years). No patients sustaining a GI bleed had any postoperative cardiac embolic events. No patients sustained a GI bleed resulting in mortality. A single patient sustained 2 GI bleeds postoperatively.

All patients who sustained a GI bleed and on clopidogrel were restarted on the medication POD#1 (Table 2). All these patients obtained preoperative cardiology clearance. The cardiologists stated that clopidogrel should be held 5-7 days preoperatively in these 5 patients (100%). However, no cardiologist documented a safe time point to resume clopidogrel postoperatively. Documentation to start clopidogrel “ASAP” postoperatively was seen in 1 patient (20%).

Discussion

Our study demonstrates that symptomatic GI bleeding after TJA in our Medicare population has a prevalence of 0.4%. The GI bleeds identified in this study were all confirmed through endoscopy. The annual incidence of GI bleeding is 0.03% - 0.09% in the general population [15–17]. Pulido et al. demonstrated GI bleeding was found to occur postoperatively in 0.02% of patients undergoing TJA [3]. Adeinkinju et al. demonstrated that GI bleeding occurred in 0.12% of patients in their retrospective review of over 19,000 TJA patients [18]. Our results are in contrast to a study published by Sharma, which demonstrated GI bleeding to occur in 4.5% of patients after TJA [19]. These differing rates likely reflect differences in the sample populations and perioperative anticoagulation protocols associated with TJA.

There is an increased risk for GI bleeding after surgery [15–19]. Studies have reported numerous risk factors to be associated with GI bleeding such as postoperative anticoagulation, peptic ulcer disease, and NSAID use [18,20,21]. All patients sustaining a GI bleed in this study were on postoperative anticoagulation. Strikingly, more than 7% of patients on postoperative clopidogrel sustained a GI bleed. Patients on clopidogrel accounted for nearly 40% of GI bleeds after TJA. Known peptic ulcer disease did not influence postoperative GI bleeding in this cohort, nor did age. All patients sustaining GI bleeds in our cohort were prescribed a minimum of 3 NSAIDS during their hospitalization. Sustaining a GI bleed after TJA is likely multifactorial and influenced by anticoagulation, NSAIDs, and the stress of surgery on the GI system.

This is the first study to our knowledge to identify a significant association between postoperative clopidogrel and GI bleeding. This is in contrast to a study performed by Nydick et al., which assessed 970 patients undergoing TJA, in which there was no increase in postoperative GI bleeding in patients taking clopidogrel [22]. Similarly, Nandi et al did not find a correlation with timing of clopidogrel resumption after TJA and postoperative bleeding complications, in 116 patients [23]. However, our study had a cohort size of over 3000 patients, and hence, the power increases compared with the aforementioned literature. In other areas of medicine, increased risks of postoperative bleeding complications have been demonstrated in patients on clopidogrel. In addition, our study included patients that were part of the BPCI initiative; hence, all complications within 90 days were recorded, even when presenting to another institution.

We did not find an increased risk of GI bleeding to be associated with the use of other anticoagulants besides clopidogrel. Only 1 patient in this study was on an anticoagulant other than aspirin or clopidogrel and sustained a GI bleed. This is in concordance with Faour et al. who demonstrated low-dose aspirin to be safe and effective for venous thromboembolism prophylaxis after TKA [24]. However, other reports have demonstrated potent anticoagulants other than clopidogrel to be associated with an increased risk of GI bleeding. Nielen et al. demonstrated an increased risk of GI bleeding in patients on low-molecular-weight heparin and new oral anticoagulants (direct thrombin inhibitors/direct factor Xa inhibitors) in comparison to those on solely aspirin [25]. This study did not support those findings.

This study demonstrated GI bleeding after TJA to occur at a mean of 2 months postoperatively. Lalmohamed et al. demonstrated the risk for GI bleeding to be highest during the first 2 weeks after TJA [26]. THA had a 6-fold increase in risk during the first 2 weeks after the procedure, while TKA demonstrated a 2.3-fold risk during this time period. However, the authors concluded that the risk for GI bleeding remained increased for up to 6 weeks after TKA and up to 12 weeks after THA [26]. Their study supports our results and should make physicians aware of the importance of GI bleeding risk assessment and patient education on the signs, symptoms, and prevention of this major complication.

This study has multiple limitations. First and foremost is the bias that presents with a retrospective review of large databases. In addition, our data did not assess outpatient anticoagulation after TJA; however, it is our institutional policy to continue all postoperative anticoagulation protocol after discharge through 14 days for TKAs and 28 days for THAs, which incorporates recommendations from the American Academy of Orthopedic Surgeons (AAOS), American Association of Hip and Knee Surgeons (AAHKS), and American College of Chest Physicians (ACCP) as aforementioned. A major limitation is the poor power of this analysis due to 13 patients in the GI bleed group. However, this is in concordance with other studies on the topic which demonstrate a small risk of GI bleeds after TJA. The cohort of 13 patients is a likely reason that multiple outcomes were "trending" toward significance, but not statistically significant as defined by a P value of <0.05. This study was performed at a major urban academic medical center that was an early participant in the BPCI initiative. Our institution concurrently focused on perioperative optimization of patients known to be at a higher risk of perioperative complications, and this is a potential source of

confounding. Therefore, the rates of GI bleeding may be different in community practices with different perioperative protocols. In addition, we were only aware of patients sustaining GI bleeds within 90 days of surgery, and the number of GI bleeds may therefore be underestimated.

Conclusions

Patients on clopidogrel in the acute perioperative period demonstrated a strong association with the complication of postoperative GI bleeding. Our study demonstrates that nearly 40% of patients sustaining GI bleeds were on postoperative clopidogrel after their TJA. For the aforementioned patients, TJA was performed at a mean of 11.2 years after their stent procedure. This study raises the following question: Are we, in joint decision-making with our medicine and cardiology colleagues, only evaluating one side of the benefit-risk profile of postoperative clopidogrel, rather than the two-sided issue of thrombosis and bleeding? This study should make physicians aware of the significantly increased risk of GI bleeding after TJA in patients on clopidogrel. We must therefore work in interdisciplinary teams, and engage in evidence-based discussions, to balance the risks and benefits of resuming clopidogrel after TJA. Arthroplasty surgeons should present this information to cardiac and medicine colleagues during patient's preoperative evaluation, to help this joint decision-making in balancing both risks of GI bleeding and stent thrombosis.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

References

[1] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89(4):780.
[2] Parvizi J, Johnson BG, Rowland C, Ereth MH, Lewallen DG. Thirty-day mortality after elective total hip arthroplasty. JBJS 2001;83(10):1524.
[3] Pulido L, Parvizi J, Macgibeny M, et al. In hospital complications after total joint arthroplasty. J Arthroplasty 2008;23(6):139.
[4] Kreder HJ, Berry GK, McMurtry IA, Halman SI. Arthroplasty in the octogenarian: quantifying the risks. J Arthroplasty 2005;20(3):289.
[5] Berend ME, Thong AE, Faris GW, Newbern G, Pierson JL, Ritter MA. Total joint arthroplasty in the extremely elderly: hip and knee arthroplasty after entering the 89th year of life. J Arthroplasty 2003;18(7):817.
[6] Kennedy JW, Johnston L, Cochrane L, Boscainos PJ. Total knee arthroplasty in the elderly: does age affect pain, function or complications? Clin Orthop Relat Res 2013;471(6):1964.
[7] Petersen Jr WP, Teo GM, Friedlander S, Schwarzkopf R, Long WJ. The implications of aging population Demographics on the delivery of primary total joint arthroplasty in a bundled payment system. JBJS 2020.
[8] DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart 2006;92(8):1064.
[9] Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries: 1993–2007. Circ Cardiovasc Qual Outcomes 2012;5(1):85.
[10] Pepper AM, Novikov D, Cizmic Z, Barrett JT, Collins M, Iorio R, Long WJ. Age and frailty influence hip and knee arthroplasty reimbursement in a bundled payment care improvement initiative. J arthroplasty 2019;34(7):S80.
[11] Shroff GR, Solid CA, Herzog CA. Atrial fibrillation, stroke, and anticoagulation in Medicare beneficiaries: trends by age, sex, and race, 1992–2010. J Am Heart Assoc 2014;3(3):e000756.
[12] Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of cardiology/American Heart association task force on practice guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). Circulation 2007;116(17):1971.
[13] Maltais S, Perrault LP, Do QB. Effect of clopidogrel on bleeding and transfusions after off-pump coronary artery bypass graft surgery: impact of discontinuation prior to surgery. Eur J Cardiothorac Surg 2008;34(1):127.
[14] Jacob AK, Hurley SP, Loughran SM, Wetsch TM, Trousdale RT. Continuing clopidogrel during elective total hip and knee arthroplasty: assessment of bleeding risk and adverse outcomes. J Arthroplasty 2014;29(2):325.
[15] Lanas A, Garcia-Rodriguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol 2009;104(7):1633.
[16] Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol 2012;107(8):1190.
[17] Hreinsson JP, Gumundsson S, Kalaitzakis E, Björnsson ES. Lower gastrointestinal bleeding: incidence, etiology, and outcomes in a population-based setting. Eur J Gastroenterol Hepatol 2013;25(1):37.
[18] Adenikinju AS, Feng JE, Namba CA, Luthringer TA, Lajam CM. Gastrointestinal complications warranting invasive interventions following total joint arthroplasty. J Arthroplasty 2019;34(11):2780.
[19] Sharma S. Upper gastrointestinal bleeding after hip and knee arthroplasty. Orthopedics 2006;29(3):255.
[20] Van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. Best Pract Res Clin Gastroenterol 2008;22(2):209.
[21] Madhusudhan TR, Rangan A, Gregg PJ. Gastric protection and gastrointestinal bleeding with aspirin thromboprophylaxis in hip and knee joint replacements. Ann R Coll Surg Engl 2008;90:332.
[22] Nydick JA, Farrell ED, Marcantonio AJ, Hume EL, Marburger R, Ostrum RF. The use of clopidogrel (Plavix) in patients undergoing nonelective orthopaedic surgery. J Orthop Trauma 2010;24:383.
[23] Nandi S, Aghazadeh M, Talmo C, Robbins C, Bono J. Perioperative clopidogrel and postoperative events after hip and knee arthroplasties. Clin Orthop Relat Res 2012;470(5):1436.
[24] Faour M, Piuzzi NS, Brigati DP, et al. Low-dose aspirin is safe and effective for venous thromboembolism prophylaxis following total knee arthroplasty. J Arthroplasty 2018;33(7):S131.
[25] Nielen JT, Dagnelie PC, Emans PJ, Veldhorst-Janssen N, Lalmohamed A, van Staa TP, de Vries F. Safety and efficacy of new oral anticoagulants and low molecular weight heparins compared with aspirin in patients undergoing total knee and hip replacements. Pharmacoepidemiol Drug Saf 2016;25(11):1245.
[26] Lalmohamed A, Vestergaard P, Javaid KM, et al. Risk of gastrointestinal bleeding in patients undergoing total hip or knee replacement compared with matched controls: a nationwide cohort study. Am J Gastroenterol 2013;108(8):1277.