Arthroplasty Today 27 (2024) 101362

Contents lists available at ScienceDirect

Arthroplasty Today

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

Original Research

Acute Kidney Injury After Total Hip and Knee Arthroplasty. What Is the Culprit?

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ARTICLE INFO

Article history:
Received 13 October 2023
Received in revised form
31 January 2024
Accepted 27 February 2024
Available online xxx

Keywords:
TJA
TKA
THA
AKI
Perioperative Care

ABSTRACT

Background: Acute kidney injury (AKI) is associated with increased complications after total hip arthroplasty (THA) and total knee arthroplasty (TKA). The purpose of this study was to determine the risk factors for AKI after THA and TKA and evaluate if preoperative use of antihypertensive drugs is a risk factor for AKI.

Methods: A retrospective review of 7406 primary TKAs and THAs (4532 hips and 2874 knees) from 2013 to 2019 was performed. The following preoperative variables were obtained from medical records: medications, chemistry 7 panel, Elixhauser comorbidities, and demographic factors. AKI was defined as an increase in serum creatinine by 26.4 μmol·L−1. Multivariate analysis was performed to identify the risk factors.

Results: The overall incidence of postoperative AKI was 6.2% (n = 459). Risk factors for postoperative AKI were found to be: chronic kidney disease (odds ratio [OR] = 7.09; 95% confidence interval [CI]: 4.8-9.4), diabetes (OR: 5.03; 95% CI: 2.8-6.06), ≥3 antihypertensive drugs (OR: 4.2; 95% CI: 2.1-6.2), preoperative use of an angiotensin receptor blockers or angiotensin-converting enzyme inhibitors (OR: 3.8; 95% CI: 2.2-5.9), perioperative vancomycin (OR: 2.7; 95% CI: 1.8-4.6), and body mass index >40 kg/m^2 (OR: 1.9; 95% CI: 1.3-3.06).

Conclusions: We have identified several modifiable risk factors for AKI that can be optimized prior to an elective THA or TKA. The use of certain antihypertensive agents namely angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and multidrug antihypertensive regimens were found to significantly increase the risk of AKI. Therefore, perioperative management of patients undergoing joint replacement should include medical comanagement with a focus on careful management of antihypertensives.

Introduction

Acute kidney injury (AKI) is a relatively uncommon but significant complication that can occur following total joint arthroplasty (TJA). While the overall incidence of AKI following TJA is low, occurring in under 2% of all TJAs, various patient-specific factors can increase the risk of developing this complication [1]. These factors include age, gender, and underlying medical comorbidities, such as diabetes [1,2]. Additionally, bilateral procedures, preoperative body mass index (BMI), preoperative blood urea nitrogen levels, and lower preoperative hematocrit have been identified as significant modifiable risk factors for AKI in the setting of TJA [2]. The development of AKI in total hip arthroplasty (THA) and total knee arthroplasty (TKA) patients is associated with a significant increase in perioperative and postoperative complications [3,4]. Therefore, preoperative identification of patients at risk for AKI and appropriate preoperative optimization of modifiable patient risk factors are paramount to decreasing AKI incidence while promoting positive patient outcomes.

THA and TKA are 2 of the most common procedures performed annually, with the number of both expected to continue to increase significantly by 2030 [5]. As the number of TKA and THA increases, identifying and stratifying patients at risk for developing

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https://doi.org/10.1016/j.artd.2024.101362

complications like AKI is essential, especially as the US health system moves toward a bundled payment model [6,7]. Exceeding costs within bundled payment models for TJA poses numerous challenges to both institutions and healthcare systems, and the accurate prediction of patients likely to exceed bundled costs is an important area of study [8]. Avoidance of perioperative adverse events, such as AKI, is crucial for orthopaedic surgeons to successfully navigate bundled payment models as adverse events significantly increase 90-day episode-of-care costs through additional treatments, increased length of stay, and readmission [2,9,10]. Medical complications are second only to prosthetic infection as the most common reason for readmission following TJA, and AKI comprises the fourth most costly postoperative medical complication in patients undergoing TJA [11]. Additionally, prophylactic and treatment for certain surgical site infections (SSIs) may utilize nephrotoxic agents further increasing risk of postoperative AKI making this of particular relevance for at-risk patients [12].

Not only is the development of AKI itself a complication with potentially devastating direct impact on the patient's quality of life, but it also increases the risk for complications like myocardial infarctions and overall mortality [13-15]. Patients who develop AKI postoperatively, regardless of severity, are at risk of developing chronic impairment of renal function [16]. Even in patients who recover renal function following AKI, those with postoperative course complicated by AKI remain at increased risk for overall mortality compared to patients without AKI [17]. Currently, the literature reports a wide range regarding the incidence of AKI following arthroplasty from 0.5% to as high as 22% in certain patient populations [14,18-20]. Therefore, postoperative AKI is a serious complication potentially affecting numerous at-risk patients undergoing TJA postoperatively.

As previously described, risk factors that have been shown to have an association with the development of AKI in patients undergoing THA and TKA include intrinsic patient characteristics and medical comorbidities. Further contributing to risk of AKI development are events occurring throughout the perioperative period such as intraoperative hypotension, use of general anesthesia, administration of nephrotoxic medications, and perioperative blood transfusions [16,21]. While multiple studies have looked at chronic medical conditions like chronic kidney disease (CKD), coronary artery disease, and hypertension, few studies have looked at the impact of the management of these chronic conditions themselves on the incidence of AKI [20,22]. The current pharmacological interventions used in the management of hypertension and diabetes mellitus include angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi), which, while used to reduce renal damage, have been shown to increase risk of developing AKI in certain clinical scenarios due to inhibition of the renin-angiotensin-aldosterone pathway [23,24]. Therefore, the purpose of this study was to determine if preoperative antihypertensive drugs can play a role in predisposing patients to AKIs following TJA.

Material and methods

We conducted a retrospective review of longitudinally collected data within each institution's orthopaedic surgery department from 2013 to 2019. This was performed after approval was received from the institutional review boards of all involved institutions.

A total of 8245 patients were identified for potential inclusion in this study, with 7406 patients meeting the criteria for inclusion in this study, and the remaining 839 were excluded due to procedures involving revision arthroplasty. The 7406 patients included in this study had 4532 THA and 2874 TKA. The inclusion criteria for this study were: undergoing primary TKA or THA at one of the 2 institutions.

Patients were divided into 2 groups: those with and without AKI. Demographic information was collected, and there was no significant difference in the age, sex, and BMI of patients in the 2 groups (Table 1). Medication use was recorded for each patient. Bivariate testing including a paired t-test and Fisher's exact test were performed to compare laboratory values including complete blood count and complete metabolic panel, medications including pre-/peri-/post-operatively, and Elixhauser comorbidities of the 2 groups. AKI was defined according to the Acute Kidney Injury Network Criteria as a rise in serum creatine by 26.4 $\mu mol \cdot L^{-1}$ [25].

Multivariate regression analysis was used to determine if there was an association with postoperative AKI and the following variables: age (by year), gender, hospital size, type (academic vs nonacademic), and region, insurance status, blood loss, transfusion, blood loss anemia, iron deficiency anemia, rheumatoid arthritis, congestive heart failure, coagulopathy, depression, diabetes with and without end organ damage, hypertension, hypothyroid, liver disease, electrolyte disorders, metastatic cancer, neurologic disorders, paralysis, vascular disease, pulmonary circulatory disease, valvular disease, and weight loss. All statistical analysis was performed utilizing GraphPad Prism, version 7.0a (GraphPad software Inc., California, USA), and a P-value of <0.05 was considered statistically significant.

Results

Overall, the incidence of postoperative AKI in the entire patient cohort was 6.2% (n = 459). In total, 16% (73/459) of AKIs ultimately required intervention. Following TKA, 6.5% (187/2874) suffered an AKI, and 6% (272/4532) of THA patients suffered a postoperative AKI. There was no significant difference in the rate of AKI following THA and TKA ($P = .871$). The patients suffering an AKI had a significantly increased length of stay (8.9 ± 2.1 vs 2.6 ± 1 days, $P < .005$) and rate of intensive care unit admission. Further, BMI >40 kg/m^2 was found to increase the risk of AKI in THA and TKA patients (odds ratio [OR]: 1.9; 95% confidence interval [CI]: 1.3-3.1). There were no mortalities associated with either patient cohort.

Multivariate analysis was used to examine the association between various medical comorbidities and the risk of postoperative AKI in patients undergoing THA and TKA. Risk factors for postoperative AKI included CKD, with an OR of 7.09 (4.8-9.4). Diabetes was also identified as a significant risk factor, with an OR of 5.03 (2.8-6.06). The use of 3 or more antihypertensive drugs was associated with an increased risk of postoperative AKI, with an OR of 4.2 (2.1-6.2). Patients who were on preoperative angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) regimens were also found to be at a higher risk of developing postoperative AKI, with an OR of 3.8 (2.2-5.9). Additionally, the use of perioperative vancomycin was found to be a significant risk

Table 1
Demographics.

	With AKI (N = 459)	Without AKI (N = 6947)	*P*-value
Age (years)	67.7 (44-92)	71.2 (46-88)	.342
Sex			.515
Males	229	3480	
Females	230	3467	
Body mass index (kg/m^2)	31.7(17.8-54.2)	34.2(19.5-58.3)	.421

factor, with an OR of 2.7 (1.8-4.6). Finally, patients with a BMI above 40 kg/m2 had a slightly elevated risk of postoperative AKI, with an OR of 1.9 (1.3-3.06) (Fig. 1).

Discussion

This study is one of the first to assess the role of antihypertensive medications on the development of AKI in patients undergoing primary THA and TKA. Based on the findings of this study, it appears that the use of 3 or more antihypertensives and preoperative angiotensin axis blockade with ARBs and ACEi regimens significantly increases the risk of AKI in THA and TKA patients.

Antihypertensive medications are one of the most commonly prescribed medications, with more than 1.5 billion people worldwide expected to have hypertension by 2025 [26]. Further, the American College of Cardiology recommends ACEi and ARBs as first-line medications in the treatment of hypertension due to their long-proven efficacy [27]. In recent years, these antihypertensive medications, including ACEi and ARBs, given in the preoperative period have been linked to AKI following cardiac and oncologic surgical procedures [28,29]. Similarly, Worsham et al. found ACEi and ARB use to be associated with a higher incidence of intraoperative hypotension (12.2% vs 6.7%) and AKI (5.76% vs 3.28%) in patients undergoing elective orthopaedic procedures [30]. Nielson et al. also found that patients receiving angiotensin axis blockade therapy preoperatively were at a significantly increased risk for postinduction hypotension (12.2% vs 6.7%) and postoperative AKI (8.3% vs 1.7%) than patients not taking ACEi or ARBs preoperatively [31]. Therefore, given the widespread use of ACEi and ARBs in the general population, it is crucial for clinicians to weigh the potential risks and benefits of continuing or discontinuing these medications in the perioperative period.

The development of postoperative renal dysfunction following orthopaedic procedures is a complex phenomenon with multiple contributing factors. Kateros et al. found that in a sample of over 800 patients, diabetes, perioperative dehydration, perioperative shock, administration of nonsteroidal anti-inflammatory drugs (NSAIDs), and the use of nephrotoxic antibiotics were associated with an increased risk of postoperative renal dysfunction [32]. Because SSIs remain the most common complication following TJA, this is of particular interest to our discussion. Of particular concern is the role of SSIs, which remain the most common complication following TJA. In line with this, Courtney and colleagues found that the use of vancomycin in combination with cefazolin rather than cefazolin alone was associated with an increased risk of AKI in patients undergoing total hip and knee arthroplasty (OR: 1.82, 95% CI: 1.25-2.64) [12]. The study protocol utilized weight-based dosing of all antibiotics without specific mention of dose alteration made for patients with reduced glomerular filtration rate. Antibiotics were given within 60 minutes of surgery and were discontinued within 24 hours postoperatively, similar to perioperative antibiotic protocol for patients undergoing TJA at our institution [12]. Ultimately, the findings of Courtney et al. (2015) are consistent with our findings, in which the use of perioperative vancomycin was associated with an increased incidence of AKI development. These findings may also suggest a need for special attention to nephrotoxic antibiotic dosage in patients with low compromised glomerular filtration rate at baseline. Similarly, a study by Bailey et al. found that patients who were treated preoperatively with flucloxacillin and gentamicin were more likely to sustain AKI postoperatively than those treated with cefuroxime alone [33].

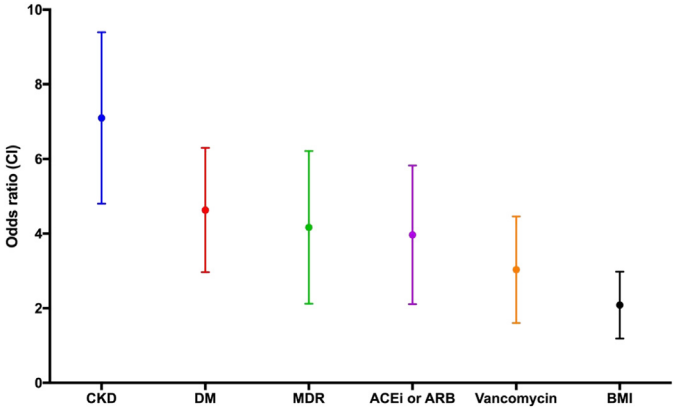

Figure 1. Risk factors for acute kidney injury. DM, diabetes mellitus; MDR, multidrug antihypertensive regiment.

The effect of NSAID use in the postoperative period on renal function should also be explored, as these agents may be utilized for analgesia and deep vein thrombosis (DVT) chemoprophylaxis. Mittal and colleagues found that patients taking combined ibuprofen for pain control and aspirin for DVT prophylaxis developed AKI at a rate of nearly 3% [34]. Similarly, Warth et al. reported the rate of development of AKI in patients following TJA who received scheduled celecoxib and as needed ketorolac postoperatively in approximately 5% of patients with adequate preoperative renal function [35]. Further research is required to better establish the exact relationship of NSAID use and postoperative AKI following TKA; however, this is relevant to our study as multimodal pain control utilizing NSAIDs as well as the use of NSAIDs for DVT prophylaxis is commonly utilized following TJA, and it is well established that a possible adverse effect of NSAID therapy is AKI [36].

Furthermore, the use of multiple antihypertensives increases the risk of intraoperative hypotension with an independent association found between the number of antihypertensive medications taken on morning of surgery and development of AKI [37]. This is especially important in the setting of TJA as intraoperative hypotension has been identified as a major risk factor for developing an AKI postoperatively [37,38]. Duceppe et al. found the incidence of AKI in patients taking a single antihypertensive did not significantly increase (OR: 1.58, 95% CI: 1.53-7.44), but the use of 2 or more medications did cause a significant increase (OR: 2.70, 95% CI: 1.13-6.44) prior to their vascular surgery procedure [37]. This is consistent with our findings that patients taking more than 3 antihypertensive agents experienced an increased risk of AKI.

When considering the above findings in the context of TJA, it can be proposed that patients with a history of CKD or diabetes who are also taking ACEi/ARBs or multiple anti-hypertensive agents require careful preoperative planning in terms of medication review, prophylactic antibiotic agent selection, and multimodal postoperative analgesia regimen.

CKD, obesity, diabetes, and hypertension are well-established risk factors for AKI following TKA and THA [39-41]. Our findings were in line with these previous studies, finding CKD, diabetes, and a BMI >40 kg/m^2 to be associated with increased rates of AKI. We also found that perioperative administration of vancomycin increased the risk of AKI postoperatively, consistent with the findings of Courtney and colleagues [12]. Additionally, our findings indicate ACEi, ARBs, and the use of 3 or more antihypertensives preoperatively are associated with an increased risk of AKI in patients undergoing THA and TKA. The incidence of AKI in our study population was significantly lower than the incidence reported in previous studies examining the incidence of AKI following THA and TKA. Kimmel et al. reported an incidence of 14.8% of patients

suffering AKI following THA and TKA, more than twice the incidence of 6.8% in our study [39]. The results of Hassan et al. analyzing renal dysfunction following TKA reported an AKI incidence similar to that of our TKA patients, 9.7% vs 6.5% [41].

Our study is not without limitations and, as such, our results should be interpreted with these limitations in mind. First and foremost, the largest limiting factor is that our study was performed using retrospective data. While the data was collected longitudinally, retrospective studies collected in this manner still have an inherent potential for bias and variability in the way the data was collected. Furthermore, the dose of medications and time of administration prior to surgery were not captured in our data set. Additionally, the specific types of ACEi and ARB medications were not recorded. The presence of a horseshoe kidney, single kidney, or other renal pathology not captured by the Elixhauser Comorbidity Index was not captured and may have predisposed patients to suffering an AKI. Complications during induction of anesthesia, including induction hypotension or intraoperative hypotension, and intraoperative fluid administration were not available, which may confound the results of our study.

Conclusions

We have identified risk factors that may be modifiable and can therefore be optimized prior to an elective THA or TKA. The use of certain antihypertensive agents, namely ACEi, ARBs, and multidrug antihypertensive regimens, were found to significantly increase the risk of AKI. Additionally, the administration of vancomycin was found to significantly increase the risk of developing a postoperative AKI, and this risk must be weighed against the risk of periprosthetic joint infection when utilizing nephrotoxic agents for antibiotic prophylaxis in individuals at increased risk of AKI. We strongly urge orthopaedic surgeons to be aware of preoperative antihypertensive medication management, particularly if additional risk factors for AKI such as obesity, diabetes, and CKD are present.

Conflicts of interest

The authors declare there are no conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2024.101362.

CRediT authorship contribution statement

Alisina Shahi: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Samantha L. Harrer:** Writing – review & editing, Writing – original draft, Project administration. **Jack W. Shilling:** Supervision, Methodology, Investigation. **Matthew L. Brown:** Writing – original draft, Methodology, Investigation. **Nicole Martino:** Data curation, Conceptualization. **Christopher McFadden:** Supervision, Investigation, Data curation.

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