KIDNEY INJURY AFTER ANTIBIOTIC SPACER IMPLANTATION FOR PROSTHETIC JOINT INFECTION

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Abstract

Background: The purpose of our study was to quantify the extent of kidney involvement during a two-stage approach for PJI.

Methods: We conducted a multidisciplinary, retrospective evaluation of all infected total hip arthroplasty (THA) and total knee arthroplasty (TKA) patients treated with a two-stage approach utilizing antibiotic impregnated cement spacers from August 2007-July 2011 at our institution. Data collected included demographics, medical co-morbidities, surgical data as well as risk factors for kidney injury, such as nephrotoxic agents, hypotensive episodes and baseline kidney function.

Results: Acute Kidney Injury (AKI) occurred in 7/34 (21%) of patients at a median of 147 days (52-596 days) and represents the time with the antibiotic cement spacer. Six additional patients showed a doubling of serum creatinine concentrations over baseline beyond the first 48 hours after surgery, giving a total incidence of 47% of post-operative kidney injury. Serum creatinine concentrations recovered to baseline in 44% (7/16) of patients. Two patients underwent dialysis for persistent elevated creatinine. Kidney injury was more likely among older patients (HR 1.4 for every 10 year increase, confidence interval [CI] 1.2-2.6; p<0.01), those with Chronic Kidney Disease represented by a lower eGFR at baseline (HR 0.7 for every 10 ml/min higher baseline eGFR, CI 0.5-0.9, p<0.01) and cardiovascular disease (CVD) (HR 4.7, CI 1.6-13.6, p<0.01).

Conclusions: Kidney injury with elevation of serum creatinine over baseline occurs frequently following the first stage of a two-stage revision arthroplasty using antibiotic cement spacers, especially in patients with baseline comorbidities. Changes in kidney function after surgery are multi-factorial therefore further prospective studies are necessary to understand the causes and consequences.

Introduction

Prosthetic joint infection (PJI) complicates 0.5% to 2% of primary arthroplasties [1-6]. The currently accepted standard of treatment for PJI is two-stage revision arthroplasty which is reported to have improved efficacy for infection eradication over either one-stage revision, resection arthroplasty or debridement in conjunction with intravenous antibiotics [7-9]. In the first stage of a two-stage revision, the infected prosthesis is removed and replaced by an antibiotic-loaded cement spacer (ALS) typically containing a combination of an aminoglycoside and vancomycin; systemic antibiotics are also given. In the second stage, once
infection is eradicated, the spacer is removed and the new prosthesis implanted. The spacer maintains the joint space and provides high local concentrations of the antibiotics, with values greater than the minimum inhibitory concentration (MIC) for most common organisms. Although systemic toxicity from ALS was believed to be rare, adverse effects such as acute kidney injury (AKI), allergic reactions, hepatic enzyme elevation and bone marrow suppression have been reported [10-17]. Despite widespread use and numerous reports of effectiveness for eradication of infection, there is limited data on the systemic harms of ALS specifically, kidney injury. We present a case series of patients who underwent a two-stage approach using a non-articulating ALS for PJI to describe the incidence of kidney injury and examine risk factors and association with clinical and joint outcomes.

Patients / Methods

Study Design
We performed a retrospective study of all patients who underwent two-stage arthroplasty with non-articulating ALS for PJI, identified from an orthopaedic database of 1054 joint replacements performed between Aug 2007 and July 2011 at a single tertiary care academic hospital. The protocol was approved by the Institutional Review Board.

Patients
All adult (> 18 years) patients who underwent two-stage arthroplasty with antibiotic spacers for PJI were identified. Of 41 such subjects, we excluded seven patients (two patients known to have end stage renal disease (ESRD), one with AKI already established at baseline, two patients whose follow up serum creatinine measurements were unavailable, one patient with ankle joint involvement and one with joint space infection after an acetabular fracture) leaving 34 patients for analysis. Patients were determined to have had prosthetic joint infection based on the recommended guidelines established by the AAOS. In accordance with those guidelines, a diagnosis of PJI was made when four of the following six criteria existed: 1. Elevated serum erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) concentration 2. Elevated synovial white blood cell (WBC) count 3. Elevated synovial neutrophil percentage (PMN%) 4. Presence of purulence in the affected joint 5. Isolation of a microorganism in one culture of periprosthetic tissue or fluid 6. Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 times magnification.

Data Collection
Using the electronic health record and chart review, we collected patient information between the first stage (spacer placement) and the second stage (spacer explant with or without definitive prosthesis) of the two-stage procedure. Data collected comprised demographic variables, baseline characteristics and co-morbidities (including chronic kidney disease, CKD) and medications. Potential risk factors for kidney injury such as intra-, peri- and post-operative events (including need for ICU care, hypotension and/or need for vasoressors, use of intravenous contrast for imaging, quantity and type of antibiotic used in the spacer, type, dose and duration of systemic antibiotics, and blood antibiotic levels when available) were noted. All available serum creatinine measurements and their time course during the study interval were recorded. Data describing development of kidney injury, need for dialysis, time to recovery of kidney function, discharge status and successful progress to second stage surgery were noted.

Definitions
Baseline kidney function was defined as the eGFR calculated with the CKD-EPI equation [18], using pre-operative serum creatinine concentrations that had been stable for at least two estimations. CKD at baseline was defined as estimated GFR (eGFR) <60 ml/min/1.73m².
AKI was defined by the AKIN (Acute Kidney Injury Network) definition for AKI (>50% rise in serum creatinine or absolute increase of 0.3 mg/dL within 48 hours) [19]. Any elevation of serum creatinine over baseline by at least 50% or by an absolute increase of 0.3 mg/dL but which did not occur within the 48 hour period was described as kidney injury but not classified as AKI by the AKIN criteria.

The incidence of AKI was also examined using the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria for injury i.e. doubling of serum creatinine from the baseline value in a seven-day period [20]. The RIFLE definition would potentially include those patients who also fulfill the AKIN criteria but continue to have a doubling of serum creatinine within the seven-day period. Again, patients who experienced a doubling of serum creatinine but not within the seven-day period were described as having kidney injury but not classified as AKI by the RIFLE criteria.

The outcome of kidney injury was subcategorized as either recovery of kidney function to baseline during the follow up period, or non-recovery with persistent serum creatinine elevation at the time of spacer explant.

Cardiovascular disease (CVD) was defined as presence of one or more diagnoses of coronary artery disease, congestive heart failure, peripheral vascular disease, or cerebrovascular disease.

Statistical methods
Baseline characteristics were reported as mean and standard deviation or percentages, as appropriate for the data. Clinical variables were compared among patients with and without kidney injury, using the T-Test for continuous variables and the chi square test for categorical variables. The time to peak serum creatinine concentration among patients with kidney injury was calculated from the date of spacer insertion and analyzed using Kaplan-Meier survival curves. Log rank test was used to test differences in time to peak serum creatinine by baseline categorical characteristics, and Cox regression models were used for continuous variables and adjusted comparisons. A maximum of 2 variables were included in the final multivariable model to avoid over-fitting in view of limited power. Analyses were performed using SPSS version 14 (SPSS Inc, Chicago, IL).

Results
Patient Characteristics
Forty-one patients with chronic PJI who underwent two stage arthroplasty using antibiotic spacers between Aug 2007 and July 2011 were identified in a database of 1054 arthroplasties (3.2%). After excluding seven patients from the analysis our case series consisted of 34 patients whose baseline characteristics and clinical course is described in this report.

The baseline characteristics of the study subjects are shown in Table 1. The mean age was 62 (SD 15) years, 88% (30/34) were Caucasian and 53% (19/34) were female. Diabetes was present in 32% (11/34) of patients and 24% (8/34) had CVD. The mean baseline serum creatinine was 0.9 (SD 0.3) mg/dl and mean baseline eGFR was 82 (SD 17) ml/min/1.73m2. Based on eGFR < 60 mL/min, CKD was present in 15% (5/34) of patients at baseline.

The affected joints were hips in 50% (17/34) and knees in 50% (17/34). The ALS was used for PJI in all patients. Patients were followed for a median duration of 153 (52-596) days between first and second stage (spacer explant) surgeries. Four patients underwent more than one ALS revisions and their follow up extended until explant of the last spacer with definitive joint surgery. Figure 1 shows the increasing yearly rate of two-stage arthroplasties at this center.
between August 2007 and July 2011. Detailed descriptions by patient with final joint outcomes are outlined in appendix table 1.

**Infection and Antibiotic Use**

In the majority of patients (18/34, 53%), no organism was isolated as the cause of PJI. Staphylococcal species accounted for the remaining infections except for an Escherichia coli infection in one patient. The staphylococcal infections included methicillin resistant Staphylococcus aureus (MRSA) in eight (24%), methicillin susceptible Staphylococcus aureus in six (18%) and Staphylococcus epidermidis in one patients (3%).

All patients received a combination of tobramycin and vancomycin in the spacer. The In most cases the amount of antibiotics used were 10.8 g of tobramycin and/or 2 g to 9 g of vancomycin per 120g of bone cement (a total of three 40g bags). Antibiotic usage was noted to increase over time with a median of 3-4 g of each antibiotic in 2009 to 8-10 g each in 2011 (p<0.01) (Figure 1). In addition, all patients received systemic antibiotics. These included vancomycin in 21/34 (62%), given either alone or in combination with another antibiotic, and oxacillin in 6/34 (18%). No patient received systemic aminoglycoside therapy. Less frequently used antibiotics either individually or in combination included cephalosporins, quinolones, clindamycin, daptomycin, linezolid and rifampin. Serum tobramycin levels (random) were measured in two patients, in whom serum creatinine concentrations were elevated following ALS, and were supratherapeutic (>2 µg/ml) in both. These values were measured 28 days and 5 days after surgery, respectively. Supratherapeutic (>20 µg/ml) vancomycin levels (random) were reported in 11 patients, eight of whom were also receiving systemic vancomycin therapy, at a median (IQR) of 4 (3, 14) days from surgery.

There was persistence of the PJI in seven patients, and infection recurred in five, (documented by re-aspiration or re-exploration) giving a failure rate for infection eradication of 35%.

**Incidence and outcome of Acute Kidney Injury**

Applying the AKIN criteria, AKI developed in 21% (7/34) of patients. With the RIFLE criteria the incidence was, at 29% (10/34). Serum creatinine peaked to a median of 2.2 mg/dL (0.95-5.4 mg/dL) over a median duration of 22 (4-168) days.

Of 24 patients who did not have AKI by either definition, a further six patients developed an elevation in serum creatinine concentration over baseline (> doubling of baseline concentration) beyond one week from surgery, and were recognized either during follow up or at the time of spacer explants. Serum creatinine peaked to a mean of 2.2 mg/dL (max 5.4 mg/dL) at a median of 22 (11-168) days. Of these six, two patients had CKD by eGFR criteria (< 60 mL/min) at baseline. Supplemental figure 1 shows the cumulative hazard for kidney injury (doubling of serum creatinine) over time during and beyond the first week from spacer placement.

The total incidence of kidney injury following antibiotic spacer placement was therefore 47% (16/34). Kidney injury recovered to baseline levels in less than half of these patients (7/16 44%) during follow up. Of the remaining nine patients in whom, no or only partial recovery of kidney function was seen, two required dialysis. Both subsequently died as did two others, with multi-organ failure after a complicated hospital course.

**Risk Factors for and Outcomes of AKI**

Table 2 shows the differences between patients who did and did not develop kidney injury, either AKI (AKIN/RIFLE) or a delayed serum creatinine elevation. Patients with kidney injury were older, with a significantly higher baseline prevalence of CVD and CKD. They had higher baseline serum creatinine concentrations and lower eGFR. The amount of tobramycin or
vancomycin used in the spacers did not differ in those who developed kidney injury. As serum levels were not available for all patients they could not be studied in relation to development of kidney injury.

On univariate analysis, (Table 3) every 10 years’ increase in age increased the risk of kidney injury by 70% (95% CI 20 to 160%, p<0.01), for every 0.1 mg/dL higher baseline serum creatinine level, the risk of kidney injury increased by 20% (95% CI 10 to 50%, p=0.01) and for every 10 ml/min higher baseline eGFR, the risk of kidney injury decreased by about 30% (95% CI 10-50%, p<0.01). Figure 2 shows the K-M survival curves for time to peak serum creatinine by the presence of CVD (Figure 2a) and CKD at baseline (Figure 2b). Patients with CVD had an almost 5-fold increased risk for kidney injury (HR 4.7, CI 1.6-13.6, p<0.01), and the presence of CKD (eGFR<60 mL/min) at baseline increased the risk 3.5-fold (95% CI 1.3-9.5). In adjusted analysis, the strongest risk factors were the presence of CKD (baseline eGFR < 60 mL/min) and CVD (Table 3).

There was also a significant association between the development of kidney injury and the need for ICU stay; patients who developed kidney injury were eight times more likely to need ICU stay. Moreover all four patients who died had kidney injury after ALS placement. Table 2 and Figure 3 show that kidney injury was significantly associated with adverse outcomes including poorer survival, greater need for ICU stay, and lower likelihood of having a successful second stage procedure.

**Joint outcomes**
Spacer explant and 2nd stage procedure was performed in 19 patients (56%). The process could be deemed successful in 14 (41%) with clearance of infection and a functioning definitive prosthesis. Infection recurred in the implant in four patients and two other patients died in the postoperative period.

Second stage surgery with definitive joint implant was not performed in the remaining 15 patients. Seven patients (20.5%) did not clear infection, despite two sequential spacer procedures in three patients and three sequential spacers in one. Of the seven, the spacer was retained in three patients and three others progressed to resection arthroplasty, joint fusion or above knee amputation respectively. Seven patients did not undergo 2nd stage for reasons other than infection clearance – one patient underwent fusion for bone loss, three patients retained the spacer as they were of advanced age (>90 years), and one retained the spacer in the setting of metastatic malignancy. Two patients died from sepsis before explant.

**Discussion**
Our retrospective analysis of 34 patients with two-stage exchange arthroplasties for revision of infected TKA/THA found a nearly 50% incidence of post-operative kidney injury. Using currently accepted definitions for AKI (AKIN and RIFLE criteria) we found the incidence of AKI to be respectively 21 and 29%. These definitions for AKI are specified by a time window within which the serum creatinine concentration elevation evolves beyond a stipulated threshold. However, in a fifth of the patients, most without kidney disease at baseline, the rise in serum creatinine was delayed. Doubling of serum creatinine, an accepted measure of progressive kidney injury was therefore discovered only beyond the time periods specified in the definitions, during follow up or at the time of spacer explant.

We identified risk factors for developing kidney injury including older age and the presence of baseline CKD and CVD. Less than half the patients with kidney injury recovered kidney function either completely or partially during the follow up period. The development of kidney injury was associated with the need for ICU stay and multi-organ failure; a total of four patients died with two initially needing dialysis.
The occurrence of acute kidney injury after two-stage arthroplasty for PJI has been reported by several investigators. While the local delivery of high concentrations of antibiotics in infected joints has been claimed as an advantage of antibiotic impregnated spacers [21, 22], systemic toxicity can occur. From a systematic review of the literature between January 1989 to June 2012, we computed the reported incidence to be approximately 5% [23]. Compared to the estimated incidence of acute renal failure of 0.55% reported by Jafari et al [24] in a retrospective survey of over 17,000 arthroplasties, the risk of AKI following two-stage arthroplasty for PJJ appears to be at least 8 to 10 – fold higher. The excess risk of renal impairment has been related to the nephrotoxicity of aminoglycoside in the antibiotic spacer [25] but infection and operative stress are also likely contributors. Vancomycin is also nephrotoxic, and the combined use of vancomycin and tobramycin may have the potential to increase the nephrotoxic effects of the aminoglycoside [26].

Our rate of spacer use was about 3.2%, higher than the nationwide rate of 1-2% reflecting the referral bias of our medical center. Between August 2007 and July 2011 we noted not only an increase in the number of patients undergoing ALS placements, but also an increase in the amount of tobramycin and vancomycin being used in the composition of these spacers. Practice patterns are variable within centers as was apparent in our data and across centers as reflected in the literature [29]. While currently there is no standardization for type of antibiotic use, its dosing, and safety in antibiotic cement spacers, the American Academy of Orthopedic Surgeons has suggested the use of high dose antibiotic (>3.6 g /40 g cement) spacers [30]. The use of more than one antibiotic in cement spacers is often necessary to increase the spectrum of antimicrobial coverage, decrease the risk of resistance, and provide synergistic effects [31] since it is well known that up to 20-30% of PJI may be bacteriologically negative [7, 8, 32, 33]. In our series no bacteria was identified in over 50% of cases. This is attributed to the inpatient transfer of many of the patients to our center without a two week antibiotic holiday. The combination of vancomycin and tobramycin is the most common one used, given the frequency of Staphylococcal species in the etiology of PJI, and because their thermostability provides favorable mechanical properties [34]. Menge et al showed that patients who received more tobramycin in cement were more likely to develop AKI. We did not find a similar relationship, likely attributable to the limited range of tobramycin dosing in our series. Moreover as serum tobramycin levels were not consistently measured, we were not able to comment on a dose-related nephrotoxic effect. It is notable however, that the median antibiotic doses used in the spacer were higher in our study than that of Menge et al - tobramycin 10.8 gm vs. 4.8 gm, and vancomycin 9 gm vs 4 gm – and may have also contributed to the higher incidence of kidney injury in our series.

Our data reflects the growing awareness that even transient worsening of kidney function and development of in-hospital AKI is associated with adverse outcomes such as increased length
of hospital stay, increased health care costs, and increased risk of developing or worsening CKD and increased mortality [1, 35-37]. Indeed, our data showed that AKI tracked with the need for ICU stay, higher mortality and poorer joint outcomes. This association could be either causal, or a marker for poor outcomes, or a marker for the high risk patient. At the present time, the long term implications of the cumulative renal toxicity in antibiotic spacer associated AKI is completely unknown. There is also an increasing appreciation that substantial mortality and failure from both reinfection and inability to perform the second stage is encountered with two-stage treatment of deep infection in primary and revision arthroplasty and may be under-reported [38]. The risk factors that result in these failures have not been systematically identified.

In summary, the incidence of kidney injury after two-stage arthroplasty with antibiotic spacers is significant and likely under-appreciated. Baseline co-morbidities form the strongest risk factors for AKI and appropriate risk stratification and assessment of eligibility and safety of surgery needs strong consideration. Preventative measures such as volume and hemodynamic support during pre- and peri-operative management should mitigate the risk of AKI. With the aging of the population, and the growing prevalence of obesity and other co-morbidities that place patients at risk for CKD, the risk for developing AKI in this setting will only increase. Future imperatives in this field lie in appropriate patient selection as indicated in our data, in raising the awareness for AKI as a potential post-operative complication with implications for adverse consequences, and in seeking a level of standardization of practice with regard to antibiotic use in spacers. Further prospective studies are necessary to further define the risk of AKI and strategies to decrease it after two-stage revision arthroplasty.

References


