The safety of high-dose antibiotic cement spacers in the two-stage revision of infected total joint arthroplasty

Allison Rae Roberts

The Safety of High-Dose Antibiotic Cement Spacers in the Two-Stage Revision of Infected Total Joint Arthroplasty

Allison Rae Roberts

The University of Toledo

2016

Dedication

This paper is dedicated to my family and friends who have supported me throughout the Physician Assistant program.

Acknowledgements

Thank you to my major advisor, Dr. Daniel Gehling, for his encouragement, hours of work spent on this project, and guidance throughout the entire process.

Table of Contents

List of Tables

Introduction

Each year in the United States, it is estimated that more than 1 million hip and knee replacement surgeries are performed (Kurtz et al., 2008). Periprosthetic joint infection (PJI) is a devastating complication that occurs in about 1-3% of total hip or knee arthroplasties (Hanssen & Rand, 1999; James & Larson, 2015; Kurtz et al., 2008; Stevens, Tetsworth, Calhoun, & Mader, 2005). In the forthcoming years, the total number of joint replacements is expected to rise, and if infection rate remains constant, the total number of infections will also increase accordingly (Kurtz et al., 2008; Menge et al., 2012). Prolonged hospitalization, loss of joint function, increased cost, and significant morbidity are among the possible deleterious effects of an infected prosthesis (Heck, Rosenberg, Schink-Ascani, Garbus, & Kiewitt, 1995; Kurtz et al., 2008; Stevens et al., 2005). These consequences are a burden to patients and healthcare costs alike. Although there are a variety of treatment strategies for PJI, the most effective and widely accepted treatment for both hip and knee PJI is a two-stage revision arthroplasty (Cui, Mihalko, Shields, Ries, & Saleh, 2007; Hsieh, Chang, Chen, Ueng, & Shih, 2006; Koo et al., 2001; Menge et al., 2012; Stevens et al., 2005; Trezies, Parish, Dixon, & Cross, 2006).

The two-stage revision method involves first a surgical removal of the prosthesis, a full debridement of infected tissue, irrigation of the wound, and insertion of a high-dose antibiotic-loaded bone cement (ALBC) spacer. A second stage is planned once the infection is tested to be no longer detectable, when removal of the ALBC occurs and then revision to a new joint prosthesis (Hsieh et al., 2006). The reimplantation timeline varies with each patient and depends on if infection eradication has been achieved. The window for reimplantation is varied, occurring between 10 weeks and 4 months after the insertion of the ALBC spacer. The dose of antibiotic(s)

in cement spacers also varies, and has been studied for efficacy in eliminating or preventing infection.

Gentamycin or tobramycin ALBC is used as a prophylactic measure against PJI, but the standard usage of antibiotics in primary joint replacement is controversial and expensive (Patrick, Rivey, & Allington, 2006). Generally, a lower dose of antibiotics is used than in those that are being treated for PJI.

The treatment of a PJI also incorporates gentamycin or tobramycin ALBC in much higher doses, and oftentimes in combination with vancomycin (Gogia, Meehan, Di Cesare, & Jamali, 2009; Heck et al., 1995; Henry & Galloway, 1995). Systemic antibiotics have a known risk of renal injury; aminoglycosides via tubular cell toxicity, and vancomycin via acute interstitial nephritis (AIN). As with most adverse drug reactions, risk of renal injury rises with increasing dose and pre-existing renal abnormalities or disease.

There has always been concern with the use of high-dose antibiotics in cement, particularly in the ability of these locally delivered antibiotics to cause harm through renal injury. There are a number of case reports, but little in terms of guidelines. At The University of Toledo Medical Center (UTMC), the cement spacers routinely have at least 20g of vancomycin and 9.6g of tobramycin total.

This research aims to determine the safety of high-dose ALBC spacers. As there is little guidance in the literature, and because UTMC practice of antibiotic dosing is much higher than previously reported, it would be of interest to determine if there is any correlation between the use of high-dose ALBC spacers and renal injury.

Literature Review

Management of Periprosthetic Joint Infections

A two-stage revision arthroplasty using an ALBC spacer is considered to be the standard of care in treating PJI (Cui et al., 2007; Dunbar, 2009; Hsieh et al., 2006; Koo et al., 2001; Menge et al., 2012; Stevens et al., 2005; Trezies et al., 2006). This concept of utilizing ALBC with the two-stage revision was introduced in 1983 (Cui et al., 2007). The process usually involves removing the infected implants and debriding the tissue, a period of infection eradication while the cement spacer is in place, followed by reimplantation of the prosthesis. Patients receive systemic antibiotics as well for a usual 6 weeks, during which the spacer is in place. The overall effectiveness of this revision strategy as well as each variation has been researched thoroughly. However, there is still no consensus on antibiotic dosing, nor is there standardization among surgeons.

Removing hardware and all foreign material without placement of a spacer can result in several issues. The muscles, tendons, ligaments, and other soft tissues surrounding the joint will contract and make the reimplantation stage extremely difficult (Cui et al., 2007; Durbhakula, Czajka, Fuchs, & Uhl, 2004). Adding to contractures, the joint is extremely unstable without a spacer or implant (Cui et al., 2007; Durbhakula et al., 2004; Hsu, Cheng, Ng, & Chiu, 2007; Trezies et al., 2006). As a result, mobility is a challenge, and immobility can lead to several harmful effects on the body. Using cement spacers during the interim period can help avoid these complications (Cui et al., 2007; Durbhakula et al., 2004; Hsu et al., 2007; Trezies et al., 2006).

The patient’s mobility is preserved with the cement spacer, and soft tissue tension is maintained (Cui et al., 2007; Durbhakula et al., 2004; Hsu et al., 2007; Stevens et al., 2005; Trezies et al., 2006). Limiting the arthrofibrosis and preserving the tissue planes facilitates

reimplantation as well (Cui et al., 2007; Durbhakula et al., 2004; Hsu et al., 2007; Stevens et al., 2005). There is also a decrease in bone loss when an articulating spacer is used versus a static spacer or no spacer (Fehring, Odum, Calton, & Mason, 2000; Park, Song, Seon, Yoon, & Park, 2010; Trezies et al., 2006). The space-occupying and articulation aspects of the cement spacer account for the prevention of negative outcomes described above. The other major benefit comes from the addition of antibiotics into the cement.

Local delivery of antibiotic via bone cement allows for a direct route of action, bypassing the need of adequate blood flow to reach the target tissue. Infection sites can have zones of avascularity with biofilm formation, making systemic antibiotic penetrance to local infection challenging without using toxic doses (Hanssen, Osmon, & Patel, 2005; Henry & Galloway, 1995; Stevens et al., 2005). The two-stage revision process allows for biofilm disruption in multiple theoretical ways. Higher local concentration of antimicrobial, combination antimicrobial therapy, sustained concentrations of antibiotics, and hardware removal with tissue debridement are all strategies in biofilm elimination (Hanssen et al., 2005).

The success rate of eradicating infections using ALBC spacers ranges from 88-100% (Cui et al., 2007; Evans, 2004; Goldstein, Kopplin, Wall, & Berland, 2001; Ha, 2006; Haddad et al., 2000; Hofmann, Goldberg, Tanner, & Kurtin, 2005; Hsu et al., 2007; Koo et al., 2001; Meek et al., 2003; Nettrour, Polikandriotis, Bernasek, Gustke, & Lyons, 2013; Pitto, Castelli, Ferrari, & Munro, 2005). This achievement results in shorter hospital stays, decreased costs, increased function and mobility, higher patient satisfaction, and decreased pain (Cui et al., 2007; Hsu et al., 2007; Stevens et al., 2005). Although the high success rates advocate the two-stage revision arthroplasty as a very effective strategy for managing PJI, there are many aspects of the process that are not yet standardized in practice.

Antibiotic Selection

Pharmacokinetic factors of antibiotics are important in successfully treating infection. They include mechanism of action, clearance, organism sensitivity to the antibiotic, half-life, interactions with other drugs, and systemic effects. One major consideration is the antimicrobial's ability to reach the infected part of the body. Joint spaces and bone are difficult to reach with systemic antibiotic administration, especially in a chronic infection (Gogia et al., 2009; Henry & Galloway, 1995). The two-stage revision utilizing ALBC for PJI management allows for local delivery of antimicrobials. The antibiotic is released in direct contact with the infecting organisms, without relying on sufficient vascularity.

The addition of antibiotics extends the list of factors contributing to the variability of the cement spacer in practice. Deviations exist, but antibiotic choice is dependent on stability with cement mixing, common orthopedic pathologic organisms, drug elution properties, dose for minimum inhibitory concentrations (MIC), and potential nephrotoxic risks.

Antibiotic stability.

The selected antibiotic(s) must be hydrophilic and thermostable. Polymerization of the cement is an exothermic reaction, and the antibiotic must be able to withstand temperatures of up to 100°C (Bistolfi et al., 2011; Henry & Galloway, 1995). Gentamicin, tobramycin, and vancomycin meet these criteria, and are the most commonly used antibiotics in bone cement (Gogia et al., 2009; Heck et al., 1995; Henry & Galloway, 1995).

Infecting organisms.

The majority of PJIs are due to gram-positive organisms such as *Staphylococcus aureus* and *Staphylococcus epidermis* (Anguita-Alonso et al., 2005; Cui et al., 2007; Hsu et al., 2007; Koo et al., 2001; Tsukayama, Goldberg, & Kyle, 2003). Other organisms found in PJIs include

Corynebacterium species, *Serratia* marcescens, *Pseudomonas* species, *Escherichia coli*, *Citrobacter freundii, Streptococcus* species, *Methicillin-resistant Staphylococcus aureus* (MRSA), and *Bacteroides* (Durbhakula et al., 2004; Hsu et al., 2007; Nettrour et al., 2013; Trezies et al., 2006; Tsukayama et al., 2003). Gentamicin and tobramycin are bactericidal aminoglycosides that act by interfering with protein synthesis (Kahlmeter, 1979). They are effective in treating most aerobic gram-negative pathogens, mycobacterium, and can be used as adjunct therapy for aerobic gram-positive species. Vancomycin, a glycopeptide, eliminates infection by inhibiting bacterial cell-wall synthesis. Vancomycin is the first line treatment for *MRSA*, and provides coverage for gram-positive organisms and some gram-negative organisms (Cui et al., 2007; Henry & Galloway, 1995; Tsukayama et al., 2003).

Drug elution.

Several factors affect the elution of antibiotics from bone cement. The elements that have been researched include; spacer surface area, cement porosity, dose of antibiotic, the use of multiple antibiotics, preparation technique of cement, and total weight of cement. Ideal drug elution would resemble a local, sustained dose of antibiotic above the MIC, with minimal systemic extraction.

There is a direct relationship between spacer surface area and drug elution. A direct relationship also exists between the porosity of the cement and how much antibiotic is released. The greater the surface area, and the more porous the cement is, the more antibiotic is extracted into local tissues (Penner, Masri, & Duncan, 1996). Surface area is directly affected by total weight of cement used. Batches of cement are typically 40g each, and several batches are often used. Porosity of cement is affected by mixing technique, amount of powdered antibiotic, and addition of other materials specifically meant to increase porosity.

Commercial cement that is premixed releases more antibiotic than cement that is hand-mixed. Vacuum mixed cement release is only slightly less than commercial (Lewis & Janna, 2004; Neut, van de Belt, van Horn, van der Mei, & Busscher, 2003). The Food and Drug Association (FDA) approved commercial ALBC is inadequate for PJI eradication, and is used only in routine prophylaxis. It is therefore necessary for surgeons and their colleagues to hand or vacuum mix cement with added antibiotic powder (Anguita-Alonso et al., 2005; Cui et al., 2007).

Adding more than one type of antibiotic to the cement spacer also seems to increase drug elution totals and rates (Penner et al., 1996). This synergistic effect is described by Penner and colleagues as *passive opportunism,* and is seen when combining an aminoglycoside with vancomycin. The addition of a second antibiotic creates a more porous cement. Thus, using multiple antibiotics not only increases the antimicrobial spectrum, but the total drug elution as well (Gogia et al., 2009; Penner et al., 1996).

Most of the antibiotic is eluted within the first 24 hours of placement, but a slowed release continues over weeks to months (Bayston & Milner, 1982; Cerretani et al., 2002; Penner et al., 1996). A study by Bayston and colleagues shows that vancomycin levels are above the MIC for *S. aureus* and *S. epidermis* even after 5 weeks (Bayston & Milner, 1982). A study by Greene et al. reveals the level of antibiotic remains above the MIC for *S. aureus* for up to 100 days for tobramycin and 32 days for vancomycin when using low-dose commercial spacers (Greene et al., 1998).

High-dose versus low-dose.

The dose of antibiotics to be used in bone cement for management of PJI is not yet standardized (Cui et al., 2007; Greene et al., 1998). Low-dose is defined as less than 2g, and

high-dose greater than 2g, of powdered antibiotic per 40g batch of bone cement (Bistolfi et al., 2011; Jiranek, Hanssen, & Greenwald, 2006). However, typical dose in management of PJI is around 6-8g of antibiotic per 40g batch of cement (Bistolfi et al., 2011). Although there is no guideline to be used for how much antibiotic to add to cement spacers, the local concentration with this route is much higher than can be safely achieved with intravenous (IV) antibiotics alone (Henry & Galloway, 1995; Springer et al., 2004).

In general, elimination of infection when treated with the proper antibiotic is thought to be dose dependent. Higher local levels of antibiotics and longer elution durations are achieved with higher concentrations of antibiotic in cement spacers (Masri, Duncan, & Beauchamp, 1998). A retrospective study completed by Netrrour et al. (2013) found that cement spacers failed to eradicate infection more often in the low-dose group than in the high-dose group.

Another constituent is the ability of the spacer to maintain form with the addition of antibiotic powder. Excessive amounts may affect the mechanical properties and durability of the spacer. More than 4.5g of antibiotic powder, or the use of liquid antibiotics, has been associated with weakened bone cement. The highest ratio that can be mixed and still allow cement molding and formation is suggested to be 8g of antibiotics per 40g of bone cement (Cui et al., 2007).

Using a sub-therapeutic dose may lead to antibiotic resistance and persistent PJI (Anguita-Alonso et al., 2005; Gogia et al., 2009; Namba, Chen, Paxton, Slipchenko, & Fithian, 2009). For this reason, caution is advised when using low-dose ALBC even for prophylaxis. Low-dose antibiotics in cement to treat PJI may still be in use for a couple reasons.

Antibiotics and Nephrotoxicity

Certain classes of antibiotics have a known risk of renal injury; aminoglycosides (gentamycin and tobramycin) via tubular cell toxicity, and vancomycin via AIN. As with most

adverse drug reactions, risk rises with increasing dose. Typical antibiotic dose in ALBC used for treatment of PJI is much higher than the dose in FDA approved ALBC for infection prophylaxis, so there is concern regarding the ability of these locally delivered antibiotics to cause systemic effects, specifically renal toxicity. There are a number of case reports, but guidelines have not been set on appropriate dosing of ALBC.

Literature reporting no renal injury.

Sustained elevations above 2mg/l of serum tobramycin is not recommended. However, the threshold for renal toxicity is believed to be 6-12mg/l. One study reveals the mean level of tobramycin from drainage fluids after 1 hour is 103mg/l. The level in local tissues is highest in the first hour after spacer placement. This level dropped to a mean of 15.1mg/l after 48 hours. The local concentrations were maintained above the MIC for common orthopedic pathogenic bacteria, while the serum levels of tobramycin never exceeded 2.1mg/l. One patient from this study that had pre-existing renal dysfunction developed a transient rise in creatinine (Cr) that was returned to baseline by post-operative day 5. All other patients from this study had normal renal function throughout the study period (Sterling, Crawford, Potter, Koerbin, & Crawford, 2003).

Similar results were found in another study measuring the local and serum levels of vancomycin. Spacers were hand-mixed and included 4g of vancomycin and 4g of aztreonam per 40g batch of cement. The mean local vancomycin concentration from joint fluid peaked on post-operative day 1 at 1,538mg/l, while the range of serum vancomycin was only 0.1-1.6mg/l. No patients were found to have renal insufficiency in the 7 day post-operative period studied (Hsieh et al., 2006).

Evans (2004) conducted a study using 4g vancomycin and 4.6g of tobramycin per 40g of bone cement. The dose of antibiotic was chosen by using the maximum amount while still being

able to form the cement. Serum antibiotic levels were checked at random intervals post-operatively, more regularly in patients receiving IV antibiotics of similar class. No renal changes were noted during the 2-year follow up period (Evans, 2004).

Another high-dose study used up to 16g of vancomycin and 19.2g of gentamicin total (mean 10.5g vancomycin and 12.5g gentamicin). Out of the 34 patients studied, only 1 had a transient rise in serum Cr on post-operative day 1. This rise normalized by post-operative day 2. The elevated Cr could not specifically be contributed to the ALBC spacer, as parenteral antibiotics were not controlled for. Regardless, none of the patients showed clinically evident renal injury (Springer et al., 2004).

The studies discussed above achieved a very high local concentration of antibiotic well above the MIC for common PJI pathogens, while maintaining a low serum concentration of antibiotic. They also report no incidence of renal failure. The literature that does report renal injury with use of ALBC spacers consists mostly of case reports.

Literature reporting renal injury.

Recent literature includes several case reports of renal injury thought to be associated with ALBC spacers. Most of these case reports depict patients with established risk factors for developing renal injury. These risk factors include acute or chronic medical conditions predisposing or causing renal deficiency, concomitant administration of other potentially nephrotoxic medications, and perioperative incidences of hypovolemia.

For example, a case study by van Raaij et al. (2002) depicts an 83-year-old female patient that received an ALBC spacer containing 2g of gentamicin along with gentamicin loaded cement beads. Many factors that could have produced renal injury were described in this case. The patient had mild renal impairment on admission, had been taking NSAIDs prior to admission,

was receiving IV flucloxacillin switched to cefuroxime, received furosemide, had a severe decrease in urine production to 25ml/h for 3 days, and had a bleeding duodenal ulcer that was surgically operated on. Although her serum gentamicin level was 2.1mg/l 6 days after the ALBC spacer was placed, there are too many confounding variables to accurately associate the spacer with this patient's acute renal failure (ARF) (van Raaij, Visser, Vulto, & Verhaar, 2002).

Another case report involves an 85-year-old man. Prior to admission for PJI, he had a history of hypertension, diabetes mellitus, and renal insufficiency (serum Cr 1.6mg/dL). A 3.6g tobramycin and 3g cefazolin per batch ALBC was placed and ARF was noted 5 days later. During his hospitalization, he received IV cefazolin, levofloxacin, vancomycin, and furosemide. A random serum tobramycin concentration of 2mg/l was detected on postoperative day 16. Pre-hospitalization factors as well as concomitant use of potentially nephrotoxic medications do not allow for a conclusion of the ALBC spacer causing this patient's ARF (Curtis, Sternhagen, & Batts, 2005).

Dovas et al. (2008) presents a case report of ARF development in a 61-year-old woman with a history of hypertension and diabetes mellitus. This case report explicitly ruled out prerenal causes of ARF with a normal exam of renal vasculature, no documented episodes of hypotension, and a fractional excretion of sodium >1%. Post-renal causes were ruled out by a negative ultrasound of the kidneys. They also considered parenteral administration of nephrotoxic medications, but no signs of drug-induced AIN, such as eosinophilia or exanthema were evident. Renal function improved without discontinuing rifampicin or ciprofloxacin. This led the authors to consider the gentamicin-vancomycin ALBC as cause for ARF. However, serum levels of both antibiotics remained well below values associated with nephrotoxicity on all eight collections. Also, normalization of renal function was achieved without removing the

ALBC spacers. Although this case report carefully reasoned for all potential causes of ARF in their patient, low levels of serum antibiotics along with ARF resolution without removal of the spacer does not allow for absolute conclusion that ALBC spacers caused ARF (Dovas et al., 2008).

A report of AIN is described by McGlothan and Gosmanova (2012). This case report differs from most in that AIN was thought to be the cause of ARF as opposed to the more commonly reported acute tubular necrosis (ATN). This differentiation is important because as mentioned previously, aminoglycosides are associated with ATN, while vancomycin is associated with AIN. The patient received a spacer containing 3g vancomycin and 3g tobramycin. The patient was also receiving 1g of IV vancomycin every 12 hours. An additional potential cause of renal injury was described as a hypotensive event caused by decreased oral intake and frequent administration of opioid analgesics. Because vancomycin was delivered by both ALBC and IV routes, it cannot be differentiated as which caused AIN in this case (McGlothan & Gosmanova, 2012).

Patrick et al. (2006) describes two cases of ARF following ALBC spacers in total hip arthroplasties. Both patients had a number of other potential causes of renal injury. One patient had pre-existing mild renal dysfunction, developed sepsis and hypotension 17 days prior to developing ARF, and had received multiple perioperative drugs with risks of potential nephrotoxicity. The other patient was also receiving potentially nephrotoxic drugs, and had a prior history of hypertension, congestive heart failure, and nephrolithiasis. This patient also had episodes of vomiting and poor oral intake that could have contributed to the development of ARF (Patrick et al., 2006).

Maximal serum Cr levels in the case studies described above all occurred 6 days to 5 months after placement of the ALBC spacer. Referencing the drug elution properties of ALBC, peak concentration of antibiotic occurs within the first 3 days after implantation. The use of potentially nephrotoxic IV drugs, patient medical history of chronic medical conditions associated with renal injury, and perioperative incidences of hypovolemia or other causes of ARF are also mentioned in the case reports (Curtis et al., 2005; Dovas et al., 2008; McGlothan & Gosmanova, 2012; Patrick et al., 2006; van Raaij et al., 2002).

Methods

Research Design

A retrospective chart review was conducted with Institutional Review Board (IRB) approval. The control group consists of patients who underwent surgical revisions for aseptic reasons. The experimental group consists of patients who underwent surgical revisions due to infection, and received an ALBC spacer. Both the control group and experimental group received perioperative systemic antibiotics. By controlling for other causes of renal damage between the two groups, and comparing postoperative serum Cr and BUN changes, the correlation between high-dose ALBC spacers and renal injury was assessed.

Sampling Methods and Analysis

Patient charts were obtained by searching billing codes of procedures included in the two study groups. For those patients undergoing a two-stage exchange, the codes searched were CPT 27488, removal of knee prosthesis. For those patients undergoing routine revision, the CPT 27486 and 27487 was searched. Patients who underwent the procedure between January 2013 and January 2015 were selected. SPSS statistical package was used for the data analysis. Paired t-test was used for determination of significance within each group, comparing pre-operative and post-operative values. The independent t-test was used for determination of significance when comparing values between the two groups.

Variables Collected

The following variables were collected into a Microsoft Excel spreadsheet: surgical site, procedure, sex, age, estimated blood loss (EBL) during surgery, volume and type of intra-operative fluid replacement, dose and type of intra-operative antibiotics, dose and type of post-operative antibiotics, dose and type of antibiotics in cement spacer, minimum and maximum

systolic and diastolic intra-operative blood pressures, and pre and postoperative lab values (serum Cr, blood urea nitrogen (BUN), and hemoglobin (Hgb)). The postoperative serum Cr and BUN values were selected by using the highest value collected in the first 3 days after placement of the antibiotic-loaded cement spacer.

Preparation of Bone Cement

Powdered antibiotics were mixed with 40g batches of bone cement. Vancomycin alone, tobramycin alone, or combined vancomycin and tobramycin was used. Typical dosing was 5g vancomycin and 2.4g tobramycin per 40g batch of cement, with 4-7 batches of cement being used for each surgery.

Results

Refer to Tables 1 through 4 for a summary of results found. It is also of importance to mention that there are no outliers in this data set.

Serum Creatinine

Mean preoperative Cr (1.11 ±0.4) is not statistically different than the mean postoperative Cr (1.09 ±0.37) in the experimental group (those who received ALBC spacers). There is also no significant difference in mean preoperative and postoperative Cr values in the control group (1.03 ±0.39 and 0.97 ±0.44, respectively). There is no difference between preoperative and postoperative Cr values within each group, nor is there any difference between the control and experimental group.

Blood Urea Nitrogen

Mean preoperative BUN (19.3 ±8.47) is not statistically different than the mean postoperative BUN (16.4 ±7.07) in the experimental group (those who received ALBC spacers). There is also no significant difference in mean preoperative and postoperative BUN values in the control group (20.4 ±8.3 and 17.1 ±8.73, respectively). There is no difference between preoperative and postoperative BUN values within each group, nor is there any difference between the control and experimental group.

Hemoglobin

Mean preoperative Hgb (10.7 ±1.35) is statistically different than the mean postoperative Hgb (8.87 ±1.22) in the in the experimental group (those who received ALBC spacers). There is also a significant difference in mean preoperative and postoperative Hgb values in the control group (12.8 ±1.88 and 10.1 ±1.43, respectively). Both groups have a significant decrease in Hgb after surgery. There is also a significant difference in both pre and postoperative Hgb values

between the control and experimental group. The experimental group has lower preoperative Hgb values than the control group and both groups have a decrease in Hgb after surgery, so the experimental group ended with a lower postoperative Hgb value as well.

Hemodynamics

Hemodynamics measured include intraoperative estimated blood loss (EBL) and minimum and maximum systolic blood pressure (SBP) and diastolic blood pressure (DBP). Refer to Table 3 for a summary of the data. No significant difference in minimum and maximum measures of SBP or DBP was seen between the two groups. There was not a significant difference ($p=0.09$) in intraoperative EBL between the experimental (442 ±504ml) and control (251 ±344ml) groups.

Antibiotics Used

Refer to Table 4 for a list of perioperative antibiotics used. Data collected on antibiotic administration includes those given locally in the ALBC spacer, systemically during surgery, and systemically post-operatively. Systemic administration includes both IV and oral routes. Antibiotics listed are all inclusive during the perioperative period, not excluding antibiotics prescribed for reasons other than PJI prevention or treatment.

Discussion

The current literature includes many case reports of ARF while an ALBC spacer is implanted. However, the authors mention concomitant IV antibiotic use as a limitation and possible cause of ARF. Prophylactic IV antibiotics are proven to reduce infection rates for patients undergoing total joint arthroplasty. For this reason, it is unethical to design a study eliminating IV antibiotics. There are many total joint revisions surgeries being done for aseptic reasons; prosthesis loosening or wear, instability, stiffness, and fractures. Aseptic revision surgeries allow for an ideal control group.

To the writers' knowledge, no published study has compared renal function after placement of an ALBC spacer, to renal function after an aseptic revision surgery without ALBC. This is of significance, because both groups require perioperative administration of IV antibiotics. With the major factor of IV antibiotic administration being controlled for, it is reasonable to determine whether ALBC is associated with renal injury. In our study of 32 patients who received ALBC and IV antibiotics, and 28 patients who received only IV antibiotics, we found no difference within or between the groups' pre and postoperative Cr and BUN values. Dosing was typically 7.4g of antibiotics per 40g batch of cement (5g of vancomycin and 2.4g of tobramycin), with total doses of up to 77.4g of antibiotic per spacer.

One published paper also accounted for concurrent IV antibiotic use in their study. This retrospective study looked at charts of 84 patients undergoing ALBC spacer placement. They then set a definition for acute kidney injury (AKI) as being more than a 50% rise in serum Cr from that patient's preoperative serum Cr value. The value also had to exceed 1.4 mg/dL, and occur within 3 months after surgery. With this criteria, they found a 17% incidence of AKI

significantly associated with ALBC tobramycin dose. They also found that the use of IV aminoglycosides or vancomycin was not associated with AKI (Menge et al., 2012).

The study by Menge et al. (2012) differs from ours. Both studies employed high-dose spacers (greater than 4g of antibiotic per batch of cement), however the composition of antibiotics differed. Menge et al. used 4g of tobramycin, where we typically used 2.4g of tobramycin. While our study compared two groups, Menge et al. focused on one group of patients undergoing ALBC spacer placement.

Our study had several limitations, mostly attributable to the aspect of data collection via a retrospective chart review. As would be possible in a prospective study, regular interval recordings of serum Cr were not available when reviewing patient charts. Also, four patients from the control group did not have recent preoperative lab values recorded. We believe the patients in our study represent a typical population of patients, with some healthy patients and some with chronic conditions. We also had 23 patients with mild renal dysfunction (serum Cr >1.2mg/dL for males, >1.1mg/dL for females) prior to ALBC placement. Cr was only followed for 3 days post-operatively, and could miss a late renal incident. However, given that the doses of antibiotics are much higher eluted from ALBC placement in the first few days than later, it was selected as a reasonable point of which to measure.

The dosages of total antibiotics used were not constant either. For those patients with minimal defects in bone, only two to three 40g batched of cement were used. Others with large bone defects used many batches of cement. However, it still should be noteworthy that even those cases with very high local antibiotic use, there was no significant increase in Cr in any case.

Conclusion

The efficacy of ALBC spacers in the treatment of PJI has been thoroughly researched and accepted as standard of care. However, the safety of using high-dose ALBC spacers has been researched, but not yet accepted. Most previous studies rely on case reports, while few follow a retrospective cohort. This retrospective study shows that patients undergoing ALBC placement have the same risk as those undergoing revision for Cr rise. Therefore, ALBC does not seem to increase the risk of renal injury.

References

Anguita-Alonso, P., Hanssen, A. D., Osmon, D. R., Trampuz, A., Steckelberg, J. M., & Patel, R. (2005). High rate of aminoglycoside resistance among staphylococci causing prosthetic joint infection. *Clinical Orthopaedics and Related Research, 439*, 43-47.

Bayston, R., & Milner, R. D. (1982). The sustained release of antimicrobial drugs from bone cement. An appraisal of laboratory investigations and their significance. *Journal of Bone and Joint Surgery (British Volume), 64*(4), 460-464.

Bistolfi, A., Massazza, G., Verne, E., Masse, A., Deledda, D., Ferraris, S., . . . Crova, M. (2011). Antibiotic-loaded cement in orthopedic surgery: A review. *ISRN Orthop, 2011*, 290851. doi:10.5402/2011/290851

Cerretani, D., Giorgi, G., Fornara, P., Bocchi, L., Neri, L., Ceffa, R., . . . Ritter, M. A. (2002). The in vitro elution characteristics of vancomycin combined with imipenem-cilastatin in acrylic bone-cements: A pharmacokinetic study. *Journal of Arthroplasty, 17*(5), 619-626.

Cui, Q., Mihalko, W. M., Shields, J. S., Ries, M., & Saleh, K. J. (2007). Antibiotic-impregnated cement spacers for the treatment of infection associated with total hip or knee arthroplasty. *Journal of Bone and Joint Surgery (American Volume), 89*(4), 871-882. doi:10.2106/JBJS.E.01070

Curtis, J. M., Sternhagen, V., & Batts, D. (2005). Acute renal failure after placement of tobramycin-impregnated bone cement in an infected total knee arthroplasty. *Pharmacotherapy, 25*(6), 876-880.

Dovas, S., Liakopoulos, V., Papatheodorou, L., Chronopoulou, I., Papavasiliou, V., Atmatzidis, E., . . . Stefanidis, I. (2008). Acute renal failure after antibiotic-impregnated bone cement treatment of an infected total knee arthroplasty. *Clinical Nephrology, 69*(3), 207-212.

Dunbar, M. J. (2009). Antibiotic bone cements: their use in routine primary total joint arthroplasty is justified. *Orthopedics, 32*(9). doi:10.3928/01477447-20090728-20

Durbhakula, S. M., Czajka, J., Fuchs, M. D., & Uhl, R. L. (2004). Antibiotic-loaded articulating cement spacer in the 2-stage exchange of infected total knee arthroplasty. *Journal of Arthroplasty, 19*(6), 768-774.

Evans, R. P. (2004). Successful treatment of total hip and knee infection with articulating antibiotic components: A modified treatment method. *Clinical Orthopaedics and Related Research*(427), 37-46.

Fehring, T. K., Odum, S., Calton, T. F., & Mason, J. B. (2000). Articulating versus static spacers in revision total knee arthroplasty for sepsis. The Ranawat Award. *Clinical Orthopaedics and Related Research*(380), 9-16.

Gogia, J. S., Meehan, J. P., Di Cesare, P. E., & Jamali, A. A. (2009). Local antibiotic therapy in osteomyelitis. *Seminars in Plastic Surgery, 23*(2), 100-107. doi:10.1055/s-0029-1214162

Goldstein, W. M., Kopplin, M., Wall, R., & Berland, K. (2001). Temporary articulating methylmethacrylate antibiotic spacer (TAMMAS). A new method of intraoperative manufacturing of a custom articulating spacer. *Journal of Bone and Joint Surgery (American Volume), 83-A Suppl 2 Pt 2*, 92-97.

Greene, N., Holtom, P. D., Warren, C. A., Ressler, R. L., Shepherd, L., McPherson, E. J., & Patzakis, M. J. (1998). In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from Simplex and Palacos. *American Journal of Orthopedics (Belle Mead, N.J.), 27*(3), 201-205.

Ha, C. W. (2006). A technique for intraoperative construction of antibiotic spacers. *Clinical Orthopaedics and Related Research, 445*, 204-209. doi:10.1097/01.blo.0000201161.52196.c5

Haddad, F. S., Masri, B. A., Campbell, D., McGraw, R. W., Beauchamp, C. P., & Duncan, C. P. (2000). The PROSTALAC functional spacer in two-stage revision for infected knee replacements. Prosthesis of antibiotic-loaded acrylic cement. *Journal of Bone and Joint Surgery (British Volume), 82*(6), 807-812.

Hanssen, A. D., Osmon, D. R., & Patel, R. (2005). Local antibiotic delivery systems: where are we and where are we going? *Clinical Orthopaedics and Related Research*(437), 111-114.

Hanssen, A. D., & Rand, J. A. (1999). Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. *Instructional Course Lectures, 48*, 111-122.

Heck, D., Rosenberg, A., Schink-Ascani, M., Garbus, S., & Kiewitt, T. (1995). Use of antibiotic-impregnated cement during hip and knee arthroplasty in the United States. *Journal of Arthroplasty, 10*(4), 470-475.

Henry, S. L., & Galloway, K. P. (1995). Local antibacterial therapy for the management of orthopaedic infections. Pharmacokinetic considerations. *Clinical Pharmacokinetics, 29*(1), 36-45. doi:10.2165/00003088-199529010-00005

Hofmann, A. A., Goldberg, T., Tanner, A. M., & Kurtin, S. M. (2005). Treatment of infected total knee arthroplasty using an articulating spacer: 2- to 12-year experience. *Clinical Orthopaedics and Related Research*(430), 125-131.

Hsieh, P. H., Chang, Y. H., Chen, S. H., Ueng, S. W., & Shih, C. H. (2006). High concentration and bioactivity of vancomycin and aztreonam eluted from Simplex cement spacers in two-stage revision of infected hip implants: A study of 46 patients at an average follow-

up of 107 days. *Journal of Orthopaedic Research, 24*(8), 1615-1621. doi:10.1002/jor.20214

Hsu, Y. C., Cheng, H. C., Ng, T. P., & Chiu, K. Y. (2007). Antibiotic-loaded cement articulating spacer for 2-stage reimplantation in infected total knee arthroplasty: A simple and economic method. *Journal of Arthroplasty, 22*(7), 1060-1066. doi:10.1016/j.arth.2007.04.028

James, A., & Larson, T. (2015). Acute renal failure after high-dose antibiotic bone cement: Case report and review of the literature. *Renal Failure, 37*(6), 1061-1066. doi:10.3109/0886022X.2015.1052949

Jiranek, W. A., Hanssen, A. D., & Greenwald, A. S. (2006). Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement. *Journal of Bone and Joint Surgery (American Volume), 88*(11), 2487-2500. doi:10.2106/JBJS.E.01126

Kahlmeter, G. (1979). Gentamicin and tobramycin. Clinical pharmacokinetics and nephrotoxicity. Aspects on assay techniques. *Scandinavian Journal of Infectious Diseases. Supplementum*(18), 1-40.

Koo, K. H., Yang, J. W., Cho, S. H., Song, H. R., Park, H. B., Ha, Y. C., . . . Kim, Y. H. (2001). Impregnation of vancomycin, gentamicin, and cefotaxime in a cement spacer for two-stage cementless reconstruction in infected total hip arthroplasty. *Journal of Arthroplasty, 16*(7), 882-892. doi:10.1054/arth.2001.24444

Kurtz, S. M., Lau, E., Schmier, J., Ong, K. L., Zhao, K., & Parvizi, J. (2008). Infection burden for hip and knee arthroplasty in the United States. *Journal of Arthroplasty, 23*(7), 984-991. doi:10.1016/j.arth.2007.10.017

Lewis, G., & Janna, S. (2004). The in vitro elution of gentamicin sulfate from a commercially available gentamicin-loaded acrylic bone cement, VersaBond AB. *J Biomed Mater Res B Appl Biomater, 71*(1), 77-83. doi:10.1002/jbm.b.30069

Masri, B. A., Duncan, C. P., & Beauchamp, C. P. (1998). Long-term elution of antibiotics from bone-cement: An in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. *Journal of Arthroplasty, 13*(3), 331-338.

McGlothan, K. R., & Gosmanova, E. O. (2012). A case report of acute interstitial nephritis associated with antibiotic-impregnated orthopedic bone-cement spacer. *Tennessee Medicine, 105*(9), 37-40, 42.

Meek, R. M., Masri, B. A., Dunlop, D., Garbuz, D. S., Greidanus, N. V., McGraw, R., & Duncan, C. P. (2003). Patient satisfaction and functional status after treatment of infection at the site of a total knee arthroplasty with use of the PROSTALAC articulating spacer. *Journal of Bone and Joint Surgery (American Volume), 85-A*(10), 1888-1892.

Menge, T. J., Koethe, J. R., Jenkins, C. A., Wright, P. W., Shinar, A. A., Miller, G. G., & Holt, G. E. (2012). Acute kidney injury after placement of an antibiotic-impregnated cement spacer during revision total knee arthroplasty. *Journal of Arthroplasty, 27*(6), 1221-1227 e1221-1222. doi:10.1016/j.arth.2011.12.005

Namba, R. S., Chen, Y., Paxton, E. W., Slipchenko, T., & Fithian, D. C. (2009). Outcomes of routine use of antibiotic-loaded cement in primary total knee arthroplasty. *Journal of Arthroplasty, 24*(6 Suppl), 44-47. doi:10.1016/j.arth.2009.05.007

Nettrour, J. F., Polikandriotis, J. A., Bernasek, T. L., Gustke, K. A., & Lyons, S. T. (2013). Articulating spacers for the treatment of infected total knee arthroplasty: Effect of

antibiotic combinations and concentrations. *Orthopedics, 36*(1), e19-24. doi:10.3928/01477447-20121217-13

Neut, D., van de Belt, H., van Horn, J. R., van der Mei, H. C., & Busscher, H. J. (2003). The effect of mixing on gentamicin release from polymethylmethacrylate bone cements. *Acta Orthopaedica Scandinavica, 74*(6), 670-676. doi:10.1080/00016470310018180

Park, S. J., Song, E. K., Seon, J. K., Yoon, T. R., & Park, G. H. (2010). Comparison of static and mobile antibiotic-impregnated cement spacers for the treatment of infected total knee arthroplasty. *International Orthopaedics, 34*(8), 1181-1186. doi:10.1007/s00264-009-0907-x

Patrick, B. N., Rivey, M. P., & Allington, D. R. (2006). Acute renal failure associated with vancomycin- and tobramycin-laden cement in total hip arthroplasty. *Annals of Pharmacotherapy, 40*(11), 2037-2042. doi:10.1345/aph.1H173

Penner, M. J., Masri, B. A., & Duncan, C. P. (1996). Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. *Journal of Arthroplasty, 11*(8), 939-944.

Pitto, R. P., Castelli, C. C., Ferrari, R., & Munro, J. (2005). Pre-formed articulating knee spacer in two-stage revision for the infected total knee arthroplasty. *International Orthopaedics, 29*(5), 305-308. doi:10.1007/s00264-005-0670-6

Springer, B. D., Lee, G.-C., Osmon, D., Haidukewych, G. J., Hanssen, A., & Jacofsky, D. J. (2004). Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. *Clinical Orthopaedics and Related Research*(427), 47-51.

Sterling, G. J., Crawford, S., Potter, J. H., Koerbin, G., & Crawford, R. (2003). The pharmacokinetics of Simplex-tobramycin bone cement. *Journal of Bone and Joint Surgery (British Volume), 85*(5), 646-649.

Stevens, C. M., Tetsworth, K. D., Calhoun, J. H., & Mader, J. T. (2005). An articulated antibiotic spacer used for infected total knee arthroplasty: A comparative in vitro elution study of Simplex and Palacos bone cements. *Journal of Orthopaedic Research, 23*(1), 27-33. doi:10.1016/j.orthres.2004.03.003

Trezies, A., Parish, E., Dixon, P., & Cross, M. (2006). The use of an articulating spacer in the management of infected total knee arthroplasties. *Journal of Arthroplasty*, *21*(5), 702-704. doi:10.1016/j.arth.2005.05.033

Tsukayama, D. T., Goldberg, V. M., & Kyle, R. (2003). Diagnosis and management of infection after total knee arthroplasty. *Journal of Bone and Joint Surgery (American Volume), 85-A Suppl 1,* S75-80.

van Raaij, T. M., Visser, L. E., Vulto, A. G., & Verhaar, J. A. (2002). Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. *Journal of Arthroplasty, 17*(7), 948-950.

Tables

Table 1.

	Experimental Group: ALBC spacer			
	Pre-operative	**Post-operative**	**P-value**	**Mean difference**
n	33	33		
Cr	1.11 (0.40)	1.09 (0.37)	0.72	0.02 [-0.09 – 0.13]
BUN	19.3 (8.47)	16.4 (7.07)	0.05	2.85 [0.07 – 5.62]
Hgb	10.7 (1.35)	8.87 (1.22)	<0.001	1.79 [1.33 – 2.25]
	Control Group: Revision Group/No ALBC			
	Pre-operative	**Post-operative**	**P-value**	**Mean difference**
n	25	25		
Cr	1.03 (0.39)	0.97 (0.44)	0.055	0.06 [-0.001, 0.12]
BUN	20.4 (8.3)	17.1 (8.73)	0.016	3.36 [0.68, 6.04]
Hgb	12.8 (1.88)	10.1 (1.43)	<0.001	2.64 [2.22, 3.07]

Comparison within groups of pre-operative versus post-operative laboratory values. Given as mean (Sample Standard Deviation) or mean difference [95% confidence interval].

Table 2.

	Pre-operative			
	ALBC Group	**No ALBC Group**	**P-value**	**Mean difference**
n	33	25		
Cr	1.11 (0.40)	1.03 (0.39)	0.45	0.08 [-0.13, 0.29]
BUN	19.3 (8.47)	20.5 (8.3)	0.60	-1.17 [-5.6, 3.2]
Hgb	10.7 (1.35)	12.8 (1.88)	<0.001	-2.1 [-2.9, -1.3]
	Post-operative			
	ALBC group	**No ALBC Group**	**P-value**	**Mean difference**
n	33	29		
Cr	1.09 (0.37)	0.97 (0.44)	0.20	0.13 [-.07, 0.33]
BUN	16.4 (7.07)	17.1 (8.73)	0.55	-0.75 [-4.6, 3.1]
Hgb	8.87 (1.22)	10.1 (1.43)	<0.001	-1.26 [-1.9, -0.6]

Comparison between groups of pre-operative versus post-operative laboratory values. Given as mean (Sample Standard Deviation) or mean difference [95% confidence interval].

Table 3.

Intra-operative Hemodynamics

	ALBC group	No ALBC Group	P-value
minSBP	81.6 (12.1)	85.3 (10.0)	0.20
maxSBP	155.5 (23.5)	151.0 (33.0)	0.54
minDBP	43.0 (11.7)	43.0 (6.9)	1.00
maxDBP	88.7 (16.6)	90.7 (17.6)	0.65
EBL	442 (504)	251 (344)	0.09

Comparison between groups of intraoperative blood pressures (mmHg) and estimated blood loss (ml). Given as mean (Sample Standard Deviation).

Table 4.

Antibiotics Used

	Systemic Intra-operative	Systemic Post-operative	Bone Cement
Tobramycin			27 (7.2-32.4g)
Vancomycin	23 (1000-2250mg)	28 (500-3000mg/day)	32 (4-45g)
Clindamycin	7 (600mg)	7 (1800mg/day)	
Daptomycin	1 (500mg)	2 (500-750mg/day)	
Cefazolin	36 (1-3g)	30 (3-6g/day)	
Ceftriaxone	3 (1-2g)	7 (1-2g/day)	
Cefepime		4 (1-2g/day)	
Cephalexin		1 (4 capsules/day)	
Ciprofloxacin		2 (400-800mg/day)	
Levofloxacin		2 (500-750mg/day)	
Amoxicillin		1 (500mg/day)	
Ampicillin		1 (4000mg/day)	
Rifampin		2 (600mg/day)	
Bactrim	1 (1 tab)	3 (2 tabs/day)	
Zosyn	4 (3.375g)	7 (10.125-13.5g/day)	
Linezolid		1 (1200mg/day)	
Unasyn		1 (6000mg/day)	

Variability of antibiotics used listed as number of patients who received (minimum-maximum doses given).

Abstract

Objective: The purpose of this study is to assess the safety of high-dose antibiotic-loaded bone cement (ALBC) spacers in regards to renal injury, while controlling for IV antibiotic administration.

Method: We conducted a retrospective chart review collecting variables for two groups, control (revision total joint arthroplasty without ALBC, n=29) and experimental (ALBC spacer placement, n=33). Variables collected include surgical site, procedure, comorbidity list, sex, age, estimated blood loss during surgery, volume and type of intra-operative fluid replacement, dose and type of intra-operative antibiotics, dose and type of post-operative antibiotics, dose and type of antibiotics in cement spacer, minimum and maximum systolic and diastolic intra-operative blood pressures, and pre and postoperative lab values (serum creatinine, blood urea nitrogen, and hemoglobin). Statistical tests were run to determine any significant differences within or between the groups in regard to serum creatinine (Cr), blood urea nitrogen (BUN), or hemoglobin (Hgb).

Results: No difference was found between preoperative and postoperative BUN or Cr values within each group, nor between the control and experimental group. There was a significant difference within and between the groups' pre and postoperative Hgb values, with the experimental group values being lower than the control.

Conclusion: The results of this study allow us to reasonably conclude that high-dose ALBC spacers do not seem to cause renal injury.