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Intrawound vancomycin in primary hip and knee arthroplasty: a safe and cost-effective means to decrease early periprosthetic joint infection

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ABSTRACT

Background: Periprosthetic joint infection (PJI) is a devastating complication after hip and knee arthroplasty. Intrawound vancomycin has been described extensively in the spine literature; however, information regarding use in arthroplasty is limited. We investigate the efficacy and safety of intrawound vancomycin in arthroplasty surgery.

Methods: All primary total hip and knee arthroplasty cases (n = 460) performed by a single surgeon from April 2016 to October 2017 were reviewed. Starting in October 2016, intrawound vancomycin was used in all total joints. Baseline characteristics, infection rates, 90-day readmission, and other complications were compared between untreated subjects and those who received intrawound vancomycin. In addition, cost data were considered. Mean follow-up durations for the control and vancomycin groups were 11.3 and 7.7 months, respectively.

Results: Baseline characteristics and comorbidities were similar for the control (n = 112) and vancomycin groups (n = 348). The vancomycin cohort demonstrated decreased both overall infection rate (0.57% vs 2.7%; $P = .031$) and PJI rate (0.29% vs 2.7%; $P = .009$) compared with the untreated group. There was no statistical difference in incidence of ototoxicity or acute kidney injury. Although there was no difference in overall 90-day readmission rate, the vancomycin subset demonstrated lower readmission rate due to infection (0.57% vs 2.7%; $P = .031$). Based on the cost of vancomycin powder and calculated number needed to treat (NNT = 47.5), the cost to prevent 1 infection with the addition of intrawound vancomycin was $816.

Conclusions: These findings suggest that intrawound vancomycin may be a safe, cost-effective means that shows promise in reducing PJI in early follow-up. Future prospective studies are warranted.

Introduction

The utilization of hip and knee arthroplasty has been steadily increasing due to an active aging population. It is projected that the number of total hip and knee replacements will approach greater than 570,000 and 3.4 million, respectively, by 2030 [1]. Despite substantial research and robust multimodal programs to mitigate infection, periprosthetic joint infection (PJI) continues to be a devastating complication to patients and the health-care system. PJI rates have continued to average between 0.5 and 2% [2-4], and it is estimated that by 2020, $1.62 billion will be spent on revisions for infection in the United States alone [5].

Many PJI prevention strategies have been developed ranging from preoperative screening, intraoperative methods, and postoperative intervention with varying levels of success. One such prevention strategy has been the use of intraoperative vancomycin powder. Although the safety and effectiveness of intraoperative vancomycin powder has been well described in the spine surgery literature [6,7], information regarding its use in the arthroplasty setting is almost nil.

Several studies do exist supporting the use of intrawound antibiotics for total joint arthroplasty in animal models. Separate in vivo rat investigations performed by Cavanaugh et al. [8] and Edelstein et al. [9] demonstrated the effectiveness of intrawound

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antibiotics on clearing *Staphylococcus aureus* from contaminated femoral implants. Johnson et al. [10] recently published data supporting the safety of vancomycin powder placed intraarticularly after arthroplasty. Although there is basic science and spine literature supporting the use of intrawound vancomycin powder, there is a paucity of clinical data in its efficacy for prevention of PJI.

The most common pathogen in infected total joint arthroplasty is staphylococcal species [11], and an increasing incidence of methicillin-resistant *S. aureus* has made vancomycin a reasonable choice for intrawound antibiotics [12]. Potential benefits of intrawound antibiotics include maximizing local bactericidal concentrations while minimizing adverse systemic effects. Despite these potential benefits, there are numerous questions regarding this practice, including safety information on seroma formation, bearing wear, nephrotoxicity, and ototoxicity. Further questions exist to whether this practice truly decreases infection rates.

The objective of this study is to determine the impact of intrawound vancomycin powder in primary total hip and knee arthroplasty on early PJI rate as the primary outcome metric. Secondary outcomes include safety metrics based on 90-day all-cause readmissions, mechanical complications, nephrotoxicity, ototoxicity, and cost data. We hypothesized that the routine use of intrawound vancomycin in primary total hip and knee arthroplasty will be a cost-effective means to decrease early PJI without increase in complications or 90-day readmission at our large-volume, academic, teaching hospital.

Material and methods

This retrospective investigation was performed in accordance with our institutional review board. Operative records for patients having undergone primary total hip or knee arthroplasty from April 2016 through October 2017 were analyzed for a single fellowship-trained arthroplasty surgeon. This timeline was selected to use contemporary data with an updated PJI prevention program rather than historical data which may introduce confounding variables. Furthermore, 1 year of clinical practice, October 2016 to October 2017, was chosen as the experimental consecutive cohort with intrawound vancomycin to be able to report all infection and complications that may occur over a year of clinical practice. All surgeries were performed at the same institution, which is a large-volume, urban, teaching hospital. Inclusion criteria included patients undergoing primary total hip or knee arthroplasty with indication of osteoarthritis, osteonecrosis, posttraumatic arthritis, as well as inflammatory arthropathies. Patients were excluded if they were undergoing a revision surgery or had less than 90-day follow-up. Standard patient preoperative screening measures included body mass index < 40, hemoglobin A1C < 7, appropriate dentition, smoking cessation, nasal methicillin-resistant S. aureus screening, and optimization of medical comorbidities such as renal failure, chronic obstructive pulmonary disease, congestive heart failure, and anticoagulation.

Preoperatively, patients received dosed intravenous cephalosporin within 1 hour before incision; however, intravenous vancomycin was administered instead for those with a history of anaphylaxis to penicillin. Hoods and cloth gowns were used during surgery. After hardware implantation, a 3-minute dilute Betadine soak of the surgical wound was performed, followed by irrigation using 1 liter of normal saline with 50,000 units of bacitracin on all patients. Starting in October 2016, the principle surgeon routinely applied 1 g of vancomycin powder on the surgical wound before closure in primary hip and knee arthroplasties. The antibiotic powder was applied on the joint and surrounding muscle, fascia, and subcutaneous tissues. No antibiotics were applied in bone cement in any hip or knee. Subcutaneous vicryl suture followed by subcuticular monocryl closure and dermabond was routinely used for hip closure, and staples with occlusive dressing (Aquacel Ag; ConvaTec, Bridgewater, NJ) were used for knee replacement.

From April 2016 through October 2017, a total of 460 primary total hip and knee arthroplasties were performed by the primary surgeon who satisfied inclusion and exclusion criteria (217 total knee arthroplasties (TKA) and 243 total hip arthroplasties) (Table 1, Supplementary data). One hundred twelve consecutive surgeries without vancomycin powder were used as the control cohort, followed by 348 consecutive surgeries used as the experimental intrawound vancomycin group. The mean follow-up period for the control group was 11.3 months (range, 3.0-25.6 months) and that for the vancomycin group was 7.7 months (range, 3.2-19.1 months) ($P < .01$).

Our institution participates in the Center for Disease Control and Prevention's National Healthcare Safety Network for surveillance and reporting of deep and superficial surgical site infections (SSIs) [13]. A review of this database located all patients who had been identified as having an SSI within the designated timeline. In addition, operative records for all patients of the primary surgeon were reviewed to ensure that all infections were in fact captured. Subjects were grouped based on whether they did receive intrawound vancomycin (October 2016 to October 2017) or did not (April 2016 to September 2016). Information regarding patient demographics, baseline characteristics, comorbidities, and operative data was collected. Culture-positive superficial wound infections and deep subfascial joint infections (PJI's) were included. Superficial wound infections were routinely treated with irrigation, debridement, and closure, followed by a course of antibiotics, whereas PJI's were treated with 1- or 2-stage revision procedures depending on chronicity. Minor postoperative wound complications such as stitch abscesses or erythema that were treated with routine postoperative wound care were not considered wound infections and thus not included in the infection data. Return to the operating room for hematoma or seroma that met Musculoskeletal Infection Society criteria for infection or simply had a single positive culture was included in the infection data. In addition, postoperative submetrics including 90-day all-cause readmission, acute kidney injury (AKI), and ototoxicity were recorded. AKI was considered an increase of >0.3 mg/dL in serum creatinine postoperatively. Student t-test was used to compare numerical variables, whereas Fischer exact test was used to compare categorical variables.

Results

Patients in the control and vancomycin groups were similar in terms of demographics, comorbidities, and other operative variables to those with (n = 348) and without vancomycin (n = 112) (Table 2, Supplementary data). The control primary arthroplasty group had an overall infection rate of 2.7%, which included 3 PJI's and 0 superficial infections. The vancomycin powder cohort had an overall infection rate of 0.57%, which included 1 PJI and 1 superficial infection (Table 3, Supplementary data). The PJI rate in the vancomycin group was 0.29%. The decrease in overall infection rate from 2.7% to 0.57% ($P = .031$) and PJI rate from 2.7% to 0.29% ($P = .009$) with the addition of vancomycin powder were both statistically significant. There was no significant difference in the incidence of postoperative AKI or ototoxicity. There was also no significant difference in sterile seroma incidence with zero and 1 observed in the control and vancomycin cohorts, respectively, ($P > .05$). The control group had a 5.4% 90-day all-cause hospital readmission rate, whereas the vancomycin group had a rate of 3.2% ($P = .14$). When analyzing various factors for readmission, there was no statistical difference in readmission rate for noninfectious wound issues, mechanical complications, or medical issues unrelated to the index

procedure ($P > .05$; Table 4, Supplementary data). The control group had a statistically higher 90-day readmission rate due to infection than the vancomycin subset (2.7% vs 0.57%; $P = .031$). Table 5 (Supplementary data) shows detailed information regarding the cases of infections in both subsets, including bacteria cultured, time to repeat surgery, risk factors, and clinical outcome. One TKA patient in the control group had multiple recurrences of infection and required an eventual above-knee amputation. The remaining 4 infections cleared clinically after surgical intervention.

Discussion

The use of intrawound vancomycin powder has been well described in the spine surgery literature with regard to safety and efficacy in reducing SSI [6,7,14]. With regard to total joints, Otte et al. [15] demonstrated a reduced infection rate for hip and knee arthroplasty with the addition of vancomycin powder but only in the revision setting. Dial et al. [16] recently showed a decreased infection rate in a series of primary hip arthroplasties but did find an increased incidence of associated sterile seroma. Results of our investigation demonstrate a significantly decreased overall infection rate (superficial plus PJI) from 2.7% to 0.57% for primary total hip and knee arthroplasty with the addition of intrawound vancomycin. More notably, the most significant reduction observed was in PJI with an infection rate of 0.29% ($P = .009$).

The PJI rate for control primary cases in our series was found to be 2.7%, which is slightly higher than the reported 0.5%-2.0% described in the literature [2-4]. This increased rate is thought to be partly attributable to the patient population seen at our institution, which is a high-volume tertiary referral center. Patients in our cohort had an average body mass index > 30, 11.3% rate of active smokers, and 10.4% rate of diabetes mellitus, all of which are known PJI risk factors after arthroplasty surgery [17-19]. In addition, patients of lower socioeconomic status have been shown to have a higher incidence of PJI, and our institution is one of the sole providers for Medicaid patients in the area [20]. Since the conclusion of the study, smoking cessation was implemented as a standard practice, and negative urine nicotine has been required at preanesthesia testing. The increased infection rate in the control group as noted previously was the impetus to evaluate a new strategy to prevent PJI, intrawound vancomycin powder.

Concerns have been raised regarding the safety of using intrawound vancomycin. Studies have demonstrated low morbidity associated with intrawound vancomycin in surgical spine cases [21]. Similarly, an investigation by Johnson et al. [10] attested to the safety of using 2 g of intraarticular vancomycin powder in arthroplasty surgery. They found highly therapeutic vancomycin concentrations in the local tissue yet at low systemic levels. Our results are in agreement with the previous published data on safety, as there was no significant difference in postoperative AKI or ototoxicity between the control and vancomycin groups. There was a low threshold in this study to include AKI as a complication with an increase in creatinine of 0.3 mg/dL. The 1 patient in the vancomycin group who experienced AKI had a correction of creatinine to baseline after 24 hours of fluid hydration with no long-term nephrotoxic sequelae. There was also no statistically significant difference in seroma formation in the vancomycin group. There was 1 patient in the vancomycin group with a seroma that required an irrigation and debridement in the postoperative period, who had 5 negative cultures and was not treated with antibiotics. The patient did heal uneventfully, and no further surgical intervention was required. The authors suggest that this work contributes to the existing literature on safety regarding the use of intrawound vancomycin powder.

The efficacy of intrawound vancomycin powder has been debated in the spine literature. Strom et al. [22] showed that the implementation of intrawound vancomycin powder is particularly beneficial in decreasing infection rates in posterior cervical fusion surgery when current high rates exist. In their study, the infection rate decreased from 10% to 2.5%. Other studies from the spine literature show that if the existing infection rate is low, then the routine use of vancomycin powder is of little benefit [23]. The authors of this manuscript cannot comment on what infection rate should trigger a root cause analysis in total joint arthroplasty, but can provide just a general guideline that if the existing infection rate is >2% [4], then an investigation with tracked solutions should be performed locally. This is the scenario that prompted the investigation and potential solution to the increased infection rate at the authors' institution (2.7%). Since the single change to protocol in October 2016, only one patient had a PJI in that year with an infection rate of 0.29%. The single infection occurred in a patient with rheumatoid arthritis who unknowingly used recreational amphetamines which may have contributed to his delayed wound healing and subsequent PJI. Despite routine drug use, the patient was included in the study in an effort to be generalizable to other surgeon's practices and for full transparency. The authors attribute the lower infection rate in this study to the use of intrawound vancomycin, as other confounders such as surgeon technique, implants, facility, and multimodal PJI prevention strategies were identical between the groups. The authors have continued to routinely use intrawound vancomycin powder on all primary and revision total joint arthroplasties.

The introduction of a crystalline substance into a prosthetic joint provokes thought about premature third-body implant wear; however, Qadir et al. [24] demonstrated no appreciable implant wear with the addition of intraarticular vancomycin in a biomechanical study. The long-term effect on polyethylene wear is unknown however. High concentrations of certain antibiotics have been shown to be cytotoxic toward osteoblasts [25]. Vancomycin exhibited one of the weakest effects on osteoblast growth and osteogenic activity, thus making it suitable for local delivery [25,26]. This concept is particularly important in the arthroplasty setting with regard to implant fixation and bony ongrowth. With the follow-up period in our investigation, we did not note any issues with aseptic loosening; however, this could be more appreciable with long-term data. Furthermore, long-term information about the osteogenic effects of intrawound vancomycin may provide insight into potential differences in outcomes between cemented or cementless implants.

The vast financial burden on patients and health-care system associated with PJI imparts particular importance when discussing the economics with intrawound vancomycin. At our institution, 1 g of vancomycin powder costs $17, which is on par with the rates at other facilities [27]. The addition of intrawound vancomycin in this investigation led to a decrease in the overall infection rate from 2.7% to 0.57%, suggesting an absolute risk reduction (ARR) of 2.13% to 0.21%. This leads to the determination of number needed to treat (NNT) as 47.5 (NNT = 1/ARR). In other words, 48 primary total hip or knee arthroplasties need to be performed with the addition of vancomycin powder to prevent one infection. At the rate of $17 per patient, the total cost with the addition of intrawound vancomycin to prevent one infection is $816. This is a relatively insignificant cost in comparison to an estimate of the 2018 average hospital cost per case of infected total hip arthroplasties ($30,329) and TKA ($25,155) [28].

There has been increased recent discussion, particularly in the spine literature, regarding the possible association of intrawound vancomycin use with predilection for gram negative and polymicrobial infections [29,30]. There was one observed gram-negative infection in the treatment group, whereas zero noted in the control group ($P > .05$). This was a superficial infection that resolved well

with routine irrigation and debridement and antibiotic course. Despite higher prevalence of gram-negative and polymicrobial infections, data from the spine literature suggest no increase in vancomycin resistance or adverse postoperative outcomes in cases of infection after intrawound vancomycin use [30,31]. Regardless, this highlights the importance of antimicrobial stewardship as resistance continues to remain a major public health concern. As such, surgeons must weigh the risks and benefits of using intrawound antibiotics. More highly powered studies are needed to truly elicit the implications of this as a routine practice.

The strengths of the study are that it is a single-surgeon series, at one institution, without change in infection prevention protocols over the study period. This potentially limited confounding variables which can be numerous in an infection study. The potential for sampling bias was limited by the fact that no patient was eliminated from either group unless it was a revision surgery. The consecutive nature of the surgeries performed in each group may afford some protection from selection bias; however, the nonrandomized and retrospective nature of the study is a limitation. The relatively short term and variable follow-up seen in the control and treatment groups is another limitation. Although we strived to capture all infections, there is the possibility that more indolent infections may have presented past the recorded follow-up period. Similarly, we acknowledge that the difference in postoperative follow-up between the control and vancomycin groups may introduce confounding variables. Other limitations include the low effect size with regard to number of SSIs. A sample size of 3416 patients would be required to adequately detect a 50% reduction in infection rate from 2.7% to 1.35% with power of 0.80 and alpha of 0.05. To obtain this number of control-group patients, a historical control infection rate would have to be used, or information from more than one surgeon should be used, which would introduce other confounding variables and protocol changes. Furthermore, several consecutive years of clinical practice would be required to identify enough vancomycin-group patients to gain appropriate power which would delay the reporting of a potentially safe and beneficial strategy in decreasing overall infection rate. Consideration was given to including data from other surgeons and institutions, but the authors believe this would have introduced numerous confounding variables in an effort to increase sample size. Future research on increasing the sample size to allow for appropriate power without introducing confounders is a worthy endeavor. The allotted sample size of 460 was, however, sufficient in detecting the significantly decreased early infection rate noted in this investigation. In addition, future higher powered investigations may consider potential variable effects on infection rate associated with total hip vs total knee arthroplasty.

Conclusions

The authors suggest that the use of intrawound vancomycin is safe in early follow-up and was effective in reducing early postoperative complications or readmissions. Its usage shows promise in reducing the incidence of early PJI, particularly if an increased rate of PJI is present or the hospital population is at risk. Furthermore, intrawound vancomycin is a low-cost option with a low number needed to treat to show value. Future prospective and randomized research is necessary before any formal recommendations for its routine use in total joint arthroplasty can be made.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.artd.2018.07.011.

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