



Intrawound Vancomycin Powder in Primary Total Hip Arthroplasty Increases Rate of Sterile Wound Complications

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Purpose: Total hip arthroplasty (THA) is a successful surgery for the treatment of hip osteoarthritis; however, the risk of a post-operative prosthetic joint infection (PJI) remains at 1% to 2%. The purpose of this study was to investigate the safety profile of using vancomycin powder (VP) to reduce infection rates by reviewing acute postoperative complications.

Materials and Methods: A retrospective review of 265 consecutive patients undergoing THA was performed. The first 128 patients, the control group, did not receive VP, and the subsequent 137 patients, the VP group, received VP at the time of wound closure. Patient demographic data, medical comorbidities, and perioperative information were compared.

Results: The primary outcome was a post-operative surgical complication within 90 days from surgery. The control and VP group's demographic, medical comorbidities and perioperative information data were statistically similar. Deep infection rate in the control group was 5.5%, whereas the deep infection rate in the VP group was 0.7% ($P=0.031$). Sterile wound complication rate was 4.4% in the VP group, and 0% in the control group ($P=0.030$). Remaining complications were not statistically different between the groups.

Conclusion: VP was associated with an increase rate of sterile wound complications compared to the control group. The rate of PJI was decreased with the use of VP. We do not recommend for or against the use of VP at time of wound closure to prevent PJI, and higher powered studies will need to be performed to demonstrate the efficacy of VP.

Key Words: Vancomycin, Prosthetic joint infection, Hip replacement arthroplasty, Surgical wound infection

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INTRODUCTION

Total hip arthroplasty (THA) is a highly successful approach for the treatment of hip osteoarthritis, with a 92% to 94% survivorship at 7 to 12 year follow up¹⁻⁵. Despite the overall success of THA, periprosthetic joint infection (PJI)-the most common cause of readmissions after total joint arthroplasty-occurs in approximately 1% to 2% of patients^{1,6-9}. PJIs are associated with significant patient morbidity and a large financial burden on the healthcare system; current estimates suggest that healthcare costs for the treatment of PJI in the United States will exceed 1.62 billion US dollars by the year

2020¹⁰.

Early postoperative PJI are likely caused by endogenous skin flora or exogenous bacteria that contaminate the joint space at the time of surgery¹¹. The most common causative organism in early infections is *Staphylococcus aureus*, and both methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) species are frequently cultured¹¹. Equipped with the understanding that early infections occur from perioperative contamination, surgeons have developed well-established modalities to mitigate infection risks (e.g., prophylactic antibiotics, preoperative skin prep, sterile draping, antibiotic cement, and medical optimization prior to surgery)¹². Despite the variety of preventative measures available, however, the infection rate during THA remains approximately 1-2%.

While the use of prophylactic systemic antibiotics is standard of care during joint arthroplasty and drastically reduce the risk of PJI, postoperative wounds have areas not reachable by intravenously delivered antibiotics (e.g., ischemic tissue or hematoma)^{13,14}. Adjunctive intrawound application of an antibiotic, however, may create a potent bactericidal environment by producing a high local tissue concentration of the antibiotic without relying on tissue blood supply¹⁵. In a mouse model, an intra-articular knee implant was surgically placed and bacterial colony counts were compared between a group who received intrawound vancomycin powder (VP) at the time of skin closure and a control group who received no VP. Bacterial colony counts were significantly decreased at the distal femur, joint capsule, and the implanted device in the VP group¹⁶. VP has been used by spine surgeons for a number of years and there is evidence demonstrating a reduction in surgical site infections. More recently, the use of VP has been gaining popularity among arthroplasty surgeons. Otte et al.¹⁷ assessed the use of intrawound VP in revision total knee arthroplasty (TKA) and revision THA, and found the infection rates in patients receiving intrawound VP was significantly lower than in patients who received no intrawound VP, 0.0% vs. 3.89%, respectively.

In a recent systematic review of VP in spinal surgery, Ghobrial et al.¹⁸ analyzed 16 cohort studies and found that the risk of SSI in patients who received intrawound VP vs. those that did not receive intrawound VP were 1.36% and 7.47%, respectively. While vancomycin is associated with adverse events (e.g., acute kidney injury, ototoxicity, and anaphylaxis), this systematic review demonstrated a lower adverse event rate related to the VP of 0.3%. Our hypothesis is that VP is a safe and effective adjunct that can potentially decrease the rate of PJIs following THA.

MATERIALS AND METHODS

1. Study Characteristics

After institutional review board approval, we retrospectively reviewed a series of 265 consecutive patients who underwent primary THA between June 2013 and February 2016 with a minimum of 3 months follow up. This cohort included all patients operated on by a single surgeon (corresponding author) in the given time period, and other than the adjuvant intrawound administration of VP at time of wound closure (starting in January 2015), the surgeon's perioperative management of patients was identical. In total, 128 patients received no VP during THA (all treated between June 2013 and prior to January 2015; control group) and 137 patients received VP during THA (treated between January 2015 and February 2016; VP group). Demographic information (e.g., age at surgery, sex, body mass index [BMI], and comorbidities) was collected. Comorbidities included hypertension, diabetes mellitus (DM), rheumatoid arthritis (RA), chronic kidney disease, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), and American Society of Anesthesiologists (ASA) physical status scores.

All THA were performed using cementless implants and an anterior-based muscle sparing surgical approach to the hip¹⁹. The indication for surgery was debilitating hip pain with loss of function secondary to hip arthritis that did not respond to conservative treatment. All patients underwent a standard infection-prevention protocol including: i) perioperative intravenous (IV) administration of cefazolin (2 g) starting prior to skin incision and ending 24 hours after the end of the operation; ii) preoperative showering with chlorhexidine gluconate (the evening before surgery); iii) standard skin preparation with 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChlorPrep; Mediflex, Leawood, KS, USA); and iv) wound closure with monofilament sutures. If a patient had a severe cephalosporin or penicillin allergy or history of MRSA, 1 g of IV vancomycin or 600 mg of IV clindamycin was administered prior to surgical incision in place of cefazolin. In the VP group, 1 g of VP was applied both intracapsularly and extracapsularly into the wound after final wound irrigation.

2. Study Outcomes

Postoperative complications (i.e., deep PJI, superficial infection and wound complications) were collected if

diagnosed within 90 days of the initial surgery. Deep PJIs were those that met the periprosthetic infection criteria described by the International Consensus Meeting on Periprosthetic Joint Infections²⁰. Superficial infections were surgical site infections that resolved with oral antibiotics and which did not require an additional operation. Wound complications were wound breakdowns that did not meet the aforementioned criteria for periprosthetic infection, and required a return to the operating room (OR) for wound debridement and closure. Intraoperative wound cultures were obtained following the onset of a wound complication, and were negative for infection. Perioperative medical complications (i.e., acute renal failure [ARF]-defined as an increase in serum creatinine of greater than 0.3 mg/dL, ototoxicity, aseptic loosening, hip dislocation, periprosthetic fracture, THA revision, return to OR, spacer, hip washout, death, myocardial infection [MI], stroke, deep vein thrombosis, pulmonary edema [PE] and anaphylaxis) were also quantified to evaluate the safety of VP.

3. Patient Demographics

Baseline demographics are presented in Table 1. Both groups were approximately 50% male with an average age of approximately 61 years and average BMI of 30 kg/m². There were no significant differences between the groups with regards to age ($P=0.837$), sex ($P=0.678$), or BMI ($P=0.851$). The control group had a significantly longer ($P<0.001$) average follow-up time of 14.4 months (range, 3.0 to 34.9 months) compared with the VP group with an average follow-up of 8.2 months (range, 3.0 to 20.1 months).

4. Statistical Analysis

Continuous data are presented using the mean, standard deviation and range and compared between the two groups using a *t*-test. Normality was assessed using the Kolmogorov-

Smirnov test and normality plots. Categorical data are presented using counts and percentages for non-missing data. Groups were compared using the chi-square or Fisher's exact tests (expected cell counts <5). Odds ratios with 95% confidence intervals are presented where possible (non-zero cells) to compare complication rates between the two groups. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses and a *P*-value <0.05 was considered statistically significant.

RESULTS

ASA scores and percentage of smokers were not significantly different between the two groups. The control group had a significantly greater ($P=0.046$) number of patients with COPD (8.6%) compared to the VP group (2.9%). All other medical comorbidities were similar between the two groups (Table 2). The indication for THA was not statistically different between the groups ($P=0.699$), with 8 cases (6.2%) vs. 5 cases (3.7%) of avascular necrosis, 1 case (0.8%) vs. 1 case (0.7%) of inflammatory arthropathy and 119 cases (93.0%) vs. 131 cases (95.6%) of osteoarthritis in the control and VP groups, respectively.

The 115 patients (89.8%) of the control group vs. 120 patients (87.6%) of the VP group received IV cefazolin as prophylactic antibiotic. Of the remaining patients in the control group, 7 patients (5.5%) received IV vancomycin and 7 patients received (5.5%) IV clindamycin. Likewise, 13 patients (9.5%) of the VP group received IV vancomycin while the remaining 2 patients (1.5%) of the VP group received IV clindamycin. When comparing the groups, there were no significant differences in the use of prophylactic cefazolin ($P=0.563$), vancomycin ($P=0.216$), or clindamycin ($P=0.094$).

When comparing the rates complications between the two groups (Table 3), the control group had a higher rate of superficial infection and deep infection, and the VP

Table 1. Patient Demographics for Each Group

Characteristic	Control group (n=128)	VP group (n=137)	<i>P</i> -value
Age (yr)	61.5±10.5 (34-88)	61.2±11.1 (33-84)	0.837
BMI (kg/m ²)	29.8±5.9 (15-46)	30.0±6.0 (15.9-51.6)	0.851
Sex, male (%)	50.0	47.4	0.678
Follow-up (mo)	14.4±7.5 (3.0-34.9)	8.2±4.5 (3.0-20.1)	<0.001*

Values are presented as mean±standard deviation (range) or percent only.

VP: vancomycin powder, BMI: body mass index.

* Statistically significant.

group had a higher rate of wound complications. While the difference in prevalence of superficial infection was not significantly different ($P=0.611$), the difference in prevalence of deep PJI was statistically significant ($P=0.031$). Likewise, the higher rate of wound complications in the VP group was statistically significant ($P=0.030$)

when compared to the control group.

Regarding the 7 patients (5.5%) in the control group with PJI (Table 4), all were managed by the infectious disease team and treated initially with a head and liner exchange and IV antibiotics. In those requiring a second procedure, the average time from index THA was 33 days. Of the 7

Table 2. Comorbidities in Each Group

Variable	Control group (n=128)	VP group (n=137)	P-value
Hypertension (%)	64.8	60.6	0.474
Diabetes mellitus (%)	14.8	11.7	0.447
CAD (%)	11.7	9.5	0.555
CHF (%)	6.3	5.1	0.688
CKD (%)	7.8	10.9	0.383
COPD (%)	8.6	2.9	0.046*
RA (%)	5.5	6.6	0.707
Smoker (%)			0.881
Never	56.3	57.7	
Active	14.8	16.1	
Former	28.9	26.3	
ASA score (%)			0.735
1	1.6	2.9	
2	71.1	67.2	
3	27.3	29.9	
Indication (%)			0.699
Avascular necrosis	6.2	3.7	
Inflammatory arthropathy	0.8	0.7	
Osteoarthritis	93.0	95.6	

VP: vancomycin powder, CAD: coronary artery disease, CHF: congestive heart failure, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, RA: rheumatoid arthritis, ASA: American Society of Anesthesiologists.

* Statistically significant.

Table 3. Comparison of Complications between Groups

Complication	Control group (n=128)	VP group (n=137)	OR (95% CI)	P-value
Superficial infection	2 (1.6)	1 (0.7)	0.46 (0.04-5.17)	0.611
Deep infection	7 (5.5)	1 (0.7)	0.13 (0.02-1.05)	0.031*
Wound complication	0 (0.0)	6 (4.4)	-	0.030*
Return to operating room	7 (5.5)	7 (5.1)	0.93 (0.32-2.73)	0.896
Periprosthetic fracture	4 (3.1)	3 (2.2)	0.69 (0.15-3.16)	0.715
Spacer	1 (0.8)	0 (0.0)	-	0.483
Hip wash	6 (4.7)	1 (0.7)	0.15 (0.02-1.26)	0.059
Hip dislocation	0 (0.0)	1 (0.7)	-	1.000
ARF	3 (2.3)	0 (0.0)	-	0.111
DVT	0 (0.0)	1 (0.7)	-	1.000
Any complication	17 (13.3)	12 (8.8)	0.63 (0.29-1.37)	0.239

Values are presented as number (%).

VP: vancomycin powder, OR: odds ratio, 95% CI: 95% confidence interval, ARF: acute renal failure, DVT: deep vein thrombosis.

* Statistically significant.

patients treated initially with head and liner exchange, infections cleared in 6 (no additional procedures were required), and the infection failed to clear in 1 (explant of all components and antibiotic spacer placement was required prior to re-implantation of a prosthetic hip).

In the VP group, 1 patient (0.7%) with PJI underwent head and liner exchange 28 days after index THA (Table 5). The infection cleared in this patient and no additional procedures were required. The VP group also had 6 patients (4.4%) with wound complications. These wound complications did not meet criteria for PJI and were thought to be secondary to a seroma. These patients were treated with wound debridement and closure without head or liner exchange and no postoperative antibiotics. Intra-operative cultures were

negative for bacterial growth for all 6 patients. The average time to second procedure from index THA was 27 days. The wounds of all 6 patients healed after the second operation and subsequent procedures were not required.

Staphylococcus was the most commonly isolated bacteria species and there 4, 2, and 1 cases of MSSA, MRSA and coagulase negative staphylococcus, respectively. There was also 1 case with no bacterial growth.

With regards to adverse events related to VP, no patients in the VP group developed ARF while 3 patients (2.3%) in the control group developed ARF which resolved by day of discharge ($P=0.111$). No patients in either group developed ototoxicity, aseptic loosening, death, MI, stroke, PE, or anaphylaxis.

Table 4. Description of Prosthetic Joint Infection Patients in Each Group

Patient	Number of secondary procedures	Secondary procedure	Time to second surgery (day)	Culture
Control group				
1	1	Head/liner exchange	23	MSSA
2	1	Head/liner exchange	19	Coagulase negative <i>Staphylococcus</i>
3	1	Head/liner exchange	24	No growth
4	1	Head/liner exchange	15	MSSA
5	1	Head/liner exchange	31	MRSA
6	1	Head/liner exchange	85	MSSA
7	3	Head/liner exchange, explant with antibiotic spacer, re-implantation	28	MRSA
VP group				
1	1	Head/liner exchange	28	MSSA

MSSA: methicillin-sensitive *Staphylococcus aureus*, MRSA: methicillin-resistant *S. aureus*, VP: vancomycin powder.

Table 5. Description of Vancomycin Powder Group Wound Complication Patient

Patient	Number of secondary procedures	Secondary procedure	Time to second surgery (day)	Culture
1	1	Wound debridement without head/liner exchange	22	No growth
2	1	Wound debridement without head/liner exchange	32	No growth
3	1	Wound debridement without head/liner exchange	23	No growth
4	1	Wound debridement without head/liner exchange	28	No growth
5	1	Wound debridement without head/liner exchange	28	No growth
6	1	Wound debridement without head/liner exchange	29	No growth

DISCUSSION

VP has been well studied in the spine literature, and has been shown to reduce deep surgical site infections (SSIs) following the use of spinal instrumentation^{15,21}. Recently, a study was published demonstrating a reduced prevalence of PJI following revision TKA or THA using VP¹⁷. However, the safety and effectiveness of VP during THA has not been well established. One concern, specific to arthroplasty, is increased third body wear rates with the addition of VP. A mechanical *in-vitro* study attempted to address this question, and did not demonstrate increased third body polyethylene wear rates following cyclic loading with the addition of intra-articular VP²².

In our study, we observed a statistically significant lower rate of PJI in the VP group. The control group underwent the same standard preoperative infection prevention protocol and did not have an increased rate of comorbidities associated increased rates of PJI (i.e., DM or RA) compared with the VP group. The control group did, however, have a statistically significant increased rate of COPD—a comorbidity which is associated with increased rates of PJI—and this could be a confounding variable for the increased PJI rate in the control group²³. While the statistically significant decreased rate of PJI in the VP group may be explained by VP use, it is unclear why our control group PJI rate of 5.4% is much higher than the 1% to 2% PJI rate reported in the literature^{1,6-9}, and this is a major limitation of this study. While the cause is unclear, during this period the hospital had an increase in infection rates and a thorough evaluation by infectious disease experts was performed with no clear cause identified. One consideration is that 6 of the 7 patients with PJI had a BMI greater than 30 kg/m² which has been shown to be a risk factor for PJI in patients having THA through an anterior approach^{24,25}. As mentioned, the higher rate of COPD in the control group could also have contributed to a higher infection rate²³. Lastly, one of the PJI in the control group received clindamycin for pre-operative prophylaxis, a bacteriostatic antibiotic, which could be associated with higher rates of PJI. Despite this limitation, the decreased prevalence of infections in the VP group does agree with the findings of multiple studies that have evaluated the efficacy of VP in reducing postoperative infections.

The use of topical vancomycin was first reported in 1989 when the application of topical vancomycin to the sternum in cardiothoracic patients reduced rates of sternal infection from 3.6% to 0.45%²⁶. Similarly, multiple studies have shown that vancomycin decreases the rate of postoperative

infections in patients undergoing spinal surgery. The first large retrospective study investigating the clinical efficacy of VP was published in 2011 and reviewed 1,732 consecutive spinal fusions and showed a reduction in infection rate from 2.6% to 0.2%²⁷. Furthermore, O’Neil et al.²⁸ found that the use of intrawound VP in patients undergoing posterior spinal stabilization after spine trauma reduced infection rates from 13% to 0%. Likewise, the use of VP in posterior cervical spine fusion has been shown to be effective with a decrease in infection rates from 10.9% to 2.5%²⁹. However, in a prospective randomized controlled trial comparing 433 patients receiving VP to a control group of 474 patients receiving no VP, Tubaki et al.³⁰ found no statistical difference in infection rates (1.6% in both groups). The authors hypothesized that the addition of VP may not be effective when the incidence of postoperative infection is low. Similarly, VP in THA may be an efficacious adjunct in reducing infection rates when the incidence of PJI is high as observed in our study.

Our study also shows that intrawound VP in THA is safe with no cases of nephrotoxicity, ototoxicity or anaphylaxis. This finding agrees with the safety profile of intrawound VP in the spine literature. A number of studies have investigated serum concentration levels of vancomycin using local VP, and all report serum concentrations well below toxic levels^{23,27-29}. In a recent systematic review investigating the complications associated with the intrawound use of VP in 6,701 cases of spine surgery, the authors found one reported case of nephrotoxicity, one case of ototoxicity, and 19 cases of seroma formation¹⁸.

Similar to reports in the spine literature, we note a statistically significant increase in sterile seroma formation requiring operative management in patients receiving VP¹⁵. Despite this known association, the mechanism of the seroma formation remains unclear. One possibility is that a local inflammatory reaction produced by the VP itself or an inflammatory reaction produced by the body’s response to the foreign VP is responsible. Seroma formation following THA, although not as deleterious as a PJI, still requires reoperation and needs to be considered prior to VP use.

CONCLUSION

The adjunctive use of VP during wound closure is a trending modality to reduce rates of PJI. Here we evaluated the impact of adjunctive intrawound use of VP during THA on the rate of infections and observed an increase in the overall risk of sterile wound complications with the

use of VP but a decreased rate of PJI. This study involved a relatively small sample size; however, and a second, higher-powered study should be performed to validate the results. Based on the results of this study, we cannot recommend for or against the use of VP during THA, however one needs to be aware of the potential benefits vs risks of adjunctive intrawound use of VP.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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