Journal of Orthopaedic Trauma Publish Ahead of Print
DOI: 10.1097/BOT.0000000000000941

Title:

Intraoperative Topical Antibiotics for Infection Prophylaxis in Pelvic and Acetabular Surgery

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Conflicts of Interest and Source of Funding:

JA Lowe is a consultant for Stryker and Accumed and has received honoraria from Stryker and Synthes. For the remaining authors, none were declared. No outside funding was received for this manuscript.

The authors received Institutional Review Board approval.

Previously presented at AO North America ONE Meeting, Las Vegas, NV, February 5, 2015, the Annual Alabama Orthopaedic Society Meeting, Destin, FL, April 10, 2015, the Annual Southern Orthopaedic Society Meeting, Asheville, NC, July 17, 2015, and the Annual Meeting of the Orthopaedic Trauma Association, San Diego, CA, October 10, 2015.

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Abstract:

Objectives: Determine if topical vancomycin and tobramycin powder reduces the incidence of surgical site infection (SSI) following pelvic ring and acetabulum fracture surgery.

Design:

Retrospective cohort study

Setting:

University of Alabama at Birmingham, Academic Level I Trauma Center

Patients/Participants:

219 patients (140 meeting inclusion criteria) with pelvic and acetabular fractures who underwent open reduction and internal fixation (ORIF) from March 2012 to November 2013.

Intervention:

One gram vancomycin and 1.2 grams tobramycin powder applied deep in the surgical wound of the treatment group.

Main Outcome Measurements:

Postoperative infection rate

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Results:

140 patients were included. Control group (n=69) and treatment group (n=71) were similar for sex, age, ethnicity, and body mass index (BMI). There was no difference between groups in regards to renal function post-op day 2 (p=0.24). The risk of infection was 14.5% and 4.2% (p=0.04) for the control and treatment groups, respectively. No significant effect of antibiotic treatment was observed overall after adjusting for EBL (OR 0.20, 95% CI 0.02-1.06). Of note, a non-significant 71% increase was observed among those with ≥1L EBL (OR 1.71, 95% CI 0.02-147.02).

Conclusions:

Topical antibiotics possibly reduce the incidence of SSI following open pelvic and acetabulum fixation without increasing risk of renal impairment. The protective effect of topical antibiotics may be limited to patients with minimal intra-operative blood loss.

Key Words: pelvis;Acetabulum;fracture;postoperative infection;topical antibiotics;antibiotic powder;vancomycin;tobramycin;trauma

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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Introduction:

Pelvic ring and acetabular fractures typically follow high-energy trauma, often requiring complex surgical operations that carry a risk for infection. While open reduction and internal fixation (ORIF) has been shown to restore function and reduce morbidity and mortality, infection rates have been reported between 1% and 23%[1-11]. Aside from increasing patient morbidity and mortality, surgical site infections (SSI) have been shown to increase health care cost by as much as 20%[12]. Risk factors for postoperative infection include obesity, diabetes mellitus, injury severity score (ISS), intensive care unit (ICU) stay, presence of a Morel-Lavallée lesion, length of procedure and blood loss/blood transfusion[1, 2, 5, 13-15].

Topical administration of 1gram vancomycin powder to the surgical site at time of wound closure in addition to standard pre-operative IV antibiotic prophylaxis reduces the incidence of surgical site infection (SSI) following spine surgery from approximately 3-15% to 0.2% or lower [16-20]. None of these studies have reported complications with topical administered vancomycin. To date no study has examined the effect of topical antibiotics following pelvic and acetabular fracture surgery. The purpose of this study is to determine if the addition of topical antibiotics (vancomycin and tobramycin) to the deep and superficial operative tissues during wound closure reduces the incidence of SSI. The authors hypothesize that topical antibiotics will reduce incidence of infection without increasing incidence of renal failure.

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Patients and Methods:

Following institutional review board approval, a retrospective review was performed using current procedural terminology (CPT) codes to identify all pelvic and acetabular fractures that underwent open reduction and internal fixation during the time of March 2012 to November 2013. This study was conducted at a single level I academic trauma center. All patients were treated using an established trauma protocol and pre-operative anteroposterior (AP) and Judet x-rays as well as 2-millimeter (mm) computed tomography (CT) scans of the pelvis. All surgical procedures were performed by one of four fellowship trained orthopedic traumatologists.

Patients included were those between the ages of 19 and 65 who suffered high-energy trauma resulting in pelvic ring or acetabulum fractures requiring ORIF. Exclusion criteria included 19 >age> 65, pregnancy, fractures amenable to percutaneous fixation without open reduction, operative fixation greater than 3 weeks from time of injury, and less than 6-month follow-up. Patient who did not return to clinic where contacted and queried as to presence of draining wounds, need for either antibiotics to treat their surgical site or secondary surgery to treat an infection. A negative response to these three questions determined the patient to not have a surgical site infection.

Patients were divided into two groups based on the method of antibiotic prophylaxis. Group 1 (10 months) received standard weight/dose adjusted cefazolin but did not receive topical antibiotics. Group 2 (10 months) received pre-operative cefazolin as well as topical antibiotic powder (Vancomycin 1gm and Tobramycin 1.2gm) applied to all levels of the surgical wound at time of closure. The decision to apply topical

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antibiotics was a change in treatment practices applied by all surgeons at this institution. Patient demographics, mechanism of injury, injury severity score, fracture pattern, associated injuries, body mass index (BMI) at time of admission, surgical approach, BUN/creatinine in first 48 hours post-op, intraoperative blood loss, total intensive care unit (ICU) stay, hospital length of stay, surgical site infection, number of transfusions during procedure and first 48-hour postoperative period, and duration of procedure were recorded. Acetabulum fractures were classified by a single fellowship trained trauma surgeon (JAL) according to Letournel and pelvic ring injuries were classified based on the Tile and Young/Burgess systems[21-23]. Surgical approaches (Pfannenstiel, ilioinguinal, posterior approach to the sacrum, Kocher-Langenbech or combined approaches) were recorded.

All patients received standard prophylactic intravenous antibiotic within 30 minutes of case start. One gram of vancomycin and 1.2 grams of tobramycin powder were spread throughout the deep and superficial tissue in the treatment group. In the case of a two-incision approach, this antibiotic regimen was used at each surgical site. Vancomycin was chosen due to a high rate of methicillin-resistant staphylococcus aureus (MRSA) at our institution. Tobramycin was chosen due to its bactericidal characteristics and a prevalence of gram-negative organisms observed both at this institution as well as within the published literature on pelvic and acetabular infections[24]. Infection was defined as postoperative drainage requiring surgical debridement with either positive deep tissue cultures or the presence of gross purulence. Serum BUN and creatinine values were followed for 48 hours postoperatively to discern any evidence of renal injury.

Statistical analysis

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Statistical significance was determined using chi-square and student's t-test for categorical and continuous variables, respectively. Exact logistic regression was used to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs) for the associated between topical antibiotic use at the time of closure and risk of infection. Models were adjusted for number of packed red blood cell (pRBC) units within the first 48 hours. In a secondary analysis, effect modification by injury type (i.e., acetabular or pelvic) and amount of blood loss was assessed by stratifying the adjusted logistic models and using an interaction term to assess statistical interaction of observed associations between strata.

Results:

A retrospective review produced 219 patients who underwent ORIF of the pelvis or acetabulum from March 2012 to November 2013. Using exclusion criteria, 140 patients were included with a mean follow-up of approximately 12.5 months. There was no difference in regards to age, race, sex, prevalence of diabetes, BMI, or prevalence of tobacco use between the two groups (Table 1). Those in the treatment group were more likely to have an acetabular fracture (69.0% vs 60.9%, p=0.01), but were less likely to have an associated-type acetabular fracture (46.9% vs 67.9%, p=0.05). Those in the control group had a higher mean number of pRBCs transfused (1.5±1.7 vs 0.9±1.3, p=0.02) and had a higher mean amount of blood loss (775.7±627.4mL vs 534.7±411.6mL, p<0.01). There was no difference between the groups in regards to approach or mean procedure length. The treatment group had a shorter mean length of hospital stay (11.3±7.1 vs 15.2±11.1, p=0.01). Five patients from the control groups and

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ten from the treatment group had a pre-operative creatinine level of 1.3 or higher, none of these patients experienced a postoperative rise in creatinine. There was no difference in serum creatinine change or BUN-to-creatinine ratio on the first and second postoperative days, ICU length of stay, and length of follow-up in the study. There were sixteen patients (eight in each group) contacted via phone interview that had less than six months follow-up. None of these patients reported history of surgical site infections requiring surgical debridement or prolonged antibiotics.

There were thirteen total patients (9.3%) with an observed infection, ten of which were among the control group (14.5%) and three in the treatment group (4.2%) ($p=0.04$) (Table 1). The risk of infection was 78% lower for those in the treatment group compared to those in the control group, although this association did not achieve statistical significance (OR 0.22, 95% CI 0.02-1.18) (Table 2). There was minimal change in the association after adjusting for number of pRBC units transfused in the first 48 hours (OR 0.20, 95% CI 0.02-1.06). In stratified analysis, similar associations were observed between those with an acetabulum fracture (OR 0.19, 95% CI 0.01-1.79) and pelvic ring injuries (OR 0.18, 95% 0.01-2.56). By amount of blood loss, there was evidence of effect modification with a significant association between the use of topical antibiotics and lower infection risk for patients with <1L of blood loss (OR 0.10, 95% CI 0.01-0.80) and a non-significant 71% increased risk observed among patients with ≥1L blood loss (OR 1.71, 95% CI 0.02-147.02).

Twenty-four species of organisms were cultured from the surgical wounds, with some organisms appearing more than once. The most common species were coagulase-negative Staphylococcus sp. (n = 5), methicillin-resistant Staphylococcus aureus (MRSA)

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(n = 2), Klebsiella sp. (n=2), and Serratia sp. (n = 2) (Table 3). There were 13 gram-positive bacterial organisms (54.2%), 10 gram-negative bacterial organisms (41.7%), and 1 yeast (4.2%) cultured (Table 3).

Discussion:

This retrospective case control is the first study to evaluate efficacy of topical antibiotics reducing SSI following ORIF of pelvic ring and acetabulum fractures. While the crude results suggest that topical application of 1 gram of vancomycin and 1.2 grams of tobramycin reduces the risk of SSI following ORIF of pelvic and acetabular fractures, the protective effect no longer remains after adjusting for units of blood transfused and fracture type. That said, despite the lack of statistical effect, there is evidence of effect modification, with the protective effect of topical application of antibiotics is present only among those cases with less than 1 liter of blood loss. Adjusted statistical analysis needs to be interpreted with caution owing to the small sample of infection in the treatment group. Finally, the results suggest that topical antibiotics are not associated with increased postoperative creatinine indicative of acute kidney injury.

Topical administration of antibiotics is not a novel prophylactic technique. Application of antibiotic powder has been shown to reduce postoperative infections of the spine to between 0-0.2%[16-20]. This effect has also been observed across other surgical specialties[25-27]. Despite these promising results, one prospective randomized trial showed no benefit to topical antibiotic powder in postoperative spine wounds[28].

One potential concern with topical application of nephrotoxic antibiotics is post treatment renal injury. While Sweet et al and others have found no adverse renal effects

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following topical administration of vancomycin, other studies have shown that topical administration of tobramycin can reach nephrotoxic levels [16, 25, 26, 29-31]. The authors found no statistically significant increase in BUN, creatinine, or BUN/creatinine following surgery. In addition there were no new cases of acute kidney injury. While 10 patients in the treatment group presented with preoperative creatinine levels of 1.3 and above, none of these patients demonstrated a postoperative increase in creatinine.

Another potential concern of applying topical antibiotics is that it may result in increased time to union or incidence of nonunion. At this time there is no consensus on this point as Chiang et al demonstrated in increase time to union while Buttaro et al demonstrated normal incorporation of bone graft after administration of topical vancomycin[16, 30,31]. In this series topical administration of antibiotics did result in an increase time to union for the control group (3.7 months) vs the antibiotic group (3.1 months) p=0.006). While statistically significant this difference is not clinically relevant, and is likely a reflection of sample size as there were no nonunions in the antibiotic group and only in the control group.

Other covariates in our analysis, including race, gender, age, diabetes, BMI, tobacco use, fracture classification, injury severity score, and hospital length of stay were not statistically significant predictors of SSI. Although not significant in our study, multiple previous studies have indicated increased risks of infection and complications with increased BMI in the treatment of pelvic ring and acetabulum injuries[1, 2, 5, 13, 14]. In a retrospective study of 326 acetabular fracture by Suzuki et al, they found that infection was 1.1 times more likely for each 1 kg/m^2 increase in BMI[1]. Sems et al., in a review of pelvis injuries, found that patients with a BMI greater than 30 kg/m^2 had a deep infection

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rate of 22.9% compared to 3.7% in non-obese patients[13]. Karunakar et al. found that increased BMI recorded as a continuous variable was significantly associated with increased risk of surgical site infection and that morbidly obese patients with a BMI of $\geq$ 40 kg/m^2 were five times more likely to have an infection[5]. Porter et al., found morbidly obese patients (BMI $\geq$ 40 kg/m^2) to be 2.6 times more likely to have a perioperative complication when undergoing acetabular fracture[32].

Previous reports have indicated an increased risk of infection in patients with increasing perioperative blood loss and blood transfusions. Pull ter Gunne et al. showed blood loss over one liter to be an independently significant risk factor for SSI following spinal surgery in adults[33]. Olsen et al. found median estimated blood loss to be higher in patients who developed SSI following spinal surgery compared to control patients[34]. In the current study population, though not part of the main results, we observed a similar pattern only among those given antibiotics, with a trend towards higher infection risk observed for those with ≥1L EBL compared to <1L EBL (18.2% vs. 1.7%, p=0.06). Infection risk was equal between EBL groups among those not given a topical antibiotic (EBL <1L: 14.3% vs. EBL≥1L: 14.6%, p=0.97). In addition, the average blood loss was similar between infected patients and non-infected patients (810mL vs. 637mL, respectively, p=0.27).

Several other studies have indicated that blood transfusions and blood loss are risk factors for postoperative bacterial infections [35-41]. In some cases, a dose-response relationship was seen between the amount of blood transfused and the infection rate where more blood transfused yielded a higher infection rate[35, 38, 42-44]. In our study, peri-operative blood transfusions were significant predictors of infection, but it is beyond the

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scope of this study to explain why the effect of topical antibiotics is lost in those patients with greater than 1 liter blood loss, though the authors again caution that this statistical observation may be a reflection of the small number of infection observed in the treatment group. These results provide reason to conduct large studies with this technique as well as consider practices to minimize perioperative blood loss and perioperative transfusions.

This study is limited by sampling bias, accuracy of the electronic health record and follow-up limitations all associated with retrospective studies. The length of the follow-up period (minimum of 6 months, mean of 12.5 months) is a limitation of this study. This is a result of being conducted in a state with a single Level 1 trauma center where patient follow up with the operative surgeon is often limited to the acute and sub-acute period after which point patient care is handed over to community surgeons closer to the patient's home. Torbert and colleagues reported that their infections presented at an average of 11wks[24]. Furthermore, 23% presented by the end of week 2, 50% by week 5, 75% by week 10, and over 90% by week 26 (6 months). Based upon these data the authors can state that for those patients with the shortest follow-up (i.e., worst case scenario), 90% of possible infections were captured. Furthermore, with a mean follow up of 12.5 months, > 95% of infections would have been observed.

The current study also was limited by heterogeneity between groups where the control group had a greater incidence of complex acetabular fractures, higher EBL, and greater number of allogenic transfusions. In addition, the study population was a heterogeneous mix of pelvic ring, acetabular and combined injuries. To address this

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limitation, analyses were stratified by the type of injury, and no differences in effect were observed between injury types.

Another limitation for the current study is the low number of infections, which decreases statistical power and efficiency to the point that the lack of statistical association between topical antibiotic application and infection risk may be due more to the small sample size rather than being indicative of a true lack of association. In addition, the low number of infections precluded secondary stratified analysis by both fracture type and EBL combined. Therefore, it is possible that the observation of a lack of beneficial effect among those with EBL >1 is due to a difference in fracture type and therefore procedure. Also, the study's conclusions on the effect of topical antibiotics to the renal system are limited by the absence of serum antibiotic levels following surgery. While the authors observed a zero incidence of postoperative acute renal injury it is possible that patients with pre-traumatic renal dysfunction may be more susceptible to post-surgical impairment. Finally this study is limited by its inability to predict the long term effect of applying high concentrations of antibiotics to the surgical site. While not observed in this study the authors must caution on the potential of this technique to yield fungal and resistant bacterial postoperative infections. Carreon et al observed the speciation profile of topical vancomycin in the spine. The authors observed no difference in SSI bacterial profile between those patients who had topical vancomycin vs those who did not.[45] McHugh et al commented that a certain surgical procedures and patients warranted topical antibiotics but cautioned against ubiquitous application in the absence of conclusive randomized controlled trials.[46]

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The use of topical vancomycin and tobramycin appears to reduce the risk of deep surgical site infection following the operative repair of pelvic and acetabular fractures. We saw a non-significant 80% decrease in the risk of deep infection following the institution of a protocol of using topical antibiotics at the conclusion of pelvic and acetabular fracture cases and a statistically significant 90% reduction in cases with low blood loss (<1 liter). It appears that the beneficial effect of topical antibiotics may be not be present in cases with excessive blood loss (>1L). Despite concerns for adverse effects on renal function, we did not identify a correlation for acute kidney injury following administration of topical antibiotics.

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Table 1. Comparison of demographic, injury, surgery, and clinical characteristics between patients with pelvic fracture treated with or without topical vancomycin and tobramycin powder

	Control group (N=69)	Treatment group (N=71)	p-value*
DEMOGRAPHICS			
Mean age (years)	39.9±12.2	39.8±13.5	0.94
< 55 years (%)	61 (88.4)	60 (84.5)	0.62
Race (%)			
White	47 (68.1)	42 (59.2)	0.30
Non-white	22 (31.9)	29 (40.8)	
Sex (%)			
Male	51 (73.9)	51 (71.8)	0.85
Female	18 (26.1)	20 (28.2)	
Diabetes (%)	6 (8.7)	8 (11.3)	0.78
Mean BMI (kg/m^2)	30.5±6.8	29.2±6.1	0.27
<25 (%)	16 (23.2)	17 (24.6)	0.83
25-30 (%)	22 (31.9)	26 (27.7)	
>30-40 (%)	26 (37.7)	21 (30.4)	
>40 (%)	5 (7.2)	5 (7.2)	
Tobacco use (%)	34 (49.3)	25 (35.2)	0.12
INJURY			
Fracture type (%)			
Acetabulum	41 (60.9)	49 (69.0)	**0.01**
Pelvis	13 (18.8)	19 (26.8)	
Combined	14 (20.3)	3 (4.2)	
Associated-type Acetabular fractures	38 (67.9)	23 (46.9)	**0.05**
Mean ISS	14.1±10.7	14.8±9.8	0.65
SURGERY			
Mean packed red blood cell units transfused	1.5±1.7	0.9±1.3	**0.02**
≥ 4 units transfused (%)	8 (11.6)	2 (2.8)	**0.05**
Approach (%)			
Anterior	19 (27.9)	17 (23.9)	0.87
Posterior	6 (8.8)	7 (9.9)	
Combined	43 (63.2)	47 (66.2)	
Mean procedure length (hours)	4.5±2.0	3.9±1.7	0.10
Mean blood loss (mL)	775.7±627.4	534.0±411.6	**<0.01**
Blood loss ≥ 1L (%)	21 (30.4)	11 (15.5)	**0.04**
CLINICAL			
Infection (%)	10 (14.5)	3 (4.2)	**0.04**
Gram positive (%)	7 (10.1)	2 (2.8)	0.09
Gram negative (%)	4 (5.8)	1 (1.4)	0.21
BUN/Creatinine Change Day 2 (%)			
Decrease	36 (52.2)	46 (66.7)	0.24
No change	3 (4.3)	2 (2.9)	
Increase	30 (43.5)	21 (30.4)	
Mean ICU length of stay (days)	5.0±9.6	3.0±5.4	0.13
Mean hospital length of stay (days)	15.2±11.1	11.3±7.1	0.01
Median length of follow-up in months (range)	13.1 (9.5-25.9)	11.8 (7.9-18.0)	0.08†

* Based on Fischer's exact and t-test for categorical and continuous variables, respectively

† Based on Wilcoxon rank sums test

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Table 2. Crude and adjusted* odds ratios† for the association between vancomycin and tobramycin powder treatment and risk of infection among all patients and stratified by amount of blood loss

	Control group (n=69)		Treatment group (n=71)		
	Risk (%)	OR (95% CI)	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
ALL PATIENTS	8 (11.6)	Ref	2 (2.8)	0.22 (0.02-1.18)	0.20 (0.02-1.06)
FRACTURE TYPE					
Acetabular	5 (9.6)	Ref	1 (2.1)	0.21 (0.01-1.95)	0.19 (0.01-1.79)
Pelvic	3 (21.4)	Ref	1 (5.3)	0.21 (0.01-3.04)	0.18 (0.01-2.56)
p-value$_{int}$=1.0000					
BLOOD LOSS					
<1L	7 (14.6)	Ref	1 (1.7)	0.10 (0.01-0.83)	0.10 (0.01-0.80)
≥1L	1 (4.8)	Ref	1 (9.1)	1.95 (0.02-164.7)	1.71 (0.02-147.02)
p-value$_{int}$=0.2028					

* Estimated from exact logistic regression
† Adjusted for packed red blood cell units transfused in 48 hours

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Table 3. Cultured organisms from control and treatment groups	
Organism	Total
Coagulase Negative Staphylococcus sp.	5
Klebsiella sp.	2
Methicillin-Resistant Staphylococcus aureus	2
Serratia sp.	2
Acinetobacter baumannii	1
Bacilus sp.	1
Bacteroides sp.	1
Brevibacterium sp.	1
Citrobacter sp.	1
Enterobacter sp.	1
Enterococcus sp.	1
Methicillin-Susceptible Staphylococcus aureus	1
Peptostreptococcus sp.	1
Propionobacterium acnes	1
Pseudomonas aeruginosa	1
Stenotrophomonas sp.	1
Yeast	1
Total	24

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