Local Injection of Aminoglycosides for Prophylaxis Against Infection in Open Fractures

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Background: The purpose of this study was to determine the efficacy of local wound cavity injections of aqueous aminoglycosides (gentamicin and tobramycin), in conjunction with systemic antibiotics, to lower the prevalence of infection in patients with open fractures.

Methods: Three hundred and fifty-one open fractures were identified by Current Procedural Terminology codes 11011 and 11012. Data on patient demographic characteristics, injury characteristics, infection, and fracture union were obtained from the electronic medical records. Patients in the control group (183 fractures) received systemic antibiotics only. Patients in the intervention group (168 fractures) received, in addition to systemic antibiotics, a locally administered aminoglycoside (2 mg/mL) at the time of the index surgical procedure. At the discretion of the attending surgeon, some wounds also received postoperative irrigations of aqueous aminoglycoside (n = 34). For wounds that could not be closed and wounds that received postoperative irrigations, negative pressure dressings were used.

Results: The deep and superficial infection rate in the control group was 19.7% (thirty-six of 183 fractures), but it was significantly lower (p = 0.010) in the intervention group at 9.5% (sixteen of 168 fractures). When comparing only the deep infections, the infection rate in the control group was 14.2% (twenty-six of 183 fractures) compared with 6.0% (ten of 168 fractures) in the intervention group (p = 0.011). After multivariate analysis to adjust for possible confounding factors, the administration of local antibiotics was found to be an independent predictor of lower infection rates in both deep and superficial infections (odds ratio, 2.6 [95% confidence interval, 1.2 to 5.6]; p = 0.015) and deep infections only (odds ratio, 3.0 [95% confidence interval, 1.1 to 8.5]; p = 0.034). The use of local antibiotics did not have an impact on nonunion rate (p = 0.881), with a type-I error rate of $\alpha = 0.05$ and 0.8 power.

Conclusions: This study suggests that local aqueous aminoglycoside administration as an adjunct to systemic antibiotics may be effective in lowering infection rates in open fractures; further research with higher-level research designs are needed.

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

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Open fractures are known to be high risk for infection, even when treated with thorough debridement, stabilization, and appropriate systemic antibiotic therapy. Infection rates can be divided on the basis of Gustilo-Anderson fracture type[1], although there is variation in the literature, with rates of 0% to 6% for type-I fractures, rates of 2% to 6% for type-II fractures, and rates of 5% to 50% for type-III fractures[2,3]. Systemic antibiotics substantially lower infection rates in open fractures[4], but the continued high infection rates leave room for improvement. Wound cavities are avascular; therefore, systemically administered antibiotics only achieve low concentrations in the fluids that collect in the cavity (that may

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serve as culture media). In contrast, locally administered antibiotics offer the potential to obtain high concentrations directly within the wound cavity while minimizing systemic toxicity. Tobramycin-impregnated polymethylmethacrylate beads have been demonstrated to significantly reduce infection in open fractures[5-7]. However, non-absorbable carriers require a second surgical procedure for removal of the beads, adding cost to the health-care system as well as additional morbidity to the patient. Another option, locally administered vancomycin powder, seems to have some efficacy in lowering wound infection rates in the spine literature[8,9], although results are inconclusive[10,11].

Promising animal studies have demonstrated the potential for prophylaxis against infection with local injection of aqueous gentamicin. Yarboro et al. demonstrated that local injection of aqueous gentamicin was more effective in lowering wound bacterial counts than a sustained release device (calcium sulfate)[12]. A subsequent study found that a combination of systemic cefazolin and local gentamicin reduced wound bacterial counts by seven orders of magnitude[13], likely from the documented synergism between cephalosporins and aminoglycosides[14]. Lovallo et al. demonstrated decreased infection rates in patients undergoing total shoulder arthroplasty and receiving intra-articular injection of gentamicin[15]. One potential disadvantage of aqueous delivery is that it does not fill dead space.

The most common organisms that infect open fracture sites are gram-negative rods and gram-positive staphylococci[2] and are mostly nosocomial[16]. Although aminoglycosides are usually not first-line treatment for staphylococcal infections, they can be used for this purpose[16] because their bactericidal activity is concentration-dependent and local administration achieves high concentrations[17].

Despite potential toxic effects with systemic aminoglycosides, local administration has been documented to be safe. In animal studies using local delivery of tobramycin via different carriers, systemic levels are undetectable by twenty-four hours, whereas levels within the wound cavity remain at high concentrations for around fourteen days[18,19]. Human studies have also documented the safety of locally administered tobramycin with calcium sulfate carriers[20] and even prolonged administration (mean, sixty-three days) via an implanted pump[21].

Regarding local tissue toxicity, studies have shown no histological impact on bone healing with tobramycin impregnation of bone graft[19]. In vitro, Rathbone et al. found that high local concentrations of gentamicin results in osteocyte toxicity, whereas tobramycin does not[22]. However, there is a threshold (200 μg/mL), after which high tobramycin levels decrease osteoblast replication[23].

At our institution, locally administered antibiotics have been used for years in a subset of patients, determined by the treating surgeon. The purpose of this multisurgeon, single-institution, retrospective cohort study was to evaluate the effect of locally applied aqueous injections of aminoglycosides (gentamicin or tobramycin), as an adjunct to systemic therapy, on the prevalence of infection in patients with open fractures. We hypothesized that locally injected aminoglycosides would result in lower infection rates with no adverse effect on union rates, compared with standard treatment with systemic antibiotics alone.

Materials and Methods

Following institutional review board approval, data were retrospectively collected from January 1, 2008, through August 31, 2013. During this period, some patients with open fractures were treated with local antibiotics and some were not, according to their attending surgeon's preference. Patients with open fractures were identified by a search for Current Procedural Terminology (CPT) codes 11012 and 11011. Five hundred and twenty open fracture operative sites in 485 patients were identified. Fractures distal to the metacarpals were excluded, as these fractures are frequently treated with irrigation and debridement within the emergency department and patients are discharged with oral antibiotics without formal operative intervention. Exclusion criteria also included preexisting infection at the operative site, known major systemic infection at the time of injury, operative fracture care delayed more than thirty-six hours after injury, and patient age younger than ten years (juvenile patients). In total, 169 fractures (33%) were excluded per Table I. This left 351 fractures, of which 183 (52%) received systemic antibiotics alone and formed the control group. One hundred and sixty-eight fractures (48%) received administration of local antibiotics in addition to systemic antibiotics and formed the intervention group.

Data were collected from the institution's electronic medical records. Consult notes, inpatient progress notes, discharge summaries, operative reports, telephone messages, and clinic notes were reviewed along with follow-up clinic radiographs. Wound types were classified according to the Gustilo-Anderson classification. Because of high interobserver variability, type was retrospectively determined by a single senior-level resident, blinded to treatment group, on the basis of preoperative and intraoperative descriptions of wounds, amount of comminution on injury films, and descriptions of the necessary debridement.

TABLE I Exclusions

Reason	No. of Fractures
Phalanx fracture	57
Known prior infection	4
Lost perioperative reports or insufficient data	8
Delayed transfer	11
No open fracture*	18
Mandible fracture	3
Patient age younger than ten years	7
Locked chart	1
Antibiotic cement for bone loss	1
Mixed groups†	19
More than thirty-six hours to surgical procedure	2
Insufficient follow-up‡	38
Total	169

*This category includes open dislocation, traumatic amputation, removal of vestigial tail, and debridement of surgical site infection from another surgical procedure. †No local antibiotics were given at the initial irrigation and debridement, but they were given at subsequent fixation. ‡This category includes death, amputation to avoid reconstruction, amputation for necrosis without infection, and no follow-up after initial discharge.

TABLE II Comparison Between Groups*

Category	Control Group (N = 183)	Intervention Group (N = 168)	P Value
Patient age† *(yr)*	36.9 ± 17.1	39.9 ± 17.0	0.096
Patient sex‡			0.911
Female	64 (35.0)	57 (33.9)	
Male	119 (65.0)	111 (66.1)	
Tobacco use‡			0.729
None or less than half a pack per day	142 (77.6)	136 (81.0)	
One to one and a half packs per day	38 (20.8)	30 (17.9)	
Two or more packs per day	3 (1.6)	2 (1.2)	
Alcohol use‡			0.915
None or occasional	101 (55.2)	91 (54.2)	
Abuse	82 (44.8)	77 (45.8)	
Illicit drug use‡			0.541
No	134 (73.2)	128 (76.2)	
Yes	49 (26.8)	40 (23.8)	
Diabetes‡			0.333
No	176 (96.2)	157 (93.5)	
Yes	7 (3.8)	11 (6.5)	
Polytrauma‡			0.452
No	84 (45.9)	70 (41.7)	
Yes	99 (54.1)	98 (58.3)	
Intensive care unit admission‡			0.232
No	102 (55.7)	105 (62.5)	
Yes	81 (44.3)	63 (37.5)	
ASA score† *(points)*	2.5 ± 1.0	2.5 ± 0.9	0.899
Fixation location‡			0.847
Upper extremity	58 (31.7)	49 (29.2)	
Lower extremity	63 (34.4)	58 (34.5)	
Tibia	62 (33.9)	61 (36.3)	
Fixation type‡			0.015
Minimally invasive§	82 (44.8)	54 (32.1)	
Open reduction and internal fixation	53 (29.0)	72 (42.9)	
Intramedullary nail	48 (26.2)	42 (25.0)	
Time to surgical procedure† *(hr)*	11.6 ± 10.3	14.5 ± 10.7	<0.001#
Fracture type‡			0.08
I	22 (12.0)	22 (13.1)	
II	77 (42.1)	62 (36.9)	
IIIA	55 (30.1)	68 (40.5)	
IIIB	25 (13.7)	16 (9.5)	
IIIC	4 (2.2)	0 (0.0)	
Nonunions‡	28 (15.3)	24 (14.3)	0.881
Duration of follow-up† *(mo)*	12.5 ± 12.5**	11.3 ± 11.1	0.278#

*The demographic, fracture, and fracture-healing characteristics of control and intervention groups are associations based on exposure to local antibiotics. †The values are given as the mean and the standard deviation. ‡The values are given as the number of fractures, with the percentage in parentheses. §Minimally invasive fixation includes closed reduction percutaneous pinning and external fixation. #The p value was determined with use of the Mann-Whitney test. **This value includes one patient who was lost to follow-up very quickly but had already developed an infection and was therefore included.

TABLE III Infection Rates

	No Infection	Deep Infection	Deep and Superficial Infection
Control group (n = 183)	80.3% (147 fractures)	14.2% (26 fractures)	19.7% (36 fractures)
Intervention group (n = 168)	90.5% (152 fractures)	6.0% (10 fractures)	9.5% (16 fractures)
P value		0.011	0.010

Both intervention and control groups received systemic antibiotics as soon as possible according to standard of care. Per intervention protocol, all patients received systemic intravenous antibiotic prophylaxis both preoperatively and postoperatively. This included 1 to 2 g of weight-based cefazolin for type-I and II fractures or 600 mg of clindamycin if penicillin-allergic. Weight-based gentamicin was added for type-III fractures and penicillin G for barnyard-type contamination. The injection protocol for the intervention group was established by the senior author. Gentamicin was used until July 2011, at which point evidence for the inhibitory effect of gentamicin on osteoblasts caused a change to use of tobramycin[22]. At the completion of the irrigation and debridement and fixation procedure, 80 mg of aminoglycoside diluted in 40 mL of normal saline (2 mg/mL) was injected by inserting the needle down to bone and any implant after wound closure, so that the injection filled the wound cavity. For lower types of Gustilo-Anderson fractures, no further local antibiotic was administered. On the discretion of the attending surgeon, in some patients with type-II and III fractures, a catheter was placed within the wound and irrigations with a 0.5-mg/mL mixture of aminoglycoside and normal saline were performed every six hours for three to five days postoperatively. These wounds were dressed with a negative pressure dressing.

Data collected included age, sex, location of injury, date of injury, smoking status, alcohol use (abuse determined by presence of ethanol on trauma screen or documentation of abuse in the alcohol and other drug consult note), illicit drug use, presence of diabetes, presence of multitrauma (two or more long bone injuries or two or more systems involved), American Society of Anesthesiologists (ASA) score, surgeon performing the procedure, time to surgical procedure, type of fixation, and duration to the time of the latest follow-up. The primary outcome measure was the presence or absence of infection (excluding pin-track infections), differentiated into deep and superficial infections, based on Centers for Disease Control criteria[24]. Nonunion was indicated by recommendation of bone-grafting or other surgical intervention for nonunion.

Statistical Analysis

Raw infection rate comparison was reported as the odds ratio between the control group and the intervention group with use of the Fisher exact test for significance. Analysis was further adjusted by confounding variables, which were chosen on the basis of the association with outcome (infection) or primary exposure (locally administered antibiotics). Chi-square test or t test was used for the association, depending on the data type. Variables with a p value of ≤ 0.1 (tobacco use, alcohol use, diabetes, intensive care unit admission, ASA score, fracture location, fixation type, time to surgical procedure, fracture type) were included in the logistic regression model for the dichotomous infection outcomes. The Mann-Whitney U test was used to analyze the impact of time to surgical procedure.

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Results

Demographic Characteristics

The demographic characteristics are shown in Table II. No significant differences were detected in the comorbidities,

TABLE IV Infection Pathogens and Resistance

Culture Data*	No. of Fractures
Intervention group	
Polymicrobial	2
Oxacillin-sensitive *Staphylococcus aureus* (penicillin G)	2
Coagulase-negative staphylococcus (clindamycin, erythromycin, oxacillin, penicillin G)	1
Aeromonas	1
Clostridium (not perfringens)	2
Enterococcus	1
No growth on culture	5
Control group	
Polymicrobial	4
Serratia (ampicillin, ampicillin and sulbactam)	1
Aeromonas (ampicillin and sulbactam)	1
Citrobacter (ampicillin, ampicillin and sulbactam, cefazolin)	1
Chromobacterium (amikacin, ampicillin and sulbactam, imipenem, tobramycin)	1
Enterococcus	2
Clostridium (not perfringens)	1
Coagulase-negative staphylococcus	2
Oxacillin-resistant *Staphylococcus aureus* (erythromycin, oxacillin, penicillin G)	2
Oxacillin-sensitive *Staphylococcus aureus*	1
Enterobacter cloacae (ampicillin, ampicillin and sulbactam, cefazolin, ceftriaxone, piperacillin and tazobactam)	2
Klebsiella (ampicillin, ampicillin and sulbactam, cefazolin, ceftriaxone)	1
Candida	1
Stenotrophomonas maltophilia (ceftazidime)	1
Pseudomonas (ceftazidime, levofloxacin, piperacillin and tazobactam)	1
No growth on culture	10

*The antibiotic resistance appears in parentheses.

TABLE V Factors Impacting Infection*

Category	No Infection (N = 299)	Deep Infection (N = 36)	P Value	Deep and Superficial Infections (N = 52)	P Value
Patient age† *(yr)*	38.3 ± 17.4	40.3 ± 14.9	0.497	38.8 ± 15.6	0.845
Patient sex‡			0.189		1.00
Female	103 (34.4)	8 (22.2)		18 (34.6)	
Male	196 (65.6)	28 (77.8)		34 (65.4)	
Tobacco use‡			0.001		0.011
None to less than half a pack per day	241 (80.6)	25 (69.4)		37 (71.2)	
One to one and a half packs per day	56 (18.7)	8 (22.2)		12 (23.1)	
Two or more packs per day	2 (0.7)	3 (8.3)		3 (5.8)	
Alcohol use‡			0.051		0.069
None or occasional	170 (56.9)	14 (38.9)		22 (42.3)	
Abuse	129 (43.1)	22 (61.1)		30 (57.7)	
Illicit drug use‡			0.154		0.226
No	227 (75.9)	23 (63.9)		35 (67.3)	
Yes	72 (24.1)	13 (36.1)		17 (32.7)	
Diabetes‡			0.096		0.162
No	286 (95.7)	32 (88.9)		47 (90.4)	
Yes	13 (4.3)	4 (11.1)		5 (9.6)	
Polytrauma‡			0.597		0.88
No	132 (44.1)	14 (38.9)		22 (42.3)	
Yes	167 (55.9)	22 (61.1)		30 (57.7)	
Intensive care unit admission‡			0.074		0.171
No	181 (60.5)	16 (44.4)		26 (50.0)	
Yes	118 (39.5)	20 (55.6)		26 (50.0)	
ASA score† *(points)*	2.5 ± 1.0	2.8 ± 1.0	0.093	2.5 ± 0.9	0.095
Fixation location			0.104		0.084
Upper extremity	96 (32.1)	10 (27.8)		11 (21.2)	
Lower extremity	105 (35.1)	8 (22.2)		16 (30.8)	
Tibia	98 (32.8)	18 (50.0)		25 (48.1)	
Fixation type‡			0.004		0.023
Minimally invasive§	107 (35.8)	23 (63.9)		29 (55.8)	
Open reduction and internal fixation	111 (37.1)	6 (16.7)		14 (26.9)	
Intramedullary nail	81 (27.1)	7 (19.4)		9 (17.3)	
Time to surgical procedure† *(hr)*	13.5 ± 10.9	10.7 ± 8.4	0.122#	10.3 ± 8.0	0.023#
Fracture type‡			<0.001		<0.001
I	42 (14.0)	2 (5.6)		2 (3.8)	
II	122 (40.8)	7 (19.4)		17 (32.7)	
IIIA	108 (36.1)	10 (27.8)		15 (28.8)	
IIIB	25 (8.4)	15 (41.7)		16 (30.8)	
IIIC	2 (0.7)	2 (5.6)		2 (3.8)	
Nonunions‡	32 (10.7)	18 (50.0)	<0.001	20 (38.5)	<0.001
Duration of follow-up† *(mo)*	11.3 ± 11.2	16.3 ± 15.6	0.04#	15.4 ± 14.6	0.034#

*The demographic and fracture characteristics are based on presence or absence of infection (i.e., associations based on outcomes). †The values are given as the mean and the standard deviation. ‡The values are given as the number of fractures, with the percentage in parentheses. §This fixation includes closed reduction percutaneous pinning and external fixation. #These p values were determined with use of the Mann-Whitney test.

fracture characteristics (type and location), and duration of follow-up between the intervention group and the control group (Table II), except for fixation type ($p = 0.015$) and time to surgical procedure ($p < 0.001$). There was a higher rate of open reduction and internal fixation compared with minimally invasive treatment (including closed reduction percutaneous pinning and external fixation) in the intervention group (42.9%) compared with the control group (29.0%). The mean time to surgical procedure was longer in the intervention group (14.5 ± 10.7 hours) compared with the control group (11.6 ± 10.3 hours).

Infection Rates

For deep and superficial infections, the infection rate in the control group was 19.7% (thirty-six of 183 fractures). The deep and superficial infection rate in the intervention group was significantly lower ($p = 0.010$) at 9.5% (sixteen of 168 fractures). For deep infections alone, the control group had an infection rate of 14.2% (twenty-six of 183 fractures), compared with the intervention group's deep infection rate of 6.0% (ten of 168 fractures), which was significant at $p = 0.011$. Table III summarizes infection rates. Table IV shows the breakdown of pathogens and antibiotic resistances on specimens taken for culture.

Factors Impacting Infection

Compared with the mean time to surgical procedure (13.5 ± 10.9 hours) for the patients without infection, the mean time to surgical procedure in patients with deep infection was not significantly different ($p = 0.122$) at 10.7 ± 8.4 hours, but in the group of patients with combined deep and superficial infection, it was significantly shorter ($p = 0.023$) at 10.3 ± 8.0 hours. Tobacco use and type of fixation had significant impact ($p < 0.05$) on infection rates, as demonstrated in Table V. There was a significantly higher rate of infection in patients undergoing closed reduction percutaneous pinning and external fixation ($p = 0.004$ for deep infections and $p = 0.023$ for deep and superficial infections).

Multivariate Analysis

Multivariate analysis was performed to adjust for potential differences between the intervention group and the control group. Alcohol, diabetes, intensive care unit admission, ASA score, fracture location, time to surgical procedure, fixation, fracture type, and tobacco use were also deemed potential confounding variables with p values of <0.1, and so were also adjusted for in the multivariate analysis (Table VI). Results were similar between the adjusted and unadjusted odds ratios for deep and superficial infection with an unadjusted odds ratio of 2.5 (95% confidence interval [95% CI], 1.2 to 4.9; $p = 0.010$) and an adjusted odds ratio of 2.6 (95% CI, 1.2 to 5.6; $p = 0.015$). This was similar for deep infections only, with an unadjusted odds ratio of 2.7 (95% CI, 1.3 to 5.8; $p = 0.011$) and an adjusted odds ratio of 3.0 (95% CI, 1.1 to 8.5; $p = 0.034$).

TABLE VI Multivariate Analysis

Analysis	Odds Ratio*	P Value
Unadjusted (deep infections)	2.7 (1.3 to 5.8)	0.011
Adjusted (deep infections)	3.0 (1.1 to 8.5)	0.034
Unadjusted (deep and superficial infections)	2.5 (1.2 to 4.9)	0.010
Adjusted (deep and superficial infections)	2.6 (1.2 to 5.6)	0.015

*The values are given as the odds ratio, with the 95% CI in parentheses.

Nonunion Rates

Exposure to local antibiotics (Table II) did not have a significant impact on nonunion rates ($p = 0.881$). With at least 160 patients in each group, we could detect a difference (based on a 15% nonunion rate in the patients in the control group and a 5% nonunion rate in the patients in the intervention group) with a type-I error rate of $\alpha = 0.05$ and 0.8 power.

Discussion

This study found that locally administered antibiotics into open fracture wound cavities independently lowered infection rates. The deep infection rate in the intervention group (6.0%) was significantly lower ($p = 0.011$) than in the control group (14.2%). Likewise, the deep and superficial infection rate in the intervention group (9.5%) was significantly lower ($p = 0.010$) than that in the control group (19.7%). There is substantial variability of infection rates reported in the literature, from 4% to 63% in one systematic review[25] and 11% to 25% in other studies[26-28]. Given this variability, the current study had the advantage of using a control group of concomitantly treated patients within the same institution with similar demographic and fracture characteristics. This supports the significance of the lowered infection rates of the intervention group.

This study supports the findings of other studies documenting the efficacy of locally administered antibiotics[5,6,8,9]. The injection protocol used in this study has the advantage of not requiring a secondary surgical procedure to remove antibiotic beads and uses the previously documented efficacy of an aqueous form of delivery[12] and the documented synergism between aminoglycosides and cephalosporins[13,14]. For thirty-four of the more severe injuries, aqueous aminoglycosides were used for postoperative irrigations. This subset of patients did not have a difference in infection rates (15% for deep and superficial infections and 8% for deep infections; $p = 0.324$) compared with the patients receiving only a single dose of local antibiotic (12% for deep and superficial infections and 5% for deep infections; $p = 0.123$). The similar infection rates suggest, but do not prove, that postoperative irrigations may be effective in severe wounds and that we were able to effectively identify which patients might benefit from augmented treatment.

An additional advantage of using aminoglycosides rather than vancomycin powder, as the spine literature suggests[8,9], is that it allows vancomycin be reserved for therapeutic, rather than prophylactic, purposes. Historically, drug resistance has paralleled increasing antibiotic usage[29-31]. Thus, there is concern that increased use of vancomycin for prophylaxis could contribute to development of vancomycin-resistant organisms[32,33].

There was a significantly higher rate (p = 0.015) of open reduction and internal fixation at the index surgical procedure in the intervention group (42.9%) compared with the control group (29.0%). Although there was a trend toward lower infection rates in the intervention group of patients undergoing open reduction and internal fixation (4.4% compared with 6.1% for deep infection and 9.7% compared with 13.2% for deep and superficial infection), this did not reach significance (p = 0.694 for deep infection and p = 0.576 for deep and superficial infection). However, the low number of patients in this subset (fifty-three in the control group and seventy-two in the intervention group) means that this subset study was underpowered to detect a difference. Subset analysis showed that patients undergoing minimally invasive fixation had higher-grade fracture types and intensive care unit admission rates. However, there was no difference in the overall fracture type, comorbidities, or intensive care unit admission rates between the intervention group and the control group. We suspect that surgeons utilizing locally administered antibiotics became more confident in their ability to immediately perform open reduction and internal fixation, rather than temporizing with external fixation. The potential for higher rates of infection with more surgical dissection in the patients undergoing open reduction and internal fixation must be countered with the realization that improved stability with open reduction and internal fixation may lower infection rates. Although we attribute the lower infection rates to the locally administered antibiotics, this emphasizes the need for a randomized prospective study that also controls for the protocol by which to select patients for administration of postoperative local antibiotics.

There were significantly longer mean times to the surgical procedure in the intervention group (14.5 hours) compared with the control group (11.6 hours), which may be due to a decreased sense of urgency for emergent debridement in surgeons using local antibiotics. A higher rate of infection was associated with a shorter mean time to surgical procedure for patients with infection (10.3 hours) compared with patients with no infection (13.5 hours), although this might be due to differential local antibiotic utilization in these patients.

Locally administered antibiotics were not associated with a difference in the nonunion rate (p = 0.881, type-I error rate $\alpha = 0.05$, 0.8 power). However, some studies suggest that higher levels of aminoglycosides, especially gentamicin, cause osteocyte toxicity[22,23]. Antibiotic levels within the wound cavity, duration, and potential local toxicity were not directly assessed in this study. The nonunion rates were similar in the two groups (15.3% in the control group compared with 14.3% in the intervention group); however, this study only had the power to detect a difference of 15% nonunion compared with 5%, so we cannot rule out a small difference. Furthermore, there is inherent variability in the determination of the nonunion end point by a decision for further treatment. Further study with more objective prospective criteria is needed to conclusively determine whether there is a negative impact on osseous healing.

This study was limited by its retrospective nature. Patients were “surgeon randomized” in that the decisions of the treating surgeons determined inclusion into the intervention group compared with the control group. Thus, there is the potential that differences in surgeon debridement techniques or fixation choices contributed to the different infection rates, especially given that the senior author contributed 46% of the patients in the intervention group. There were thirteen surgeons who only intermittently used the injection protocol, contributing patients to both groups. They may have been more likely to use local antibiotic therapy in more severe injuries, which could have resulted in higher infection rates in the intervention group than would otherwise be expected.

To minimize poor interobserver agreement with Gustilo-Anderson classification[34], all injuries were classified by a single senior orthopaedic resident blinded to treatment group. However, despite attempts to consistently stratify patients, observer variability makes it possible that fractures in this study would be classified differently by others. Hence, infection rates as a function of Gustilo-Anderson classification in this study may not be comparable with other reports.

This study concurs with basic scientific studies[12,13] demonstrating the efficacy of local aqueous aminoglycoside administration as an adjunct to systemic antibiotics in lowering infection rates. The intervention group receiving locally administered aminoglycosides, by our protocol, demonstrated a significantly reduced infection rate compared with the control group receiving systemic antibiotics alone. Although this study was limited by its retrospective nature and the confounding variable of surgeon experience or technique impacting results, we hope that it will provide support for future prospective, blinded, and randomized trials comparing locally injected aqueous aminoglycosides to both systemic antibiotics alone as well as other forms of local antibiotic delivery. ■

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