Dose effectiveness of piperacillin/tazobactam in prophylaxis of type III open fractures

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Abstract:

Background
Open-fractures are commonly classified using the Gustilo-Anderson classification system. A type III fracture is defined as an open segmental fracture, open fracture with extensive soft tissue damage, or a traumatic amputation. Patients with type III fractures have up to a 40% chance of developing an infection at the site of injury. Piperacillin/tazobactam is sometimes used for post-operative prophylaxis in this patient population, however optimal dosing strategies are unknown. This study explored the safety and efficacy of different doses of piperacillin/tazobactam in the prevention of surgical site infections in contaminated type-III open fractures.

Methods
This study was a retrospective chart review comparing the safety and efficacy of different doses of piperacillin/tazobactam in the prevention of surgical site infections in contaminated type-III open fractures. Patient charts were reviewed from December 01, 2017 to November 30, 2021. Patients were included in the study if they were 18 years or older, received at least one dose of piperacillin/tazobactam 4.5 or 3.375-grams for open fracture post-op prophylaxis, and had a contaminated Gustilo-Anderson type III open fracture of a long bone (humerus, radius, ulna, femur, tibia, fibula). Patients were excluded if they expired within 24 hours of admission, amputation of the injured extremity occurred within 24 hours of arrival, or if the patient received other systemic antibiotics during the post-operative prophylaxis period. The primary outcome was the rate of development of identified surgical site infections (SSI) within 30 days after initial surgery. Secondary outcomes within 30 days after the initial surgery included rate of AKI, rate of Clostridioides difficile positive test, in-hospital mortality, dose compared to actual body weight versus rate of surgical site infection, dose appropriateness of piperacillin/tazobactam post-op versus creatinine clearance, and dose/creatinine clearance compared to rate of surgical site infection.

Results
There were 27 patients identified with contaminated type III open fractures. A total of 15 patients received piperacillin/tazobactam 4.5-grams while 12 patients received the piperacillin/tazobactam 3.375-gram dosing strategy. There was a total of 6 surgical site infections in these patients within 30 days of initial surgery, 4 of which received piperacillin/tazobactam 4.5-grams versus 2 who received 3.375-gram dosing (26.7% vs. 16.7%, P=0.66). There was a difference in 30-day mortality favoring the higher dosing strategy of 4.5-grams (0% vs. 33.3%, P=0.028) however the mean injury severity score was higher in the lower dosing strategy of 3.375-grams (11.9 vs. 20, P=0.035). This suggests that patients receiving the 3.375-gram dosing strategy had more severe injuries than those that received the 4.5-gram dosing strategy.

Conclusion
There was no difference in the rate of surgical site infections at 30 days in patients with contaminated type-III open fractures who received either piperacillin/tazobactam 4.5-grams or 3.375-gram dosing for post-op prophylaxis.

Keywords: open-fracture, type-III, piperacillin/tazobactam, trauma

1. Background

Open-fractures caused by trauma can lead to postoperative complications including surgical site infections. Surgical site infections may be responsible for surgical revision, loss of function, loss of limb, and/or longer hospital stays. These types of complications can cost the United States up to $10 billion every year.[1]

These types of fractures are classified using the Gustilo-Anderson classification system.[2] A type I open-fracture will have a laceration of less than 1 cm while a type II open-fracture will have a laceration larger than 1 cm without soft tissue damage. Type III open-fractures are considered the most devastating and range from segmental fractures with extensive soft tissue damage to traumatic amputations.[2,3]

For these types of injuries, the Eastern Association for the Surgery of Trauma (EAST) guidelines recommend administrating postoperative prophylaxis with an aminoglycoside and a cephalosporin. Furthermore, the addition of high dose penicillin is recommended when there is gross contamination.[4] Gross contamination of an open-fracture increases the risk of Clostridium species infection.[5] These guidelines were published in 2011 and newer data are now available.

A 2016 study conducted by Redfern and colleagues found no difference in surgical site infection rate in type III open-fractures in patients that received cefazolin plus gentamicin versus patients receiving piperacillin/tazobactam.[6] An aminoglycoside sparing regimen may be beneficial in the trauma population due to the concern of giving nephrotoxic agents in patients that may lack renal perfusion due to blood loss or hypotension. Another concern is that trauma patients may have augmented renal clearance, defined as a creatinine clearance (CrCl) greater than or equal to 130 mL/min. Achieving and maintaining therapeutic aminoglycoside concentrations in this patient population is challenging.[6,7] To date, there is a lack of literature defining the optimal dose of piperacillin/tazobactam in the prevention of surgical site infection after a contaminated type III open-fracture. This study aims to explore that dose by comparing dosing regimens of piperacillin/ tazobactam 4.5-grams versus 3.375-grams.

2. Methods

A retrospective chart review was conducted from December 1st, 2017 to November 30th, 2021 at the University Medical Center of Southern Nevada (UMCSN). Patient data was extracted from the UMCSN trauma registry using ICD-10 codes for type III open-fractures. Electronic health records were searched for patients who had documented grossly contaminated type III open-fractures and received piperacillin/tazobactam for post-operative prophylaxis. Eligible patients had to be 18 years of age or older, had received either piperacillin/tazobactam 4.5-grams or 3.375-grams, and the antibiotic had to be administered within 12 hours postoperatively. Patients were excluded if they expired within 24 hours of admission, if the injured limb was amputated within 24 hours, if other antibiotics were given during the postoperative prophylaxis period, or if the subsequent dose of piperacillin/tazobactam was changed from the initial dose given.

The primary outcome was rate of surgical site infection within 30 days after the initial surgery. Secondary outcomes included rate of acute kidney injury, defined as an increase in serum creatinine of 0.3 mg/dL or more over 48 hours while on piperacillin/tazobactam, *Clostridioides difficile* positive test within 30 days of receiving piperacillin/tazobactam, and in-hospital mortality. Additionally, two subgroup analyses were performed. Patients with augmented renal clearance (CrCl ≥ 130 mL/min) were examined

looking for differences in surgical site infection rates and mortality between the two different doses of piperacillin/tazobactam. Actual body weight of patients were compared against dose of piperacillin/tazobactam versus surgical site infection and mortality rates.

Descriptive statistics were used for demographic data. For dichotomous data and proportions χ^2 test or Fisher's exact test were utilized. A Student's t-test was used to compare continuous data.

3. Results

216 patients were identified within the UMCSN Trauma Registry that had type III open-fractures. 152 of these patients did not receive piperacillin/tazobactam and another 37 patients did not meet the pre-specified inclusion criteria. The 27 patients remaining were included in the analysis with 15 patients receiving piperacillin/tazobactam 4.5-grams and 12 patients receiving piperacillin/tazobactam 3.375-grams for post-operative prophylaxis (figure 1). Baseline characteristics were mostly similar between both arms of the study and are listed in table 1. The mean injury severity score was significantly higher in the 3.375-gram dosing group signifying worse injuries when presenting to the hospital (20 vs. 11.9; p = 0.04).

For the primary outcome, the rate of surgical site infections at 30 days post-operatively did not differ between both groups (26.7% vs. 16.7%; p = 0.66). Detailed results of the primary outcome can be found in table 3.

There was no significant difference in AKI rate (6.7% vs. 16.7%; p=0.57) and no patients had a *Clostridioides difficile* positive test within 30 days of receiving piperacillin/tazobactam.

There was a significant difference detected in regards to mortality. No patients expired in the piperacillin/tazobactam 4.5-gram dosing group while 4 patients expired in the 3.375-gram dosing group (0.0% vs. 33.3%; p = 0.03). The detailed results of the secondary outcomes can be found in table 4.

A subgroup analysis on patients experiencing augmented renal clearance identified 5 patients in each cohort. Rate of surgical site infection did not differ (0.0% vs. 40%; p = 0.44) and no patients expired within 30 days of their original injury. When analyzing patients in regard to weight, there were no differences found in the rates of surgical site infections or mortality in patients greater than or equal to 95 kg or less than 95 kg. Analysis of these subgroups are summarized in table 5.

4. Discussion

This study compared the incidence of surgical site infections in contaminated type III open-fractures utilizing different doses of piperacillin/tazobactam. We found that within the initial 30 days after initial surgery there was no statistical difference in rate of surgical site infections between patients receiving piperacillin/tazobactam 4.5-grams or 3.375-grams for postoperative prophylaxis. Our infection rate was similar to those found in previous studies.[6]

There was no difference in amount of AKIs patients developed and no patient experienced a positive *Clostridioides difficile* test which reinforces piperacillin/tazobactam's safety profile in a trauma population.

There was concern that augmented renal clearance may reduce the efficacy of renally cleared antibiotics and result in treatment failure.[7] Our subgroup analysis found no difference in surgical site infection rate or mortality rate when we examined patients with CrCl $\geq$ 130 mL/min. Although the patient population was small these findings may be important in determining the efficacy of piperacillin/tazobactam in trauma patients as a whole.

4.1 Limitations

There were several limitations in this study. It was a retrospective, single-centered study so the generalizability of the results may be questionable. There was a significant difference found in the baseline injury severity score which may have affected the mortality outcome. Patients who received piperacillin/tazobactam 3.375-grams had higher mortality rates but were also more significantly injured at presentation. This study relied on ICD-10 codes and proper charting to find patients which may have caused a selection bias due to missing patients from our data pull.

5. Conclusion

There was no difference in the rate of surgical site infections at 30 days in patients with contaminated type-III open fractures who received either piperacillin/tazobactam 4.5-gram or 3.375-gram dosing for post-op prophylaxis. Patients that received the piperacillin/tazobactam 3.375-gram dosing had a higher mortality rate but they were also more severely injured. Randomized, prospective trials may be warranted to determine the most appropriate dosing strategy for piperacillin/tazobactam for prophylaxis in contaminated type-III open fractures.

Conflicts of Interest

The authors of this manuscript have nothing to disclose and no conflicts of interest.

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Figures and Tables

Figure 1:

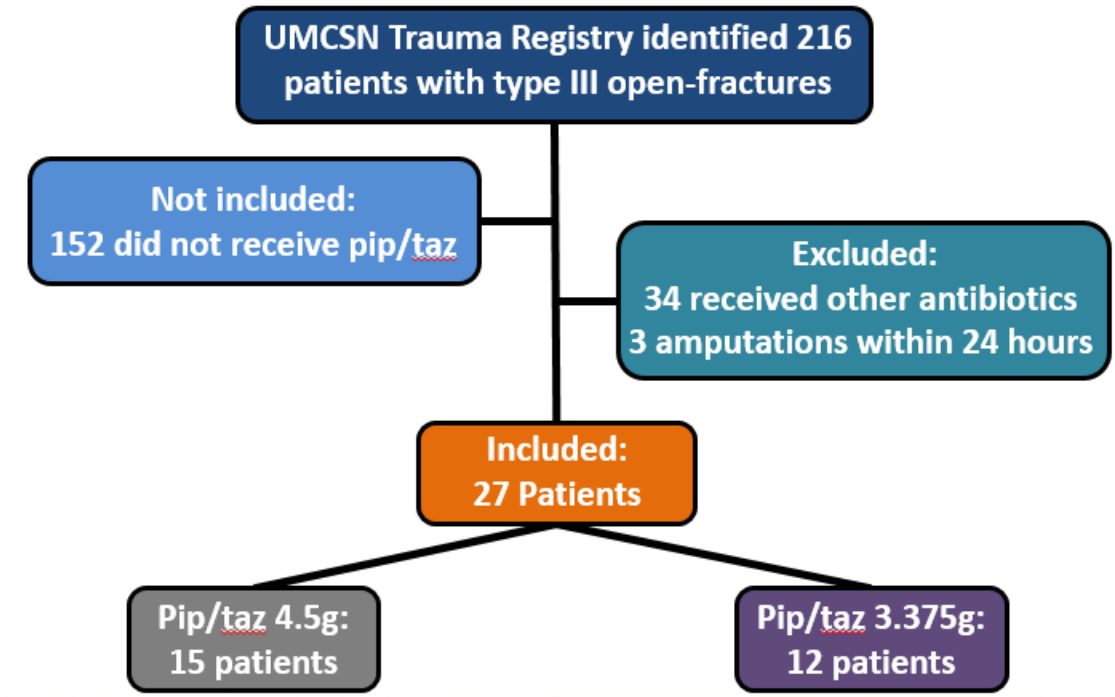

Table 1: Baseline characteristics

	Pip/taz 4.5g n=15	Pip/taz 3.375g n=12	P value
Age, yr, mean (±SD)	46 (±16)	40 (±19)	0.21
Male, n (%)	11 (73.3)	8 (66.7)	0.52
CrCl, ml/min, mean (±SD)	130.7 (±80.9)	114.3 (±65.9)	0.30
Weight, kg, mean (±SD)	102.1 (±33.6)	86.8 (±24.5)	0.10
Duration of stay, d, mean (±SD)	8.4 (±9.2)	6.8 (±5.3)	0.30
ISS, mean (±SD)	11.9 (±4.6)	20 (±15.9)	0.04
ARC, n (%)	5 (33.3)	5 (41.7)	0.48

Baseline characteristics were similar between both cohorts except for the injury severity score

Table 2: Primary Outcomes

n (%)	Pip/taz 4.5g n=15	Pip/taz 3.375g n=12	P value
SSI	4 (26.7)	2 (16.7)	0.66

SSI: Surgical site infection

Table 3: Secondary Outcomes

n (%)	Pip/taz 4.5g n=15	Pip/taz 3.375g n=12	P value
30 day mortality	0 (0)	4 (33.3)	0.03
AKI	1 (6.7)	2 (16.7)	0.57
***Clostridioides difficile* positive test**	0 (0)	0 (0)	-

AKI: Acute kidney injury

Table 4: Augmented renal clearance subgroup analysis

Patients with ARC at admission			
n (%)	**Pip/taz 4.5g n=5**	**Pip/taz 3.375g n=5**	**P value**
SSI	0 (0)	2 (40)	0.44
30 day mortality	0 (0)	0 (0)	-

SSI: Surgical site infection

Table 5: Actual body weight subgroup analysis

Actual body weight ≥ 95 kg			
n (%)	Pip/taz 4.5g n=8	Pip/taz 3.375g n=3	P value
SSI	2 (25)	0 (0)	0.51
30 day mortality	0 (0)	0 (0)	-
Actual body weight < 95 kg			
n (%)	Pip/taz 4.5g n=7	Pip/taz 3.375g n=9	P value
SSI	2 (28.6)	2 (22.2)	0.61
30 day mortality	0 (0)	4 (44.4)	0.07

SSI: Surgical site infection