The Effect of Gel Containing Teicoplanin and Gentamicin the Prevention of Early Onset Bone Infection in Patients with Ga Type Ii and Iiiopen Fractures

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Research Article

ABSTRACT

Introduction: Wound infection is still one of the main complications leading to osteomyelitis. Systemic antibiotics reduce infection in the open fracture while local delivery of antibiotics can provide higher doses to wounds without toxic systemic effects. The aim of the present study was to compare the efficacy of systemic antibiotics alone and systemic antibiotics plus a local antibiotic gel in the treatment of patients with Gustilo-Anderson (GA) type II and III open fractures.

Methods: 102 patients with GA type II and III open fractures and delayed fixation were included. The sterile gel and antibiotics (teicoplanin and gentamicin) were mixed under sterile conditions during surgery and then administrated at the fracture site. Microbial samples for culture and antibiogram were taken before and after fixation, and before first debridement. Patients were followed up for 3 weeks after surgery.

Results: In general, 36% of patients who were debrided more than twice and 0% of those with more than 5 times debridement developed infection in the antibiotic gel group compared to 50% and 100% of those in the classic treatment group, respectively. The mean number of debridement times was different between the two groups, being less in the antibiotic gel group, but the difference was not significant (p=0.079). Twenty percent of GA grade IIIC cases developed wound infection compared to 40% of the classic group (p=1.00).

Conclusion: Local antibiotic gel resulted in a lower rate of infection compared to classic treatment, yet the difference was not significant. The difference between the two groups for higher degree fractures (GA type IIIC) and more severe infection was more remarkable, meaning that patients with more severe fractures may benefit more from locally delivered antibiotics.

Keywords: Open fracture, Infection, Local antibiotics

INTRODUCTION

Wound infection prevention is one of the main concerns of surgeons in the treatment of open fractures. Open fractures are usually contaminated and infection is one of the major complications. Despite the numerous advances in the treatment of open fractures with novel surgical techniques, wound infection is still one of the main complications leading to osteomyelitis, reduced limb function, increased disability and even septic conditions [1]. In general, the risk of infection depends on the severity of injury, the amount of skin loss, mechanism of injury and the patient's general condition, e.g. a history of chronic diseases, smoking and obesity [2-4]. The Gustilo open fracture classification system is the most commonly used classification system for open fractures. It was created by Gustilo and Anderson [5] and then further expanded by Gustilo et al. [3].

This system uses the amount of energy, the extent of soft-tissue injury and the extent of contamination for determination of fracture severity. Progression from grade 1 to 3C implies a higher degree of energy involved in the injury, higher soft tissue and bone damage and higher potential for complications. Important to recognize that grade 3C fracture implies vascular injury as well (Chart 1).

Chart 1. Gustilo-Anderson open fracture Classification.

I	Open fracture, clean wound, wound <1 cm in length
II	Open fracture, wound >1 cm but <10 cm in length without extensive soft-tissue damage, flaps, avulsions
III	Open fracture with extensive soft-tissue laceration (>10 cm), damage, or loss or an open segmental fracture. This type also includes open fractures caused by farm injuries, fractures requiring vascular repair, or fractures that have been open for 8 h prior to treatment
IIIA	Type III fracture with adequate periosteal coverage of the fracture bone despite the extensive soft-tissue laceration or damage
IIIB	Type III fracture with extensive soft-tissue loss and periosteal stripping and bone damage. Usually associated with massive contamination. Will often need further soft-tissue coverage procedure (i.e., free or rotational flap)
IIIC	Type III fracture associated with an arterial injury requiring repair, irrespective of degree of soft-tissue injury

The rate of infection has been reported as 0-2% for type I fractures, 2-10% for type II fractures and 10-50% for type III fractures by some studies [3,4]. The degree of soft tissue injury is usually defined by the Gustilo-Anderson (GA) classification [2]. For example, in tibial fractures the infection rate varies from 1.7% for GA type I to 9.2% for GA type IIIB fractures with intramedullary nails [5].

The current management of open fractures consists of wound irrigation, serial radical debridement, systemic antibiotics and bone stabilization [6]. A systemic review published in 2004 showed that prophylactic systemic antibiotic administration might reduce the absolute risk of early wound infection by 60% [7]. Although intravenous antibiotics provide adequate antibiotic concentration in the blood, yet infection recurrence, high cost of antibiotics and poor patient compliance are common problems [8].

Therefore, considering the importance of wound infection in the patients' outcome and related morbidity, many attempts have made by clinicians to develop new techniques for reducing the risk of infection. One suggested approach is to increase the effectiveness of antibiotics by local delivery at the wound and implant site [9-11]. In a meta-analysis conducted by Craig et al. in 2014, the augmentation of prophylactic antibiotic therapy by delivering local antibiotics proved to be beneficiary to patients with severe fractures [1]. Other human and animal studies have also confirmed the effectiveness of local antibiotics in decreasing the rate of wound infection in open fractures [12-15].

Many factors such as upper versus lower extremities, healed versus non-healed fractures, quality of the soft tissues overlying the affected bone, as well as the patient's comorbidities affect the application of local antibiotics. These factors must be considered in daily practice [16]. Some researchers have used local antibiotics in the form of cement or antibiotic beads [17,18]; on the contrary, some others have used a combination of absorbable gel and antibiotics [19].

The advantage of using absorbable gel to cement the absence of a foreign body in the wound and prevent thermal damage and surgery again to remove cement. Nonetheless, there is no standard treatment method due to the variability of clinical presentations. The aim of this study was to compare the effectiveness of systemic antibiotics alone and systemic antibiotics plus a local antibiotic gel in the prevention of early onset bone infection in patients with GA type II and III open fractures.

MATERIALS AND METHODS

In this case-control study,102 patients with GA type II and III open fractures who were referred to Shahid Kamyab Hospital (Mashhad, Iran) were enrolled. The patients' age ranged from 16 to 60 years and final fixation was delayed up to 24 h after admission due to several reasons such as head trauma, inappropriate general condition, etc. Patients with a history of recent admission to hospital or antibiotic usage, immunocompromised patients or those under corticosteroid therapy, diabetic patients, patients with a history of cancer, osteomilities, sensitivity to antibiotics, nephropathy or hearing impairment, children, pregnant women and those older than 60 years were excluded from the study. The participants were then randomly assigned into two groups of classic treatment (n=50) and classic treatment plus local antibiotic gel (n=52).The two groups were matched for age, gender and type of fracture.

By considering the probable germs, antibiotic complications and their general effects on the body after release in the local site, teicoplanin and gentamicin were chosen for antibiotic combination of the topical gel. The gel was prepared by the combination of carbopol,

By considering the probable germs, antibiotic complications and their general effects on the body after release in the local site, teicoplanin and gentamicin were chosen for antibiotic combination of the topical gel. The gel was prepared by the combination of carbopol, propylene glycol and EDTA. Triethanolamine or sodium hydroxides were used for pH adjustment. The prepared gel was sterilized by autoclave. The final antibiotic gel was prepared during surgery by mixing of

sterilized gel with 160 mg of gentamicin and 800 mg teicoplanin the antibiotic dosage was chosen based on the standard dose used in polymethylmethacrylate (PMMA) and was adjusted according to the type of antibiotic gel [28].

The prepared antibiotic gel was then applied on the fracture site and the surrounding tissue. Microbial samples for culture and antibiogram were taken both before and after fixation, and before initial debridement. Patients were followed for 3 weeks after surgery regarding infection and other complications. If infection was detected (with local redness, discharge, wound dehiscence), another sample was taken for culture and antibiogram analysis. Several methods for preventing infection in open fractures, including the use of gel foam soaked in antibiotic use and orthopedic cement, the use of absorbable calcium phosphate cement and absorbing gel impregnated with antibiotics approved ethics committee. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences and an informed consent was obtained from each participant prior to study entrance.

Statistical Analyses

The collected data were analyzed by the SPSS software ver. 15. Chi-square test, Mann-Whitney test and independent sample t-test were used wherever appropriate. The significance level was set as $p<0.05$.

RESULTS

All 102 patients with GA type II and III open fractures and delayed fixation completed the study. The mean age of patients in the classic treatment group was 42.5 years, consisting of 30 (60%) male patients. In the antibiotic gel group, 34 (65.38%) patients were male and 18 (34.62%) female with a mean age of 40 years. We found no significant difference between the two groups regarding age (p=0.36), type of fracture (p=0.608), mechanism of injury (p=0.724), type of infection after 72 h of first debridement (p=0.43), primary wound type (p=0.28) and the fixation plan (p=0.698) **(Table 1)**. The mean number of hospitalization days differed between the two groups, yet indicating no significant difference (p=0.23) **(Table 1)**.

Table 1. Comparison of demographic data and fracture-related variables between the two studied groups.

Variable	Classic treatment No. (%)	Antibiotic gel No. (%)	P-value
Gender			
Male	30 (60)	34 (68.38)	0.574
Female	20 (40)	18 (34.62)	
Mean age (years)	42.5	40	0.3
Fracture type			
II	27 (54)	34 (65.38)	0.608
IIIA	8 (16)	7 (13.46)	
IIIB	10 (20)	6 (11.54)	
IIIC	5 (10)	5 (9.62)	
Mean duration of hospital stay (day)	5.5	5	0.23
Mechanism of trauma			
Car accident	9 (18)	8 (15.38)	0.724
Crush	8 (16)	4 (7.69)	
Fall	8 (16)	9 (17.31)	
Motor cycle accident	22 (44)	27 (51.92)	
Work accident	3 (6)	4 (7.69)	
Primary wound type			
Non infected	37 (74)	43 (82.69)	0.28

Infected	13 (26)	9 (17.31)	
Fixation plan			
IMN	25 (50)	24 (46.15)	0.698
Plate	25 (50)	28 (53.85)	

Among the 52 patients treated with antibiotic gel, wound infection during the treatment period occurred in 7% of those with a primary clean wound, 25% of patients with soil-contaminated wounds and 50% of the cases who had wounds with other types of contamination. The same figures were 7%, 37.5% and 62.5% for the classic treatment group, respectively. Accordingly, wound infection during treatment occurred in 12.5% of patients with car accident, 25% of those with crush injury, 0% with fall accident, 18.5% of those with motorcycle accident and 50% of those injured in work place. The same figures were 33% (car accident), 25% (crush), 18% (motorcycle accident) and 66% (workplace injuries) in the classic treatment group.

With respect to the fracture type, 14.7% of patients with GA type II, 14.2% with type IIIA, 33% of grade IIIB and 20% of grade IIIC developed wound infection during the treatment period in the antibiotic gel group. In the classic treatment group, 29.62% of patients with GA grade II, 12.50% of grade IIIA, 20.00% of grade IIIB and 40% of grade IIIC were affected with wound infection.

Primary culture results revealed that in the antibiotic gel group, infection occurred in 11% of those treated with one antibiotic and 44% of patients who received two antibiotics. Among patients having received the classic treatment, 6% of those treated with one antibiotic, 75% of patients treated with 3 antibiotics and 60% of patients receiving Primaxin® (imipenem/cilastatin), developed infection during the treatment period. The second culture results in the gel group indicated that none of the patients treated with vancomycin alone, but 50% of patients who had received vancomycin plus Primaxin® developed infection during the treatment period. The same results showed that all patients treated with vancomycin and Primaxin® in the classic group developed infection despite none of the patients treated with vancomycin alone.

Regarding the number of wound debridements, 36% of patients who received more than 2 times debridement and 0% of those with more than 5 times debridement developed infection in the antibiotic gel group. In the classic treatment group, 50% of patients with more than 2 times debridement and 100% of those who received more than 5 times debridement developed infection. Comparison of the mean debridement times showed a difference between the two groups, being less in the antibiotic gel group, however the difference is not significant (p=0.079).

DISCUSSION

Bone infection is still a serious problem following trauma and surgery in spite of the newly advanced surgical techniques and the availability of new broad-spectrum antibiotics [20,21]. The preferred typical approach to bone infection includes surgical debridement and antibiotic therapy [22]. Although intravenous antibiotics provide adequate blood concentration, yet the infection occurrence and recurrence is still a major obstacle for surgeons [8]. Since Buchholz introduced the original concept of incorporation of antibiotics into PMMA, this method has been commonly used and investigated [23].

Many researchers have compared the application of additional locally delivered antibiotics with classic prophylactic antibiotic regimens in the prevention of infection in open fractures in animal and human studies. In animal study, Penn-Barwell et al. used local bismuth thiols (BTs) in rat implants contaminated with Staphylococcus aureus. The results showed that the local administration of BTs to the infected open fracture wounds augment the effect of systemic antibiotics and reduce the infection rate [19]. Other researchers also investigated the effectiveness of local antibiotics as an adjunct to systemic antibiotics in treating animal fractures and found it to be an effective method [24,25]. In this study, we aimed to compare the effect of local antibiotic gel besides classic treatment and classic treatment alone in decreasing the rate of infection during the treatment period in GA type II and III fractures. The patients in the two groups showed no significant difference regarding age, type of fracture, mechanism of injury, type of infection after 72 h of first debridement, type of primary wound and the fixation plan. The mean number of hospitalization days also revealed no significant difference between the two groups (5 days in the gel group vs. 5.5 days in the classic treatment group).

Regarding the development of delayed infection, we found no significant difference between the two groups based on the primary wound cleanness, type of contamination, type of trauma and type of fracture. Among the patients in the classic treatment group, 29.62% of GA type II fractures, 12.50% of GA type IIIA fractures, 20% of GA type IIIB fractures and 40% of GA type IIIC fractures were infected during the follow up period. The related infection rate for patients in the antibiotic gel group were: 14.7% for type II, 14.2% for type IIIA, 33% for type IIIB and 20% for type IIIC. Although the

reduction in infection rate between the two groups for different GA type fractures was not significant, for GA type IIIC fractures the difference between the two groups for delayed infection was considerable (40% in the classic group vs. 20% in the antibiotic gel group); which indicated that antibiotic gel was relatively effective in decreasing the risk of infection in GA type IIIC fractures (p=1.00). Furthermore, the mean number of wound debridement was also less in the antibiotic gel group but the difference was not significant (p=0.079). Cai et al. [9] evaluated 28 patients with open fractures of long bones who were treated with calcium sulfate mixed with vancomycin. The authors stated that this technique could decrease the incidence of deep infection without impairing the bone healing process. In another study, Agarwala et al. used local antibiotics in the form of absorbable calcium sulfate beads in four patients with infected hip or knee joint prostheses and found it to be an effective adjuvant to standard debridement, parenteral antibiotics and revision of implants [26]. These results are somehow similar to ours, showing the efficacy of additional locally delivered antibiotics in decreasing the infection rate.

Craig et al. [1] in a systemic review of patients with open tibia fractures treated with intramedullary nails compared patients receiving additional locally delivered antibiotics with those receiving standard care. They concluded that local antibiotics in addition to the prophylactic antibiotic regimen are effective in reducing the risk of infection and those with severe fractures will receive the greatest benefit [1]. Our findings are similar to Craig's, showing a decreased rate of delayed infection in the antibiotic gel group. We also found that patients with more severe fractures benefit more from the local antibiotic gel. To note, in Craig's study, the results of different studies were compared and the authors admitted that in no trial the two treatments were directly compared with each other. However, in this study we compared the effects of the classic prophylactic antibiotic regimen with additional local antibiotic gel.

Nevertheless, in Lawing et al.'s study, the efficacy of local injection of aminoglycosides besides systemic treatment was evaluated in patients with open fractures [27]. This study included 351 patients (183 in the control group and 168 in the intervention group). They found a significant decrease in the overall rate of infection in patients receiving local antibiotics. Their results were also similar to ours, showing the efficacy of local antibiotics in reducing the infection rate. However, the reason that we did not find a significant difference in our study could be related to our small study population.

CONCLUSION

Local antibiotic gel resulted in a lower rate of infection compared to classic treatment, yet the difference was not significant. The difference between the two groups for higher degree fractures (GA type IIIC) and more severe infection was more remarkable, meaning that patients with more severe fractures may benefit more from locally delivered antibiotics.

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