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Research Article

A Randomised Control Trial to Compare Topical Use of Antibiotic Versus Conventional Management of Open Fractures

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Abstract

Introduction: The evidence is building that adding topical antibiotic to standard systemic antibiotic in management of open fractures is lowering the infection rate and complications, however, there is a scarcity of studies in low resource settings. This study aims to evaluate the effect of topical antibiotic on infection rate in open fractures managed in limited-resource settings.

Methods: This is a prospective randomised controlled trial comparing topical antibiotic (aqueous gentamycin) and non-topical antibiotic groups. The primary outcome measures were chronic infection rate while the secondary outcome measures included the length of hospital stay, number of surgical procedures and rate of non-union.

Results: We recorded a significant reduction of infection rate in the 2nd ($p = 0.015$) and 6th ($p = 0.045$) weeks, but non-significant reduction at 6th month ($p = 0.3$) in the topical group compared to the non-topical group. As compared to the non-topical group, for the topical group we recorded a reduced number of procedures ($p = 0.004$), reduced length of hospital stay ($p = 0.006$), the rate of non-unions at 6-month follow-up ($p = 0.01$).

Conclusion: This study shows that in the management of open long bone fractures in low-resource settings, the use of local aqueous gentamycin administration as an adjunct to conventional management is effective in lowering the infection rates, reducing the number of operations, reducing length of hospital stay and non-union rates. Despite some methodological limitations, the authors hope the study contributes to the body of evidence for the use of topical antibiotics in the management of open fractures.

Keywords: *Open Fractures Management; Topical Antibiotics; Infection Rate; Non-Union Rate*

Introduction

The World Health Organisation (WHO) estimates that 5.8 million people die each year from traumatic injuries and 90% of those deaths occur in low and middle income countries [1]. Motor vehicle accidents, violence and war were reported to be the leading cause of injuries in the developing countries [2]. Non-communicable diseases are estimated to cause 56% of all deaths in Papua New Guinea and 8% were due to injuries [3]. In the Western Pacific region, incidence of injuries is as high as 333 per 100 000 in a population based study in Fiji [4]. The reports on trauma from Papua New Guinea (PNG) pointed out that trauma is a leading surgical admission and the main cause of death in the reproductive age group [5,6]. Following more frequent trauma in low and middle-income countries, open bone fractures frequency is expected to be higher there than in high-income countries, it is estimated to be 11.5 per 100, 000 persons per year [7].

Since the infection rate is relatively high in types II and type III, the current practise of management involves immediate use of systemic antibiotics, debridement, irrigation, early closure and the stabilisation of the fracture [8-10]. The evidence is growing that the use of a prophylactic systemic antibiotic in combination with a topical antibiotic has lowered the infection and osteomyelitis rates compared to the use of prophylactic systemic antibiotics alone [9-19].

Goal of the Study

The main goal of this study is to investigate in a low-resource setting whether adding a topical antibiotic to routine management of open fractures makes a difference in the infection rate.

Methodology

Study design

We performed a prospective randomised controlled trial to determine the efficacy of the topical use of aqueous gentamycin in combination with other systemic antibiotics and conventional management in open fractures. The study was conducted at the Orthopaedic Ward of Madang Provincial Teaching Hospital, Papua New Guinea, between January 2019 and December 2021. We used a table for calculating minimum sample size as 50 in each allocation group assuming standardized difference at 0.8, power as 0.8, and significance level at 0.05. Objectives of the study were: 1/ Assess effect of topical gentamycin on infection rate; 2/ Evaluate effect of topical gentamycin on other postoperative outcomes, such as length of hospital stay, number of procedures, and rate of non-union.

Inclusion criteria

All consecutive patients with clinical and radiological diagnosis of open long bone fractures with Gustilo-Andersons Type II, IIIA and IIIB admitted to the orthopaedic ward were included in the study. They were enrolled after obtaining their informed written consent.

Exclusion criteria

Patients who had chronic illness and immunosuppression (i.e. on long term steroid use, cancer, pathological fractures, diabetes, tuberculosis or HIV infection), at the extreme of age (< 10 and > 60 years), and those who declined to participate were excluded from the study.

Group allocation

After assessing the eligibility criteria and obtaining their informed consent, the participants were assigned randomly either to topical gentamycin and non-topical gentamycin group. The random allocation was performed in a blind manner by hand drawing from a box of sealed opaque envelopes in batches of 20 for each group. The selected, sealed envelope was opened by the scrub nurse (who was not involved in the study) in the operating theatre before the first procedure and the patient's group allocation was marked on the research form. The patients were blinded with regards to group allocation, while the blinding of the investigators was not possible.

Outcome measures

The primary outcome measure was acute infection rate. We applied IAFF definition to diagnose infection after fracture fixation [19] except CRP and culture, which were not available, and added the presence of sinuses as a sign of chronic osteomyelitis.

The secondary outcome measures included the length of hospital stay, number of surgical procedures and rate of non-union.

Patient management protocol

The patient's variables were recorded on a predesigned research form. These included demographic characteristics, type and localization of fracture, time from the injury to first debridement, antibiotic regimen (type, dose, duration and route), type of surgical treatment, infection, complications, length of hospital stay and time to bone union.

Both groups were managed using the standardized protocol adapted to our local setting. On admission all patients were administered with intravenous antibiotics, tetanus toxoid; fractures were immobilised in a slab; and wounds were dressed with povidone iodine before the first debridement.

Because of delayed presentation and time to first debridement, open fracture wounds were treated as infected and parenteral antibiotic therapy continued usually for 4 - 5 days after the debridement and bone covering. Typically, it consisted of intravenous flucloxacillin 1 q.i.d. and gentamycin 7 mg/kg once a day. For Gustilo Anderson grade III metronidazole was added. Replacement of recommended cephalosporines by gentamycin was dictated by the recent local studies on bacterial profile and antibiotic sensitivity in bone infections which showed that Staphylococcus aureus is the major cause of surgical wound infection and chronic osteomyelitis in our setting. Further, these studies have shown that most of the staphylococcus strains isolated were ß-lactamase-resistant to methicillin (MRSA) and in 70% of cases, resistant to cefazolin but remain to be highly susceptible to gentamicin (98%) and chloramphenicol (83%) [20,21]. Pain was controlled with oral paracetamol, and if required, opioids.

Before the debridement, daily dressing with povidone iodine was applied. After the debridement, saline dressing was applied. If required other procedures followed aiming for early bone covering with viable soft tissue. Intraoperatively, wounds were debrided, irrigated with normal saline, fractured bone was stabilised with external or internal stabilization, or Plaster of Paris as appropriate. Topical antibiotic 160 mg gentamycin was applied to each participant in the topical antibiotic group during the first debridement and during the following procedures. The wound was either closed, or left for delayed closure. We aimed at bone covering by local flaps within 7 to 14 days. Following the procedure, all patients received dressing with gauze soaked with saline covered with a few layers of sterile orthopaedic wool and compressed with an elastic or crepe bandage.

Once discharged, the patients were followed up at the orthopaedic consultation clinic at the 2nd and 6th weeks, and at the 6th month. On the first visit, the patients were clinically assessed for signs of infection. On the 2nd and 3rd visits, the patients were clinically and radiologically assessed for signs of chronic infection and bone union. During the follow-up period, patients with chronic infection and non-union were treated according to the available local protocol.

Ethical consideration

The ethical approval was obtained from the Madang Provincial Teaching Hospital Research Committee (MHEC 18.07). A rule of voluntary participation was ensured by informed and written consent.

Data analysis

All analyses were performed as intention-to-treat by substituting the missing outcome values by mean or median from the treatment allocation group appropriately. We used SPSS version 22 and Microsoft Excel for the analysis. To compare frequencies of categorical variables between two groups the Mann-Whitney U test was used. Continuous variables were expressed as means and standard deviation and analysed by two-way t-test for two groups. The association between acute wound infection, chronic infection and non-union rates between the topical gentamycin applied group and the non-topical group were analysed by the Chi-squared test with Yates correction and Fisher's Exact test. A p-value of less than 0.05 was considered significant.

Results

Demography

A total of 200 patients with open long bone fractures were admitted, of which 120 patients gave consent and were randomly allocated into the study groups. Eighty patients were excluded from the study (See table 1). Figure 1 shows the flow chart of the study.

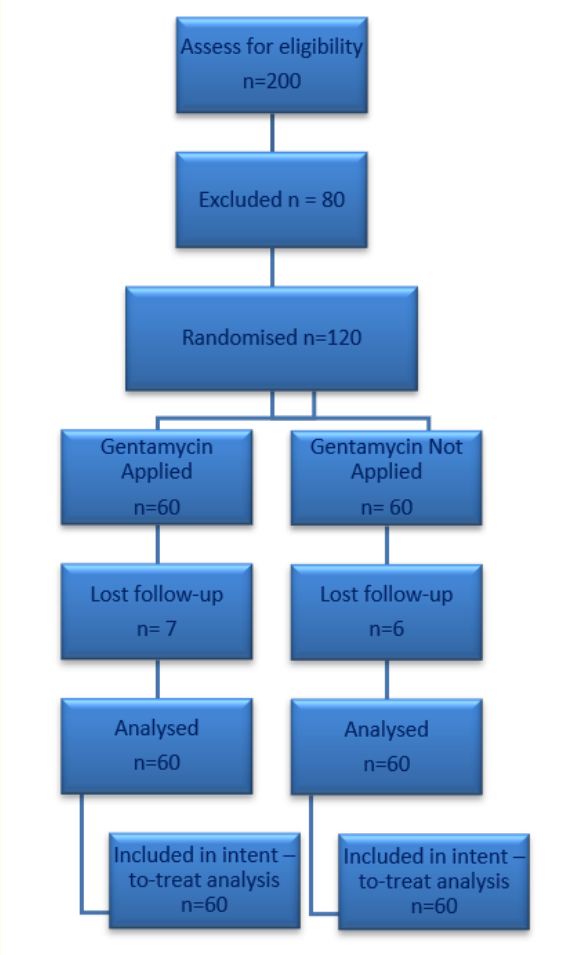

Figure 1: *The flow chart of the study.*

Reasons for exclusion	Number of patients admitted with open fractures
Chronic Illness	6
Age < 10	10
Age > 60	9
Decline or Withdraw Consent	22
Gustilo-Anderson Type I	25
Gustilo-Anderson Type III C	8

Table 1: *Reasons for exclusion from the study.*

The mechanisms of open fracture injury were bush knife wound, n = 82 (68%), gunshot wound, n = 18 (15%), fall from a height, n = 16 (14%), and motor vehicle accident, n = 4 (3%) respectively.

Category	Non-topical antibiotic group (SD)	Topical antibiotic group (SD)	p-Value
Age	28.1 (+/-9.2)	25.6(+/-9.2)	0.27(t)
Sex			
Male	56 (93.3%)	50 (83%)	0.15(mw)
Female	4 (6.7%)	10 (17%)	
Smoking			
Yes	39 (65%)	41 (68%)	0.70(mw)
No	21 (35%)	19 (32%)	
Hemoglobin (g/dL)	9.4 (+/-2.3)	9.2 (+/-2.2)	0.52(t)
Time from injury to operation (days)	6 (+/-5.5)	5 (+/-4.8)	0.32(t)
Sites of long bone fractures			
Humerus	9 (15%)	10 (17%)	
Ulna/radius	33 (55%)	35 (58%)	
Femur	4 (7%)	4 (7%)	0.91(mw)
Tibia/Fibula	14 (23%)	11 (18%)	
Gustilo-Anderson Classification			
GA II	5 (8%)	4 (7%)	
GAIIIA	12 (20%)	13 (21%)	0.96(mw)
GA IIIB	43 (72%)	43 (72%)	

Table 2: *Demographic characteristics of study participants.*

Legend: SD = Standard Deviation; mw = Mann-Whitney U test; t = t-test for Mean Comparison of Two Groups (Two-Way); Significance value (p) = 0.05.

There were no significant differences in terms of demographic features between two allocation groups (See table 2).

Category	Non-topical antibiotic group n = 60, (%)	Topical antibiotic group n = 60, (%)	p-Value
Rate of infection at 2nd week	8 (13.3) OR = 1.89, Cl 95% (1.4 - 2.57)	3 (5) OR = 0.2, Cl 95% (0.03 - 1.33)	0.015(mw)
Rate of infection at 6th week	7 (11.6) OR = 1.36, Cl 95% (0.907 - 2.04)	3 (5) OR = 0.673, Cl 95% (0.35 - 1.32)	0.045(mw)
Rate of infection at 6th month	7 (11.6) OR = 0.66, Cl 95% (0.36 - 1.19)	4 (6.7) OR = 0.57, CI 95% (0.17 - 1.85)	0.309(mw)

Table 3: *Primary outcome measures in non-topical and topical antibiotic group in management of open fractures, Madang, 2019 -2021.*

Legend: mw: Mann-Whitney U Test; OR: Odds Ratio; CI: Confidence Interval; p: Significance Value.

While addition of topical gentamycin significantly lowered the infections presentation in the early postoperative period (in 2 and 6 weeks) compared to the non-topical antibiotic group, the difference in the infection rate between both groups at 6-month follow-up was not significant (See table 3).

Category	Non-Topical antibiotic group n = 60 (%)	Topical antibiotic group n = 60 (%)	p-Value
No. of surgical procedures			
Once	41 (68)	55 (91.7)	
Twice	15 (25)	5 (8.3)	0.004;(t)
Three times	4 (7)	0	
Length of hospital stay (days)	28.1 (+/- 9.2)*	12.4 (+/-8.4)*	0.006 (t)
Delayed union at 6th week	37 (62)	23 (38)	0.011(mw)
Non-union at 6th month	10(17)	4 (7)	0.011(mw)

Table 4: *Secondary outcome measures in non-topical and topical antibiotics group in management of open fractures Madang, 2019 -2021. Legend: *: Standard Deviation (SD), mw: Mann-Whitney U test; t - t-test for mean comparison of two groups (two-way) and significance value (p) = 0.05.*

As compared to the standard protocol group, addition of topical gentamycin (See table 4) significantly reduced the number of procedures (p = 0.004), the length of hospital stay (p = 0.006), the rate of delayed union (p = 0.01) and the rate of non-unions at 6-month follow-up (p = 0.01).

Discussion

In our study, there was a significant reduction of infection rate at the 2nd and 6th week but non-significant reduction at 6th month in the topical group compared to the non-topical group. Our findings concur with the results of other studies demonstrating lower infection rates in the topical antibiotic group compared to the conventional protocol [11-18]. Similarly, another study showed that local application of gentamycin compared to systemic antibiotics alone reduces the rate of osteomyelitis [18]. The systematic review of RCTs and pooled meta-analysis showed a marked reduction of infection rate in the groups of locally applied antibiotics when compared with systemic prophylaxis and this reduction was noted in all three main Gustilo-Anderson grades [15].

Several studies reported reduction of the infection rate by using various carriers for local antibiotics such as impregnated PMMA beads, microporous hydroxyapatite, biodegradable composite bone cement, and calcium sulphate [22-27]. It was also reported that there is relative rapid dissolution of antibiotics from bio absorbable material which avoids prolonged low-level antibiotic release [25-27] and it is believed that it may reduce the risk of growing antibiotic resistance. In our study, patients did not experience gentamycin toxicity or side-effects which are analogous to the study done by Lawing., *et al*. (2015) [14].

Our mean time from the injury to time of first debridement was 6 days. The delay was caused by delayed presentation and poor access to the operating theatre. Longer delay between the injury and surgery reported by another study (average 64 hours) found no difference between surgery done within 6 hours and that done more than 6 hours from the injury [28].

Although most of the surgical guidelines recommend early debridement of open fractures within 6 - 8 hours, the strong evidence supporting that is lacking. Several studies reported no significant increase in the infection rate with delay of debridement for open fractures

beyond 6 hours. However, these were not randomised studies and not powered to provide strong evidence. In addition, the delay in these studies was less than 24 hours [29-34]. One multicentre prospective study recorded a significant relationship between time from open fracture injury and admission to hospital and infection rate but no relation between time from injury to debridement [35]. However, few studies with the use of modern antibiotic guidelines and surgical techniques reported increased incidence of osteomyelitis with delay in debridement of open fractures [36,37].

Limitation of the Study

The limitations in this study include: single study location; single-blinded study (assessors not blinded); a relatively small sample size; substantial delay to the first debridement; lack of laboratory tests (infection markers like C-reactive protein (CRP) and other infection markers); culture and antibiotic sensitivity; and magnetic resonance imaging (MRI) to confirm the presence of infection which may add strength to our clinical findings. The study also had a relatively short follow up (6 months). A longer follow up to one year and the availability of laboratory and radiological studies to confirm presence of infection could have changed the infection rates.

Conclusion

This study shows that in the management of open long bone fractures in low-resource settings, the use of local aqueous gentamycin as an adjunct to conventional management is effective in lowering the infection rates, reducing number of operations, reducing length of hospital stay and non-union rates. The authors hope the study contributes to the body of evidence on the use of topical antibiotics in the management of open fractures.

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Declaration of Conflict of Interest

The authors declare no conflict of interest.

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