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The use of adjuvant local antibiotic hydroxyapatite bio-composite in the management of open Gustilo Anderson type IIIB fractures. A prospective review

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1. Introduction

Open fractures of the tibia are the most common open long bone fracture reported in literature with annual incidence of 3.4 per 100,000.[1] Most of these fractures are secondary to high velocity trauma. Road traffic accident is the cause in over 50% of patients.[2] Gustilo and Anderson classified open fractures into three subtypes.[3] Type I fractures have a less than one cm wound with simple fracture pattern and minimal soft tissue damage. Type II are fractures with wounds of 1–10 cm with moderate soft tissue injury. Type III are severe forms and are further subdivided into; III A > 10 cm wound with adequate soft tissue cover, III B > 10 cm wound requiring plastic surgical soft tissue cover, III C have vascular injury requiring repair. Despite low interobserver agreement, Gustilo Anderson classification remains the most widely used classification system for open fractures.[4,5] The system also has a prognostic value with complication rates, and infection rates increasing with the grade of the injury.[4,5] Type III B are the most severe type of open fractures with a historical reported rate of infection in up to 52% cases and up to 16% amputation risk.[6]

The standards of management of open fractures have evolved over the last 40 years. In 1974, Patzakis et al reported on the relative reduction in rate of infection with the use of systemic antibiotics (13.9% without antibiotic therapy v 2.4% with antibiotic therapy).[7] Patzakis and Wilkins subsequently demonstrated that antibiotic administration within 3 h of the injury had the maximal benefit in comparison to delayed therapy (4.7% infection rate v 7.4% infection rate).[8] The role of radical early debridement of the wound in reduction of infection was advocated by various authors (Gustilo 1976,[3] Patzakis 1983,[9] Russel 1990[10]). Godina in 1986 demonstrated a significant reduction in infection rates after such fractures with early soft tissue coverage.[11] This has been further reinforced by the studies of Caudle (1987),[12] Fisher (1991)[13] and Gopal (2000).[14] These studies form the evidence base for the current UK standards published by the British Orthopaedic Association (BOA) and British Association of Plastic Reconstructive and Aesthetic Surgery (BAPRAS).[15] The guidelines support a combined orthopaedic and plastic surgical management of these complex injuries in a timely manner.

Despite advances in the management of these injuries, deep infection continues to remain a problem especially in III B fractures. Henley in 1998[16] reported a 15% risk of infection and Rohde[1] in 2007 a 10% risk. Doshi in 2017 reviewed and reported on 787 tibial fractures with a 53.8% infection rate with IIIB injuries in comparison to 7.7% infection rate in type I fractures.[17]

The use of local antibiotics in open fractures is not a new concept. In the 1800s, Joseph Lister first used carbolic acid on wounds.[18] In 1920, Alexander Fleming advocated the use of local antiseptics to wounds to reduce the burden of bacteria.[19] Jensen in 1939 reported the instillation of sulfanilamide crystals and the reduced infection rate for open fractures.[20] Dombrowski and Dunn in 1965 published on the benefits of closed wound irrigation-suction with antibiotics.[21] Osterman published on a series of 1085 open fractures with significantly lower infection rates with combined adjuvant local antibiotic bead use in comparison to

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systemic antibiotic therapy in isolation (3.7% v 12%).[22] The findings of Osterman were further reinforced by Keating et al. (4% deep infection with combined systemic and local adjuvant therapy vs 16% deep infection with systemic antibiotics alone).[23] Craig et al., in 2014 published a systematic review and meta-analysis of the additional benefit of local prophylactic antibiotic therapy for infection rates in open tibia fractures treated with intramedullary nailing with a reduction in infection rates in III B & C fractures from 31.18% to 8.76%.[24]

Aim of this study is to look at the infection and union rate for Gustilo Anderson IIIB fractures in our unit with fix and flap approach using local antibiotics.

2. Materials and methods

We present a review of prospective data collected on Gustilo Anderson III B open fractures which were managed in our orthoplastic unit. Patients either presented directly or they were referred from other local hospitals after initial debridement and provisional stabilization. As per protocol, all patients received systemic antibiotics (Co-Amoxiclav 1.2 gm IV 8 hourly) at presentation. Additionally, at the time of first debridement, a single dose of Gentamicin at 5 mg/kg (reduced to 3 mg/kg in moderate to severe renal impairment) was administered. Patients with penicillin allergy were given Teicoplanin, Gentamicin and Metronidazole in age and weight appropriate doses. Systemic antibiotic therapy was continued until definitive wound closure. All patients underwent a single stage "fix and flap approach", with definitive skeletal stablization, followed by soft tissue coverage in the same sitting. Peri-operatively multiple deep tissue and bone samples were collected and sent to microbiology for extended culture and sensitivity. In this study, we used Cerament G at the fracture site per-operatively after skeletal stabilization to bone voids and gaps. Cerament G is gentamicin eluting synthetic bone graft substitute, in a powder form, mixed into to a paste for application. Cerament G consists of hydroxyapatite and calcium sulphate, which has shown incorporation into bone radiologically in follow up studies.[25,26] Cerament G contains 17.5 mg/ml of gentamicin as a paste which been designed to have a neutral pH (7.0–7.2), so it does not reduce antibiotic activity. Mixing and injection devices ensure a homogenous distribution of antibiotic, whilst the material properties of Cerament mean that all of this antibiotic is made available for elution and delivered in a controlled fashion. All patients were followed up until fracture union and wound healing. Patient and injury demographics, orthopaedic and plastic surgical treatment details, microbiology, deep infection rates, fracture union rates and complications are presented and compared with published literature.

3. Results

3.1. Patient demographics

Fifty-one patients with mean age of 40.9 years (11–90 yrs) were included. Forty were male (78.4%), 11 were female (21.5%). The mechanism of injury was road traffic accidents in 26 patients (50.9%), work related injuries in eight, a fall from height in nine, blast injuries in four patients and a further four with various other mechanisms. The location of fracture was the tibia in 30 patients (58.8%), pilon and periarticular ankle in 10 (19.6%) and foot in five (9.8%). Six patients (11.7%) had multiple fractures involving multiple limbs. The location of injury was diaphysis tibia in 30 patients (58.8%), metaphysis in 13 (25.4%) and articular in 8(15.6%) patients.

3.2. Orthoplastic interventions

The method of fixation was plating in 19 patients (37.2%), circular frame in 16 patients (31.3%) and intramedullary nailing in eight patients (15.6%). Internal fixation was supplemented by external fixation in three patients for additional stability (5.8%). The remaining five patients (9.8%) had various other fixations such as malleolar screws or krischner wires for foot fractures. All patients had initial wound debridement, washout and provisional fracture stabilization with an external fixator on the next available trauma list, which was within 12 h in 24 patients (47%) and > 12 h in 27 patients (53%). Mean time to first debridement from admission was 11 h (3–19 h). Vacuum dressings were used to temporarily cover the wound. There was a mean interval of 8.2[1–23] days before patients had definitive surgery and soft tissue coverage. This was due to patient co-morbidities and delay in transfer. For soft tissue cover, a free anterolateral thigh flap was used in 21 patients (41.1%) and a local rotational flap in 23 patients (45%). One patient had latissimus dorsi flap and six patients (11.7%) had other forms of soft tissue cover including split thickness skin grafting. Soft tissue reconstruction was tailored according to the severity of soft tissue loss, availability of healthy tissue for transfer and patient fitness. Fourteen patients (27%) had greater than 50% circumferential loss of bone on anteroposterior and lateral views. Segmental loss of bone was dealt with acute shortening (maximum 4 cm) in three patients.

3.3. Microbiology results

Microbiology culture results from deep tissue samples collected at the time of definitive surgery were available for all except one patient. 28 samples (54.9%) were culture negative. 14 samples (27.4%) grew a single organism and eight (15.6%) grew mixed organisms at time of definitive fixation and flap surgery. Gentamicin resistance was detected in three of the organisms isolated; Staph. epidermidis in two samples and S. hemolyticus in one. Vancomycin Resistant Enterococci (VRE), was found in one sample. Staphylococcus. spp was the most commonly found organism and was isolated in 11 samples as a single pathogen and as a mixed growth in four samples. Among the Staphylococci spp., Staph. aureus was isolated in nine samples, Staph. epidermidis in five samples and Staph. hemolyticus in one sample (Fig. 1).

Outcome Data - All patients were followed up until union and wound healing. The mean follow up was 13.9 months (6–45 months). There were no deep infections encountered in our series. Primary union rate in our study was 84.3% (43/51). Mean time to achieve union was 32.5 weeks (15–42 weeks).

Delayed union was present in 4 patients (7.8%) who had no radiological progression of healing. These patients had autologous bone marrow aspirate concentrate (BMAC) applied to the fracture site at a mean of 37 weeks (range 25–50 weeks) with subsequent evidence of union at a mean of 53.7 weeks (range 45–75weeks).

Non-union developed in 3 (5.8%) patients. All of them had external fixation which was revised to internal fixation with autologous bone grafting at a mean of 15 months (13–17 months). Deep tissue microbiology samples at revision were all negative for deep infection. Clinical union was achieved at a mean of 7 months from revision (range 6–10 months).

In all 7-delayed and non-union cases, the fracture was diaphyseal in location. Six out of 7 cases (85.7%) had an external circular frame and 1 was internally fixed using plate. None of them had any significant bone loss. The commonest denominator linking these failures to unite was smoking (6 out of 7 cases).

Incidence of pin site infection was 3/19 (15%). Two settled with oral antibiotics and one patient needed exchange of pin. The mean number of surgical procedures per patient was three (range 2–7), including the first debridement.

One patient required amputation (1.9%) due to early soft tissue reconstruction failure within the first week of definitive fixation. He was a 24 years old male, presented with a tibia shaft fracture with severe soft tissue injury. Due to the severity of the injury, primary amputation was discussed from the outset. On the patient's wish, reconstruction was attempted using a circular frame and anterolateral thigh flap. However, the flap developed early necrosis leading to exposed bone, requiring below knee amputation within first 2 weeks.

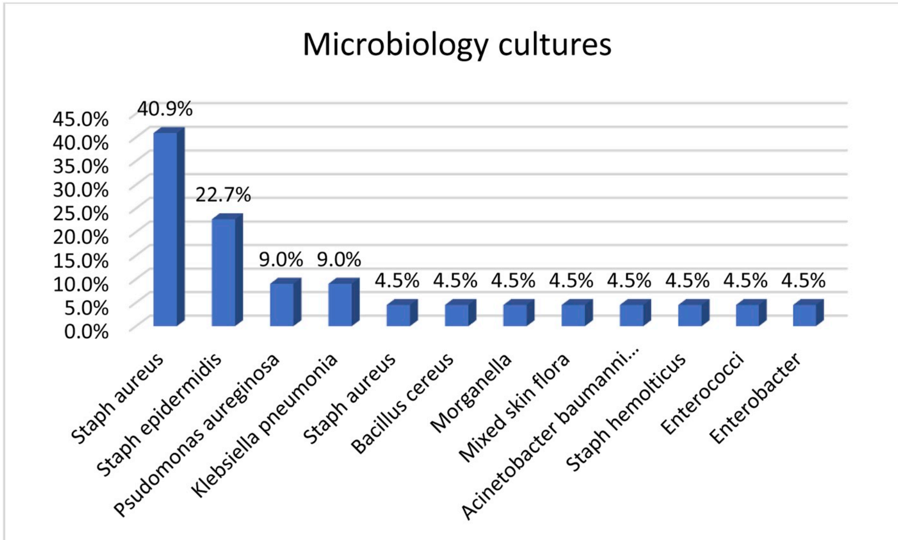

Fig. 1. Microbiology culture results.

4. Discussion

The primary aims of treatment in open fractures are management of soft tissue injury, prevention of infection and skeletal stabilization with aim of restoring function of the extremity.[1,27] Thorough and radical debridement, removal of devitalised tissue and necrotic bone fragments is the key to reduce future infection risk.[28,29]

Orthopaedic dogma would suggest that debridement and washout of open fractures should be done within 6 h - probably on the basis of studies which looked at the proliferation of micro-organism load following contamination.[30] However recent reviews have not found any significant differences in infection if debridement is done earlier than 6 h or delayed.[28–32] Our data would support that there is no difference in deep infection rates, union rates and limb salvage if the initial debridement is done within 12 h or within 24 h from time of injury.

The fracture union rates achieved by us (84.3%) is comparable to those published by Doshi et al., in 2017 (83.5%)[17] and Naique in 2006 (85%).[33] The mean time to union from our study (32.5 weeks) is also comparable those achieved by Tielinen in 2007(35 weeks)[34] and Naique (29 weeks).[33] The limb salvage rate in our series was 98.1%, this also compares well to earlier published reports by Rohde in 2007 (94%)[35] and Naique 93%.[33] Tampe et al., reported 7% risk of amputation for patients with Gustilo Anderson III B and C.[36] In our study, only 1(1.9%) patient required an amputation due to soft tissue reconstruction failure, although it is important to note that none of our patients had vascular injury requiring repair.

Historic studies have shown incidence of infection of up to 52% in open fractures (Gustilo 1984).[6] Patzakis et al., in 1974, pointed out that early systemic antibiotics in open fractures reduces the infection risk.[7] This has been supported by recent Cochrane review that demonstrated that the use of early systemic antibiotics reduces relative infection risk by 59%.[37] Despite use of systemic antibiotic therapy the infection rate in open III B fractures remains high (Doshi 2017- 8%,[17] Matthew 2015–14.9%,[38] Mohseni 2011–16%,[39] Rohde 2007–18.4%,[35] Naique 2006–8.5%[33]).

A recent move to a combined Orthoplastic "fix and flap" approach has shown a reduced risk of infective complications.[40] A retrospective study from Bristol demonstrated that if soft tissue cover is not achieved at the time of fracture fixation, infection rate was 34.6%, which reduced down to 4.6% with fix and flap approach.[38]

Local antibiotics at the fracture site are effective in reducing infection, especially in Gustilo Anderson III fractures, without associated systemic toxicity.[42,43] They can be used in powder form[44,45] or aqueous solution.[46] Disadvantages of not using a carrier is that the levels of antibiotic in local area are not sustained for longer period and the delivery is not predictable or effective (antibiotic dumping).[47] All the patients in our series had a combined orthoplastic fix and flap approach with adjuvant local antibiotic therapy. Whilst our union rates, time to union and limb salvage rates are comparable to some of the best outcomes in published literature for such injures, we had no deep infections. We feel this could be due to the added benefit conferred by local adjuvant antibiotics. In vitro studies have shown gentamicin elution from Cerament G has a high initial peak (> 1000 g/mL) and remains above minimum inhibitory concentration (MIC) for at least 28 days. It has been proven that serum antibiotic levels remain in safe range despite high local tissue concentration.[48] These levels of gentamicin can be effective in biofilm prevention and eradication. In vivo studies have shown that it offers local gentamicin concentration levels 64–150 times higher than MIC for gentamicin sensitive pathogens such as Staph. aureus and *Pseudomonas aeruginosa*. We believe that local antibiotics are also effective in planktonic form after debridement. In addition, the dissolution of calcium sulphate allows high early release of antibiotics leaving a more porous hydroxyapatite scaffold to support ingrowth of blood vessels and subsequent new bone formation with no secondary removal procedure required. Studies have questioned the routine use of tissue cultures in open fractures due to lack of correlation between positive cultures and future infection risk.[49,50] It is important to note that in our study, deep tissue cultures collected at the time of definitive fixation were positive in 44% of our patients despite initial radical debridement. Gentamicin resistance was also detected in 6%, yet none of these patients had deep infection at follow up. We feel this is likely due to the very high local tissue concentration of Gentamicin achieved with no true antibiotic resistance.[51] Like McNally et al. we believe that lab culture reported gentamicin resistance refers to concentrations which can be given systemically without toxicity and the effectiveness of antibiotic at levels up to 1000 the MIC is not known.[52] In our series, there was no case of systemic antibiotic toxicity. Bowen and Widmaier[53] reported that the risk of infection in open fractures is multifactorial. Our results of no infection, high union rates and high limb salvage rates, may be due to the combination of different factors. We would highlight that adequate initial debridement, removal of dead tissue, multiple bacteriological sampling, skeletal stabilization, soft tissue cover and the collaborative MDT approach including plastic surgeons and infectious disease specialists is an important element of success with these challenging cases. We accept that the results reported by this study may not be due only to the Cerament G application.

Table 1
Gustilo Anderson IIIB Open fracture, Outcomes from literature.

Study	N	Deep Infection n(%)	Union time wks	Union rate with primary surgery	Reoperation	Limb Salvage
Gustilo 1984[6]	77	52%				
Naique 2006[33]	76	6 (8.5%)	29	85%		93%
Tielinen 2007[41]	19		35	53%	47%	
Rohde 2007[35]	38	7(18.4%)	–	71%	36.8%	94%
Mohseni 2011[39]	25	4 (16%)				
Mathew 2015[38]	46	2(4.2%)	24.4			
Doshi 2017[17]	21	7 (33.3%)		83.5%		
Our study	52	0 (0%)	32.5	84.3%	21.5%	98.1%

However, our results are superior in comparison with other studies[6,17,33–35,38,39] (Table 1). Our results would therefore suggest that this new biodegradable CAS/HA composite may offer significant added advantages in the management of this cohort of patients.

5. Conclusion

Open fractures are challenging cases and require a multidisciplinary approach. Although relatively low in number, our series is one of the largest due to rarity of these injuries. Our infection and reoperation rate are amongst the lowest, with comparable union rates in published literature. We propose that successful outcomes can be achieved by meticulous technique and a multi-disciplinary approach. We believe that Cerament G provides high local antibiotic concentration locally at the fracture site and could be beneficial in local prophylaxis to reduce the risk of biofilm formation on metalwork, while the hydroxyapatite scaffold could improve union rates. This improves patient experience and reduces healthcare costs. Additional, long term studies are required, and will help to improve our understanding of the use of local antibiotic delivery systems in such injuries.

Conflict of interest

Noman Jahangir declares that there is no conflict of interest.

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