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Prevention of Surgical Site Infection in Gustilo-Anderson Open Type IIIA and IIIB Fractures Using Antibiotic Laden Bio-Absorbable Calcium Sulfate Granules an Observational Study

[1]B.S. Gokul, [2]M. Mruthyunjaya and [3]T. Adarsh
[1-3]JSS Medical College, Mysore

Abstract
Open fractures are associated with a high infection rate and varying degrees of soft tissue and bone loss. Local antibiotics delivered through a carrier can provide high concentration of antibiotics locally at the wound site with minimal systemic toxicity. Calcium sulfate is a bio-absorbable bone graft substitute that can also act as anosteoconductive material to hasten bone healing. This study aims to evaluate the outcome of antibiotic-laden calcium sulfate granules in the primary prevention of infections in Gustilo Anderson open type III-A and III-B fractures of long bones. A prospective clinical observational study was conducted on 50 patients, who underwent surgery for Gustilo Anderson open type IIIA and IIIB fractures. Fractures were treated with thorough wound debridement followed with an appropriate choice of skeletal fixation. Vancomycin laden calcium sulfate beads prepared on site under aseptic precautions and were placed into the wound and areas of bone defects at the time of the surgical procedure. Patients were followed up for any signs of surgical site infection post-operatively and time taken for fracture healing up to one year. The complications related to the procedure were analyzed. A total of 41 (82%) patients showed no signs of infection at the wound site. 9 (18%) patients developed discharge from the wound site which was positive for pathogenic bacteria. All the fractures showed signs of fracture union between 6-9 months. Antibiotic-laden calcium sulfate is a safe and effective mode of delivering a high concentration of antibiotics locally for the primary prevention of infections in Gustilo-Anderson type IIIA and IIIB open fractures. Calcium sulfate also helps in the formation of callus due to its osteoconductive capability. Unlike polymethyl methacrylate, due to its bio-absorbable nature, it does not need second surgery for the removal of beads. The other advantage of calcium sulphate is even heat labile antibiotics can be mixed with it to prevent infection. There were no serious complications related to its use.

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Key Words
Surgical site infection, open fractures, local antibiotic delivery, calcium sulfate granules, vancomycin

Corresponding Author
T. Adarsh,
JSS Medical College, Mysore

Author Designation
[1]Resident
[2]Former HOD
[3]Assistant Professor

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INTRODUCTION

In open injuries, the fracture or the fracture hematoma communicates with the outside environment[1].In these fractures, depending on the location of the injury, the contaminants may vary from mud, tar, dust, soot, grease, vegetable matter, etc. This allows for the colonization and growth of various pathogenic bacteria[2]. These fractures are difficult to treat as they have a high risk of infection associated with varying sizes of bone loss and neurovascular compromise. The complications may vary from superficial or deep space infections to osteomyelitis and the need for multiple revision surgeries becomes mandatory. Thus, it places a considerable social and financial burden on the patient's life and of their family members[3].

Furthermore, various host immune responses, immune-compromised states like diabetes mellitus and personal habits like smoking and alcohol consumption are poor prognostic factors. Antibiotics break the life cycle of bacteria at various stages and impede their further growth. Antibiotics are administered systemically to reduce the rate of infection but the persisting high level of infection rate leaves scope for improvement[4]. Wound cavities are relatively avascular. Hence, systemic antibiotics reach the fluid that fills these cavities in low concentrations[5].

On the other hand, local antibiotics have the advantage of being in high concentration at wound sites with less systemic adversities. Calcium sulfate as a bio-absorbable mode of the local antibiotic delivery system has a long history of use in orthopaedics. Recently, surgical-grade calcium sulfate bone graft substitute has become available. This material has the advantage of having few trace elements, a uniform crystalline structure and a predictable resorption rate[6].

In this study, we implanted calcium sulfate loaded with vancomycin (2g/10cc of cement) during the treatment of Gustilo-Anderson Open Type 3A and 3B fractures of long bones with appropriate fixation method and investigated its effect on the incidence of infection and bone union.

Objectives

Primary Objective: To assess the outcome of bio-absorbable antibiotic-laden calcium sulfate granules in the prevention of surgical site infection in Gustilo-Anderson Open Type IIIA and IIIB fractures.

Secondary Objectives:

- To assess the factors responsible for the incidence of surgical site infection (SSI) pre-operatively like age, mechanism of injury, diabetic status, smoking or alcohol history, etc
- To assess the adverse effects, if any, related to antibiotic-laden calcium sulfate granules

MATERIALS AND METHODS

Our study is a hospital-based prospective observational study. A total of 50 patients with open fractures of long bones Gustilo-Anderson Type IIIA and IIIB fractures were included in the study. The study was conducted from June 2019 to March 2021in a tertiary care hospital.

Patients of all age groups presenting with Gustilo-Anderson open type IIIA and IIIB fractures of long bones were included in the study.Patients undergoing amputation for open fractures and patients with vascular injury were excluded from the study.

Study Setting and Method of Collection of Data: All patients presenting to the casualty with open fractures were thoroughly examined. The wound was inspected, the surrounding area of the wound was cleaned, the limb was immobilised, necessary x-ray radiographs were taken and planned for emergency surgery. Intravenous antibiotics were started immediately, after the test dose according to Hospital Infection Control Committee Protocol for open fractures. All Patients with open type III fractures received intravenous Cefuroxime, Amikacin and Metronidazole for the first 2 days following the injury and only Cefuroxime was continued tilloperativeday. No further IV or oral antibiotics were given once the antibiotic impregnated beads were added during the surgery. Hospital based checklist for the prevention of SSI was followed.

Intra operatively, a detailed wound inspection was done again. Thorough wound irrigation using normal saline and thorough debridement is carried out. Fractures were stabilised with suitable implants. Antibiotic granules were prepared using bio-absorbable bone cementby adding 2 grams of vancomycin with the mixing solution as per the instructions provided by the manufacturer. The paste is then applied to a pre-mold bead mat where 6mm beads were prepared. The granules were inserted in areas of bone defect, tissue spaces and soft tissue coverage was provided as much as possible over the bone depending on the severity and type of open injury.

Post-operatively, follow-up of patients was done to look for any complications. All intravenous antibiotics were stopped 24 hours post-surgery. In patients with externalfixators, pin tract care was explained to the patient. Patients were advised to follow up at regular intervals of 2 weeks, 4 weeks, 3 months, 6 months and 1 year. Patients were taken up for secondary surgeries like split skin grafting, intra medullary nailing, etc after satisfactory wound healing and absence of infection. Patients with exudate from the surgical site were evaluated with swabs taken from the discharge siteordeeper planes like soft tissue or bone depending on the depth of involvement and sent for pus culture and sensitivity. Infection was said to be present if the culture showed growth of pathogenic

bacteria. Additional signs of local infection in the patient like the local rise of temperature, swelling, redness and fever were also evaluated at follow-up. Radiographs were taken to assess fracture healing and to find out the rate of resorption of calcium sulphate granules. Health and hygiene education was done for all the patients treated under the study.

Statistics: The descriptive procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which the researcher specifies. Following descriptive statistics were employed in the present study Mean, Standard deviation, Frequency, Percent, Inferential Statistics and Chi-Square Test. The Chi-Square Test procedure tabulates a variable into categories and computes a chi-square statistic. This goodness-of-fit test compares the observed and expected frequencies in each category to test whether all categories contain the same proportion of values or that each category contains a user-specified proportion of values. Fisher's Exact significance values were considered when cell entries were less. SPSS for Windows version 20 was used for data analysis.

RESULTS AND DISCUSSIONS

A total of 50 patients with open type IIIA and IIIB fractures of long bones were recruited prospectively into the study. All patients underwent respective soft tissue and bony procedures and were implanted with antibiotic-laden bio-absorbable calcium sulfate granules.

The age wise distribution showed a majority of the patients belonged to 21-40 years age group (46%). There was a total of 40 males and 10 females in this study with a mean age of 35.8 years for males and 49.3 years for females.

At 3 months follow up, a total of 9 patients developed discharge from the surgical site which was positive for pathogenic bacteria on microbiological testing. All were superficial surgical site infections classified according to CDC criteria for SSI[7].

The total incidence of infection was found to be 18% (9 patients) in our study, of which all were superficial surgical site infection.

All the patients with SSI were treated with local wound care and targeted systemic antibiotics based on microbiological culture and sensitivity. The wounds of all nine patients healed completely at 3 to 6 month follow-up.

The majority of patients were treated with internal fixation as the primary procedure and all the SSI events in this study developed in them. The patients undergoing external fixation were fewerandSSI never occurred in them. There were 4 cases of sterile serous

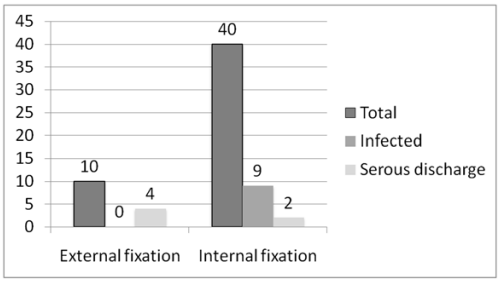

Fig 1:Association with the type of fixation used and incidence of infection and culture-negative serous discharges among them. (p>0.05)

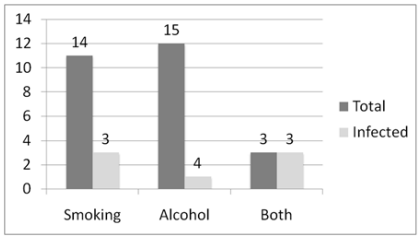

Fig 2: Distribution of infections with patients with history of smoking and alcohol intake.

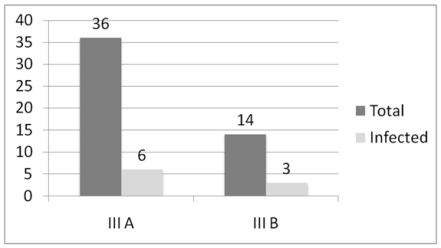

Fig 3: Distribution of infections among Gustilo-Anderson Open type IIIA and IIIB fractures.

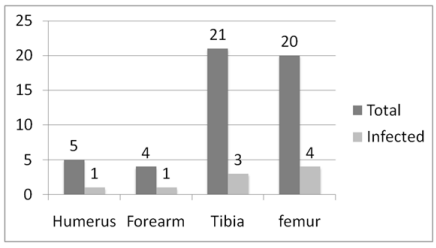

Fig 4: Distribution of various open fractures of long bones enrolled in this study and the incidence of infection in them.

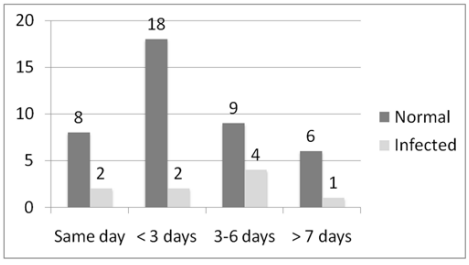

Fig 5: Distribution of SSI with time to surgery

Table1: Descriptive Statistics of time for CaSo4 dissolution and time for bone union

	Number	Minimum	Maximum	Mean	Std. Deviation
CaSo4 dissolution (weeks)	50	4.00	6.00	4.7600	0.65652
Boneunion (months)	50	4.00	10.00	6.4490	1.18693

Table 2:Various organisms cultured in patients with infected discharge.

	Distribution based on microbiological pus culture	
Organism	**Frequency**	**Percent**
A. Baumannii	1	2.0
ENT. Cloacae	1	2.0
MRSA	2	4.0
No growth	7	14.0
P. Aeruginosa	2	4.0
S. AUREUS	3	6.0

discharge in external fixation cases and 3 in internal fixation cases respectively which had no growth on culture.

It was found that 14 patients in this study had a history of smoking and 3 patients among them suffered an incidence of infection (P value=0.033) and15 patientsconsumed alcohol and 4 out of them suffered infection(p value=0.109). So infection was significant among smokers in our study.

Of the total 36 IIIA cases, 6 (16%) were found to be infected and of the 14 IIIB cases, 3 (21%) were infected. Of the 14 IIIB cases 6 cases underwent split skin grafting in the same sitting as the skeletal procedure and 2 were found to be infected and 7 cases were taken up for skin grafting on a later date and 1 patient had SSI among them. One patient underwent skin graftingwith medial gastrocnemius flap and had uneventful post operative period.

Out of the various open fractures enrolled in this study, 5 werehumerus, 4 were forearm, 20 cases of femur fractures and 21 cases of tibia fractures.One case eachofhumerus and forearm open fractures were found to be infected. Among the 21 open tibia fractures, 3 were infected and 4among the 20 open femur fractures were infected.

The rate of calcium sulfate dissolution was studied in serial radiographs. In most cases, the granules were absorbed in 1 month with the meantime to the dissolution being 4.76 weeks. The mean time to the bony union as evidenced on serial radiographs was 6.44 months with the earliest union achieved at 4 months and the maximum time for the union was 10 months.

Eight patients were operated on the same day of injury in which 2 patients presented with SSI. There was a delay in remaining patients due to associated head injuries, medical co-morbidities,and late presentation to the hospital[2]. patients were Covid-19 positive with pulmonary complications and the ongoingpandemic further delayed the time for surgery. Regardless, there was no statistical significance found between time to surgery and incidence of SSI (p value=0.494). This suggests that along with thorough debridement, wound irrigation, parental antibiotics and the use of local antibiotic beads play a vital role in preventing SSI associated with open fractures.

Based on the microbiological culture it was found that most of the cases of SSI had gram-negative bacilli infection at a rate of 8%.Pseudomonas aeruginosa was found in two cases (4%) and one case each was infected with Acinetobacterbaumannii and Enterobacter cloacae with an infection rate of 2% each. These are bacteria usually associated with nosocomial infections and point to probable hospital-acquired infections.This was followed by Staphylococcus aureus infecting 3 cases (6%). Next, methicillin-resistant staphylococcus aureus (MRSA) with a 4% infection rate infecting 2 cases. All cases with Staphylococcus aureus and MRSA were sensitive to vancomycin or erythromycin. Whereas, cases with Pseudomonas aeruginosa and Acinetobacterbaumanni needed more attention as they were multi-drug resistant and found sensitive to Colistin and Tigecycline respectively.

Helgeson *et al*.[8] investigated the efficacy of antibiotic-laden calcium sulfate in blast-related injuries and reported a 22.2% infection rate. Cai *et al*.[9] reported no infection rate in 28 fractures fixed with internal fixation and using antibiotic mixed with calcium sulfate as an antibiotic carrier.In our study, 18% of patients developed superficial SSI which later healed by local wound care and sensitivity directed systemic antibiotics.

In a study done by Weber *et al.*, out of 162 open III A fractures, 15 were infected (9%) and of 96 open III B 16 were found to be infected (16%)[10]. In a study by Lawing *et al*. of the 123 open IIIA fractures 15 were infected (28.8%) and of 41III B fractures 16 were found to be infected (30.8%)[11]. The incidence of infection among open type IIIA and IIIB in our study supports findings in the literature. In our study, of the 36 III A fractures 6 were infected (16.7%) and among14 III B fractures, 3 were infected (21.4.%) with superficial SSI.

The effect of smoking had a statistically significant impact on infection rates in the study done by Lawing *et al*.[11] In our study there was a significant (p value=0.03) number of infections among smokers,butthe number of patients with a history of smoking was less.

The site of infection was found not to be significant in a study done by Lawing et al.11 and the infection rate in tibial fractures was found to be 48.1%. This was probably due to the large volume of tibial

fractures enrolled in this study (123 of 351).Patzakis and Wilkins[12] reported that the rate of infections following tibia fractures was 10% versus a 5.3% infection rate for other sites combined. In our study, the incidence of infection after tibial fractures were 14.3% (21 of 50) and the site of infection and its impact on infection rates was not significant.

Of the infections, gram-negative infections were found in 55% (11 of 20) in a study by Chen *et al*.[13] Whereas in our study, gram-negative infections were was found to be 44% (4 of 9). The most cultured pathogens in our study were gram-negative bacilli and only 2 cases of MRSA were found. We recommend using antibiotic like Vancomycin locally at the wound site than develop resistance when used parenterally. Theoretically, this provides the best-targeted control of infection than a broad-spectrum antibiotic.

Calcium sulfate is an osteoconductive material that is resorbed at a rate similar to that of bone formation[14]. In our study, the meantime to the bony union as evidenced on serial radiographs was 6.44 months with the earliest union achieved at 4 months and the maximum time for the union was 10 months.

The most common complication associated with the use of calcium sulfate is serous drainage from the wound, which occurs in from 4-51% of cases. However, this tends to resolve as the calcium sulfate is resorbed[15]. There were 7 cases in this study that had serous discharge from wound site post-surgery but all these cases had no growth on microbiological culture. Furthermore, the serous discharge subsided with the dissolution of calcium. Hence, the rate of serous discharge was found to be 14% in this study.

CONCLUSION

The use of vancomycin-laden calcium sulfate granules is a safe and effective system of local antibiotic delivery for the primary prevention of infection in Gustilo-Anderson open type III A and III Bfractures of long bones. Thus reducing the incidence of deep SSI. The osteo-conductive capabilities of calcium sulphate can promote callus formation and bony union. Calcium sulphate isbio-absorbable and need for secondary surgery to remove the antibiotic beeds are not required. Since, heat generated by mixing of calcium sulphate is less compared to polymethyl methacrylate, heat labile antibiotics can be used as well. There were no serious complications related to calcium sulphate use that arose in this study.

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