

Antibiotic Bead Pouches In Open Fractures: Elution of Antibiotics From Pmma Bead Pouches In Open Fractures

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Abstract: The increasing incidence of open fractures has led to higher infection rates leading to higher incidence of non-union and morbidity. Antibiotic impregnated PMMA (polymethyl methacrylate) bone cement, (in the form of bead pouch) is used to deliver higher concentrations of local antibiotics to prevent bone infection in open fractures. This study demonstrates the effectiveness of combination antibiotic impregnated bone cement in infected open fractures. This study shows that local antibiotic elution through antibiotic impregnated bone cement is more potent and helps in controlling the infection. Combination antibiotics added to bone cement are more effective against a wide spectrum of bacteria than single antibiotic (gentamicin as provided by manufacturer).

Keywords: antibiotic bead pouch, Open fractures, gentamicin, PMMA (polymethyl methacrylate) bone cement.

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I. Introduction

The treatment of compound wounds is a challenge faced by many orthopaedic surgeons. Traditionally, the treatment strategy has been prevention of infection followed by procedures to achieve bone union. Debridement and intravenous antibiotics have been used for the control of the infection and external fixators have been used for stabilizing the fracture^{[1] [6]}. Antibiotic impregnated polymethyl methacrylate (bone cement) is a method used to deliver higher concentration of local antibiotics to treat bone infections. It is formed into bead pouches in open fractures^{[2] [11] [15]}. This study demonstrates the effectiveness of combination antibiotic impregnated bone cement in open fractures. In open fractures whatever the cause, the major complication is post operative infection due to contamination. These cases can be treated well with a through wound wash with pulsavac, temporary fixation(external fixator) and local implantation of bead chains or pouches until the soft tissues heal, for a span of 2 weeks. After the signs of infection like ESR, CRP, WBC counts return to normal, a secondary rigid fixation can be performed. This reduces hospital stay, morbidity and is cost effective^{[3] [5] [7]}.

Evolution of antibiotic beads:

With the development of joint arthroplasty in Europe (in 1970s), the local use of antibiotics to prevent skeletal infections gained wide spread acceptance. Buchholz and Engelbrecht reported that penicillin, erythromycin and gentamicin mixed into the cement used to affix prostheses to bone was found to provide high concentrations of antibiotics for extended periods of time and results in prophylaxis of infection.⁷ In 1979, Klemm created gentamicin-impregnated beads and used them to occupy dead space after debridement of infected bone.

Use of antibiotic beads is a simple procedure and often performed at time of initial debridement of open fracture. Usually, the beads are prepared from commercially available cement in the operating room just prior to placement. Bead placement aids significantly in the management of large dead-space defects and bathes the hematoma in constant high levels of antibiotic. Local antibiotic therapy with beads decreases the risk of complications of systemic antibiotic therapy including end-organ failure and gastrointestinal side effects and is also less expensive. But the disadvantage is bead placement generally requires a second operation for removal. So as to cope up with this problem biodegradable substrates were considered.

Most of the antibiotics when mixed with PMMA have been shown to maintain efficacy. But the main requirement of the antibiotics is that they should be heat stable and hydrophilic. The most commonly preferred antibiotics include gentamicin, tobramycin and vancomycin. Gentamicin sulphate, an aminoglycoside acts as an excellent additive to PMMA due to its broad spectrum of action, its bactericidal characteristics, low rate of

primarily resistant pathogens, and good thermo stability. Combination antibiotics are mixed into bone cement to show increased antimicrobial spectrum i.e. synergistic effect.

Elution characteristics from PMMA antibiotic beads vary for each individual antibiotic. The size and shape of the beads have significant differences in concentrations of antibiotics released.¹⁵ The mechanism of elution is through leakage of antibiotic from minute cracks in the cement.¹⁶ The elution procedure can be altered by either increasing or decreasing the porosity with the addition of solvents such as glycine.

Passive opportunism, a term coined by Penner, refers to the addition of a second antibiotic to the cement serves as a solvent thus increasing elution of both antibiotics by increasing cement porosity.¹⁴ Hoff et al demonstrated that the local antibiotic delivery from cement beads is more effective than does systemic therapy.¹⁷ Wahlig et al tested the elution properties of gentamicin from PMMA in a buffer solution and found 600 mg/L of gentamicin per bead eluted on the first day, 120 mg/L on the 10th day and 10 mg/L on the 80th day.¹⁸ Adams et al compared elution properties of clindamycin, ticarcillin, tobramycin, ciprofloxacin, and vancomycin in 15 large mongrel dogs. Clindamycin proved to have the best elution profile, with the highest seroma, granulation tissue and bone concentrations. Vancomycin demonstrated excellent bone concentrations, and tobramycin had high seroma and granulation tissue levels. Cefazolin, ciprofloxacin, and ticarcillin all failed to maintain seroma concentrations above breakpoint sensitivities for more than 14 days.

Generally, 40 g of cement powder is mixed with variable amounts of antibiotics. Hanssen recommends use of 3.6 g antibiotic per 40 g cement is effective. In case of premixed antibiotic beads, we prefer to use no more than 2.0 g per 40 g packet of cement. So, the commercially available antibiotic cements are both ineffective and economically prohibitive as a lone treatment for infection.

This study demonstrates the effectiveness of combination antibiotic impregnated bone cement in open fractures.

Aims And Objectives:

1. To study antibiotics elution through antibiotic impregnated bone cement.
2. Combination antibiotics are more effective.
3. To study the time of union.

II. Methodology

The study was carried out in Amar orthopaedic hospital and the numbers of cases studied were 40 with the youngest 21 yrs and the oldest 50yrs.

The intention of this study was to determine ELUTION OF VANCOMYCIN AND GENTAMICIN FROM PMMA BEAD POUCHES IN OPEN FRACTURES.

Participants:

Inclusion criteria:

All open fractures Gustilo Anderson type 2, 3a and 3b.

Exclusion criteria:

Known hypersensitive to antibiotics.

Co-morbid conditions like coronary artery disease.

Procedure:

On admission demographic data was recorded, followed by through history and clinical examination was performed. We assessed the soft tissue injuries in the emergency department and graded them into 2, 3a or 3b compound fractures.

For compound wounds after stabilising the patient haemodynamically, culture swab was taken from the wound site and a through wound wash was given and patient was immediately given tetanus toxoid, analgesics and started on empirical antibiotics (3rd generation cephalosporins, aminoglycosides and metronidazole). Wounds were closed with stay sutures temporarily, fracture was immobilized and sterile betadine dressing applied over the wound.

Pre-Operative Planning:

Routine blood examination was done for haemoglobin %, total and differential blood counts, fasting blood sugars, blood urea, serum creatinine, bleeding and clotting time, HIV, HBsAG, HCV.

Examination of urine was done for presence of albumin and sugar. Blood pressure and ECG were recorded for all the patients.

Physical fitness and the consent for the surgery were obtained for all the patients and a pre anaesthetic check-up was done.

Radiographic Evaluation:

In cases of open fractures standard AP and LATERAL views of the suspected part of the bone are obtained and the findings like comminution, gap between fracture sites were noted.

Surgical procedure:

The duration from the time of injury to the time of operation ranged from 0-3 days (avg 1.5 days).

Anaesthesia:

The operation was performed either under spinal anaesthesia or general anaesthesia.

Position and tourniquet:

Patients with compound wounds were placed in supine position with fracture table whenever required. No tourniquets were used in any of the cases.

Technique:

In open fractures first a through wound wash with pulsavac is performed with 6liters of normal saline. Fracture is stabilized with external fixator. Gentamicin antibiotic cement 40g is taken and 3g of vancomycin is added to it and cement mixing is started and placed in the mould with stainless steel wire in between for the required number of beads and allowed to set. After setting of the cement the ends of the stainless wire are made into a knot so as the beads don't slip during removal. Wound closure is done with simple sutures. Betadiene dressing done and compression bandage applied with enough padding.

Post operative procedure:

In the immediate postoperative period, care was given to the general condition, fluid balance, IV antibiotics and analgesics as per the protocol. Operated limb was kept in elevated position to reduce oedema.

Mobilisation:

In patients treated with external fixator range of motion exercises and isometric muscle strengthening exercises were done from post operative day 2 based on patient compliance and only isometric exercises were done in cases where a spanning external fixator was used.

Secondary Procedure In Compound Fractures:

Patients underwent a secondary procedure of external fixator, bead pouch removal and definitive fixation from 2-3 weeks of time of first surgery. With post operative immobilisation and early range of motion exercises and isometric exercises depending on stability of fixation.

Follow Up:

The first follow up of patients who underwent antibiotic bead pouch implantation was done after 4weeks of the secondary procedure and later on regularly for 6-8 weeks interval.

1. The course of fracture healing was documented radiologically with minimum 6 wks interval. The moment of complete healing was defined as radiologically complete bone regeneration at fracture site.
2. Partial weight bearing is done when signs of callous formation were seen on the x-ray and later on full weight bearing with the next visit.
3. Evaluation of any possible loss of alignment.
4. Signs of infection and inflammatory markers.
5. Assessment and analysis of any complications.

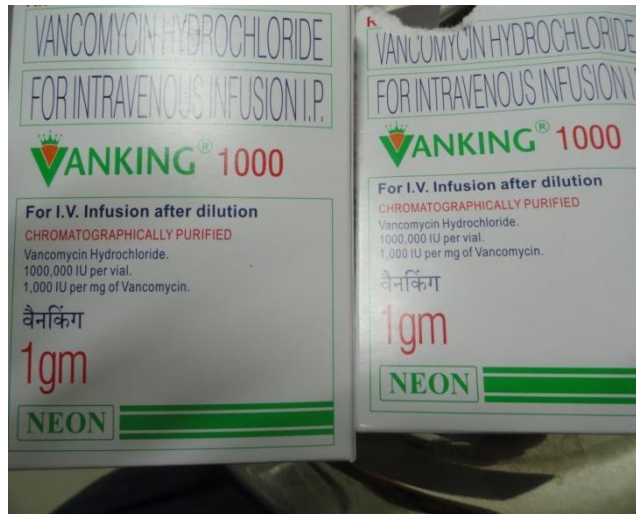
Follow up of patients ranged from 16 to 64 weeks.

Materials Used:

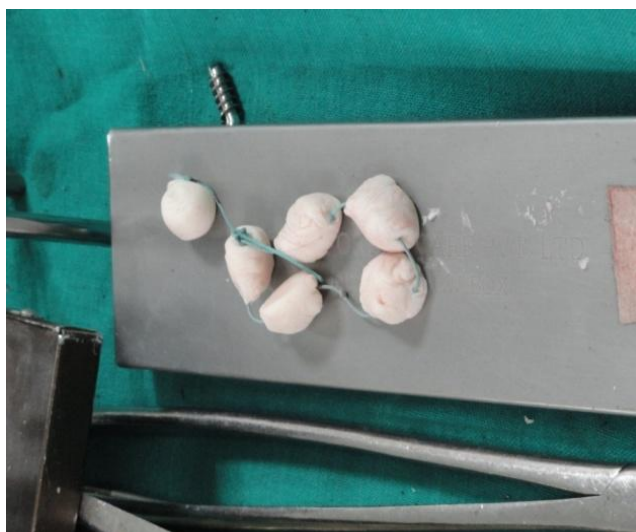
Antibiotic cement:



Antibiotic solution:



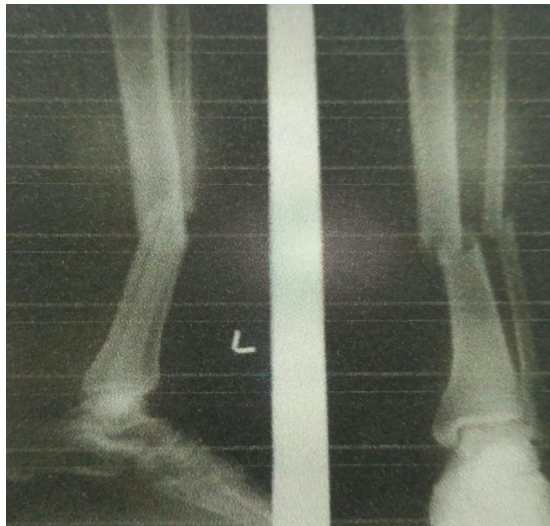
Antibiotic bead cement preparation:



Compound grade 2 fracture:

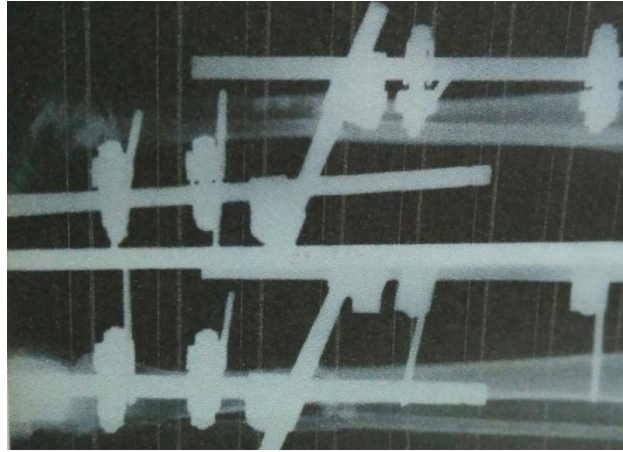


Fracture shaft of tibia and fibula middle 1/3rd

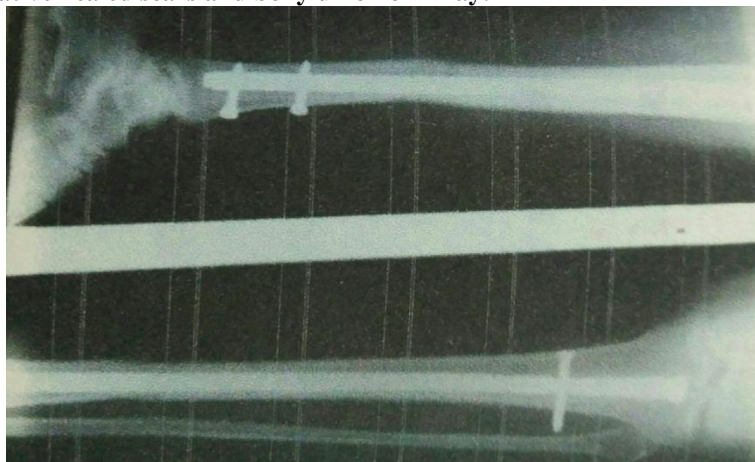


Antibiotic bead placement with external fixator application:





2 months post operative healed scars and bony union on x ray:

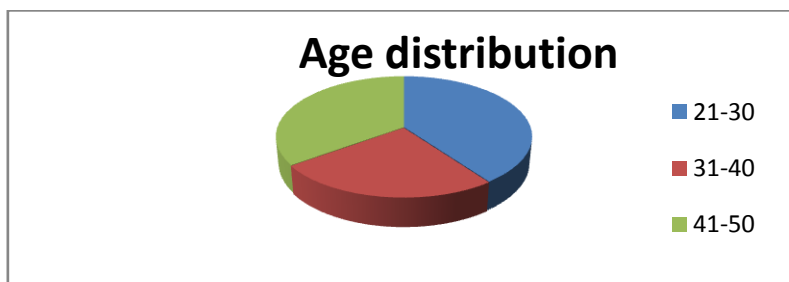


III. Results And Observations

We studied 40 patients (open fractures of long bones) of age group 21 to 50 yrs.

Table 1 (age distribution):

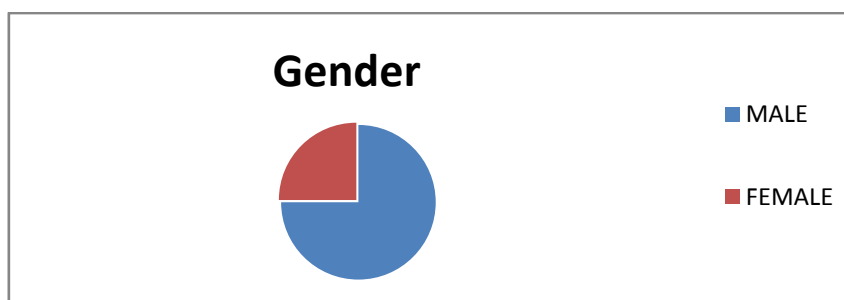
Age group (year)	Number of patients	Percentage (%)
21-30	16	40
31-40	10	25
41-50	14	35
Total	40	100



In our study most of the cases are observed in patients of age group 21-30 yrs they occupy 40% and 25% cases were observed in age group 31-40 occupying the lowest and 35% of cases were observed in 41-50 age group. Hence most of the fractures were observed in 21-30 age group.

Table 2 (Gender distribution):

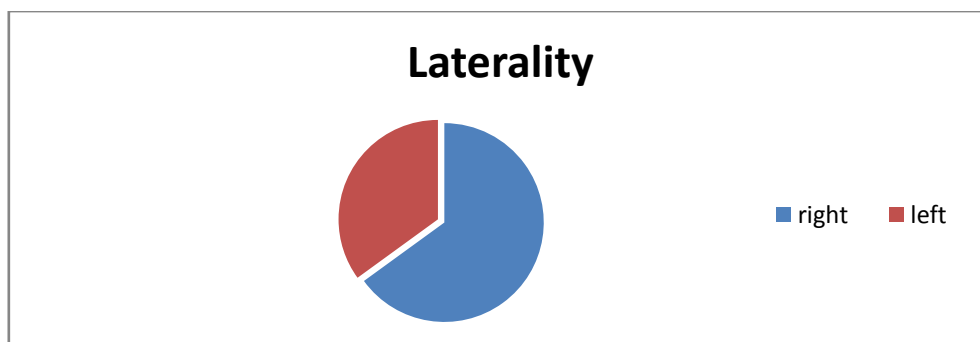
Gender	Number of patients	Percentage (%)
Male	30	75
Female	10	25
Total	40	100



Out of the total population, most of the patients were male who about 75% were and females were about 25%. According to our study males are more prone to fractures when compared to females.

Table 3(laterality):

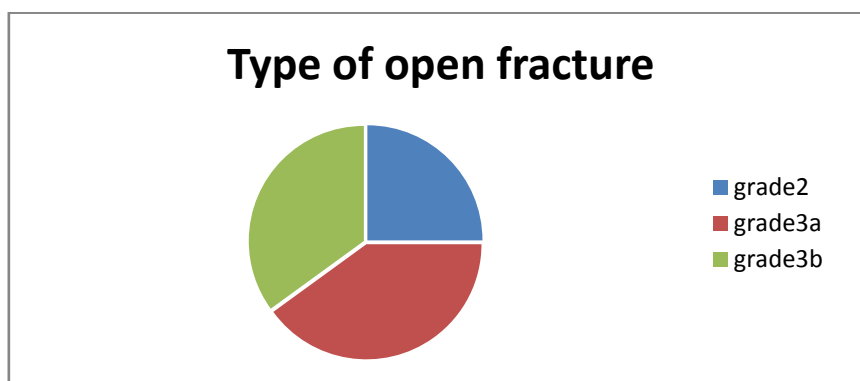
Laterality	Number of patients	Percentage (%)
Right	26	65
Left	14	35
Total	40	100



Subjects in our series are more affected on right side (65%) when compared to left side (35%).

Table 4 (type of open fracture):

Type of open fracture	Number of patients	Percentage (%)
Grade 2	10	25
Grade 3a	16	40
Grade 3b	14	35
Total	40	100



Of all the open fractures, grade 2 open fractures include 25%, grade 3a includes 40% and grade 3b includes 35%.

Results in open fractures treated with antibiotic beads:

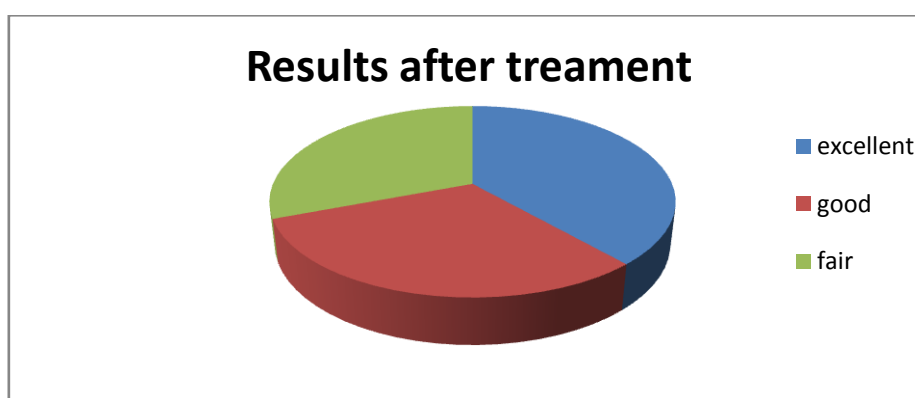
Excellent: Open wounds treated with primary fixation and antibiotic beads attain bony union without any secondary procedure.

Good: Open wounds treated with external fixator as primary procedure with antibiotic beads placement and secondary procedure of IMIL nailing or plating done attaining bony union.

Fair: Bony union attained with complication (shortening, deformity, stiffness and nerve injury)

Table 5 (results based on outcome in open fractures treated with antibiotic beads) :

Outcome	Number of patients	Percentage (%)
Excellent	15	37.5
Good	12	30
Fair	12	30
Total	40	97.5



Results show 37.5% of excellent healing, 30% of subjects treated with antibiotic beads for open fractures good healing, 30% of subjects showed fair healing and the remaining 2.5% showed reinfection.

The average time taken for healing open wounds was 2 weeks for patients treated with antibiotic beads.

The average time taken for bony union for patients treated for open fractures was 12-24 weeks.

IV. Discussion

The increasing incidence of open fractures has led to higher infection rates leading to higher incidence of non-union and morbidity. The single most important factor that results in chronicity and sustained infection in

open fractures is the formation of biofilm. The behaviour of bacteria in biofilm varies greatly from that in the active state¹⁰. In our study, we used antibiotic impregnated polymethyl methacrylate (bone cement) to deliver higher concentration of local antibiotics to treat bone infections, in the form of bead pouch technique in open fractures.

In clinical situation the susceptibility or resistance of bacteria to a particular antibiotic is measured by the minimal inhibitory concentration (MIC) which is approximately 6 microgram per ml. The application of bead pouch increases the local concentration by 50-100 times, at this concentration the organisms that are deemed to be resistant to the particular antibiotic will also be eradicated without the associated systemic side effects. A local antibiotic delivery system is appealing, as it offers a high local concentration of the antibiotics with low serum levels³.

In this series we used PMMA as a vehicle to deliver a localized dose of antibiotics to an area at risk for infection (i.e. compound fracture wound). The strategy of using a localized antibiotic delivery system is that it avoids the potential toxicity of intravenous antibiotics. The side effects of even short courses of IV antibiotics are well documented.

Edward J. McPherson et.al, Out of 250 procedures there were 29 complications (11 hips and 18 knees) for a complication rate of 11.6%. Eight of the 29 complications had wound related complications (3 hips and 5 knees). There were nine failures (3.6%) in this study. Six failures were a result of infection. Excluding the above infection failures, all remaining patients had a normal C-reactive protein when tested between 6 and 12 months post-operatively¹.

In our study out of 40 procedures, the complication rate was 2.5% due to reinfection and the remaining cases were normal.

Use of two antibiotics namely gentamicin and vancomycin with bone cement widens the spectrum of activity and also enhances the elution properties of the two antibiotics by Buchholz and Engelbrecht². The most common organism that was found in the wounds was *Staphylococcus aureus* followed by *klebsiella* species. Direct application of antimicrobial drugs into open fracture wounds was found to be of no benefit. In 1939, Jenson et al⁴ presented their experience of treating open fractures with sulphanimide powder poured directly into the wound before closure and credited introduction of this technique with a reduction in their infection rate from 30% to 5%. The attraction of the local delivery is that high concentrations of antibiotic can be achieved in the wound even in avascular areas, without the cost or toxic effects associated with systemically administered antibiotics.

Buchholz et al² in Germany first developed the use of PMMA cement blended with antibiotics to treat infected joint prosthesis. This approach was then adapted to treat chronic osteomyelitis by Klemm³ who published his experiences in 1974.

In 1995, Ostermann et al⁵ published a similar comparison of 240 patients with open limb fractures who received IV antibiotics and 845 patients who received both IV antibiotics and antibiotic-PMMA beads. He found an infection rate of 12% in the IV only group compared with 3.7% in the IV / antibiotic- PMMA bead group (p=0.001). It should be noted that neither of these studies randomised the treatment groups. In our study, the infection rate was about 2.5%.

Moehring et al⁶ described a trend towards superiority of antibiotic beads but it did not reach significance in 67 patients studied. Interestingly, animal studies have failed to convincingly establish a significant benefit of augmenting systemic antibiotics with antibiotic PMMA beads in musculoskeletal infections. Preformed antibiotic-PMMA beads are available (septopal) but cost constraints prevent wide spread usage. Surgeons frequently prepare beads intra operatively from PMMA cement and antibiotic powder. Despite their wide spread use there is recognition that PMMA beads do not represent the ideal delivery vehicle for local antibiotics. They are bulky and not bio absorbable, which potentially complicates wound closure and necessitates subsequent removal. This prevents their use during definitive closure. In complex, high energy wounds, there is concern that antibiotic eluting from the discrete depots of a PMMA bead will not diffuse sufficiently to reach all the recesses of a wound, an effect exacerbated by the concurrent use of negative wound pressure wound therapy, Schurman, D et al⁸ which is well supported as a beneficial technique to reduce infection in open fractures.

The commercially available antibiotic PMMA beads septopal (biomet, bridgend,UK) contains gentamicin alone, however when antibiotic PMMA beads are manufactured de novo in the operating room, they are frequently formulated with both amino glycoside and vancomycin to ensure coverage of both gram positive and gram negative organisms. This study mimicked this clinical practise and used both amino glycoside and vancomycin. Other local antibiotic delivery vehicles have been used, gentamicin impregnated collagen sponges have been tested as bio absorbable vehicle. However, in a non-orthopaedic recent clinical randomised controlled trial of (Innocoll, Gallowston, Ireland), the sponge group had a higher rate of surgical site infection (30% Vs 20% P=0.01). It was speculated that the antibiotics eluted faster than the sponge degraded, leaving foreign material in the wounds without antibiotics.

Recent development work has focussed on other absorbable antibiotic vehicles including a range of synthetic bone grafts impregnated with antibiotics. Osteoset "T" (Wright Medical, Arlington, TN) are calcium sulphate pellets with 10% Tobramycin by weight, has been used clinically to treat Osteomyelitis with positive results 25 and has found to be as effective at treating as antibiotic delivery through PMMA beads, with a requirement for less surgery. Investigators have examined gel-based vehicles for delivering antibiotics in preclinical in vitro models of orthopaedic infection. No clinical trials of a gel capable of being spread throughout a wound have yet been reported.

The ideal release profile for a local antibiotic delivery vehicle used to prevent infection in open fractures is not known. It is speculated that eluted local antibiotics should quickly rise above the minimum inhibitory concentration of relevant bacteria, be sustained above this level for several days, then rapidly drop to avoid bacteria being exposed to sub inhibitory antibiotic concentration, promoting resistance. It is entirely possible that the ideal release profile of local antibiotic vehicles used for treating established osteomyelitis will be different and may require a more sustained release.

Cement beads fill the dead space and also allow a high concentration of local antibiotics. The effectiveness of the antibiotic impregnated cement beads in the control of bone infection is well established. The antibiotic beads after removal from the subjects after two weeks showed 3 times more than the normal systemic antibiotics by disc diffusion technique⁹.

V. Conclusion

At the end of this study, following conclusions could be drawn from the treatment of open fractures with Gentamicin and vancomycin antibiotic impregnated bone cement.

- Use of Gentamicin and Vancomycin combination has effect on both gram positive and gram negative organisms.
- Antibiotic bone cement has 3 times higher zone of inhibition than the systemic antibiotics at the infection site.
- Use of gentamicin bone cement with the addition of 3 gms vancomycin per 40 gms pack of PMMA is cost effective.
- Use of antibiotic beads in open fractures helps in control of infection and achieves bone union.

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