

Original Research Article

A prospective study on the effectiveness of antibiotic impregnated beads in treating osteomyelitis in diabetic foot patients

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ABSTRACT

Background: Diabetic foot infections are the most common skeletal and soft tissue infections in diabetic patients. Oral antibiotics with good oral bioavailability and local delivery of antibiotics in the form of beads are being used. In this study, we analysed the effectiveness of antibiotic-impregnated beads in treating osteomyelitis in diabetic foot patients. We also analysed the microbiological profile among the study groups.

Methods: This was a prospective comparative study where 60 patients were selected from the general surgery and podiatry departments at Amrita Institute of Medical Sciences, Cochin, between August 2017 till August 2019. Antibiotic beads were used in the 'bead' group and oral antibiotics in the 'no bead' group, with empirical i.v. antibiotics in both groups. All patients were reviewed for six months, and ulcers not healing within six months were taken as failed therapy.

Results: Among the 60 patients in the study population, 51 showed healing, and 9 did not heal. Out of the nine which did not heal, 7 (23.2%) belonged to the no bead group and 2 (6.7%) to the bead group. The mean healing duration in the no bead group was 74.70±30.25 days, while that in the bead group was 81.18±30.80 days. The most typical isolated organism was *Staphylococcus aureus*, which was found in 38.3%.

Conclusions: We have found that using antibiotic beads improves patient convenience by reducing hospital visits and the need for daily dressing without compromising the healing rate.

Keywords: Antibiotic beads, Diabetic foot, Osteomyelitis foot, Topical antibiotics

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to a defect in insulin secretion, its action, or both. The long-term effects of diabetes can cause damage, dysfunction, or even failure of various organs. The pathogenesis ranges from autoimmune destruction of the β -cells of the pancreas to insulin resistance. The microvascular complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy, causing diabetic foot diseases. Myocardial infarction, transient ischemia, and stroke are macrovascular complications.

Diabetic foot disease continues to be a devastating preventable complication of diabetes mellitus. Foot ulceration and infections are significant causes of high morbidity in patients. The lifetime risk of diabetic foot patients is 25%, which is one of the leading causes of lower limb amputation and prolonged hospital stay.^{1,2} According to epidemiological studies, 2.5 % of the population develops diabetes each year, and 15% develop diabetic foot diseases.³

Diabetic foot results from peripheral neuropathy, peripheral vascular disease, and infection.⁴ Diagnosis of diabetic foot infection includes clinical assessment supported by radiological investigations and bone culture.

In the case of a foot ulcer in a diabetic patient exposed to the underlying bone, the possibility of osteomyelitis should be ruled out with an x-ray and bone culture. Osteomyelitis in the diabetic foot may also present as an inflamed digit requiring debridement and culture from the bone. Glycaemic control, adequate foot care, and appropriate footwear remain the three major steps in managing diabetic foot.

Treatment of diabetic foot osteomyelitis remains challenging. Earlier, intravenous antibiotics were the mainstay of treatment along with debridement. Higher concentrations are required to achieve high serum levels of antibiotics, which can cause various complications, including nephrotoxicity and ototoxicity. However, many patients remain medically unfit for prolonged intravenous antibiotic therapy or may develop multi-organ failure due to long-term antibiotic usage. Recent literature shows no statistically significant difference between oral and intravenous antibiotics in treating diabetic foot osteomyelitis.⁵

In 2017, in a study conducted in Spain, Senneville et al said that it is logical to prefer antibiotics that have got a high diffusion into the bone (bone: blood ratio of more than 0.3) and also those with good oral bioavailability (more than 90%) due to the need for a prolonged duration of treatment required for treating diabetic foot ulcer with osteomyelitis.⁶ Local delivery of antibiotics in the form of beads offers an optimal concentration of chosen antibiotics at the site of infection. This has been a significant development in treating osteomyelitis in diabetic patients, making it much more convenient for the patients.⁷

Beads are generally prepared from commercially available cement and specific antibiotic. The beads are prepared under sterile conditions in the operating room and then placed onto the ulcer. This mode of antibiotic delivery leads to low systemic levels of antibiotics and a high tissue concentration, reducing systemic side effects. It is now becoming an effective method of dead space management in diabetic foot osteomyelitis.

The technique of local application of antibiotics in the form of beads has been widely studied and used in the western population.⁸⁻¹⁰ However, there is scant literature about the same in the Indian population. Hence, this study was conducted to assess the effectiveness of antibiotic-impregnated beads in treating osteomyelitis in patients with diabetic feet in an Indian setup. This study also looked at the microbiological profile of the wounds.

METHODS

A prospective comparative study was conducted from August 2017 to August 2019 in general surgery and podiatry departments at Amrita Institute of Medical Sciences, Kochi, Kerala. The study was conducted following the ethical standards of the institutional

research committee and with the 1964 Helsinki declaration and its later amendments. The data were collected after obtaining ethical clearance from the Institutional Research Board and Ethics Committee Amrita School of Medicine (IRB-AIMS-2018-224). Informed consent was taken from the patient and the caregiver for participation in the study and further use of the data included in the study.

Selection and description of participants

All diabetic patients with a chronic foot ulcer for more than three weeks and underlying osteomyelitis proved with culture were included in the study. For our study, these patients were gathered from the departments of general surgery and podiatry. Patients were categorized into the 'bead' group and the 'no bead' group. All chronic diabetic foot ulcers of size less than or equal to 5 cm² were included. Patients with immunocompromised status (on steroid treatment, chemotherapy, methotrexate, and radiation) were excluded.

Based on our pilot study with ten patients in each group, the mean and standard deviation of the number of days healing was 61.86±22.56 days and 85.60±39.48 days in the 'bead' group and 'no bead' group, respectively. With a 95% confidence interval and statistical power of 80% in a 2-sided test, the required sample size per group was 29. We aimed at a sample size of 30 in each group. Hence the total sample size was 60 in our present main study. They were randomly distributed among the two groups.

Technical information

The primary objective was to study and compare the effectiveness of antibiotic-impregnated beads in treating osteomyelitis in diabetic foot patients. The secondary objective was to analyze the microbiological profile of the study group.

A proper history was taken, and a thorough clinical examination was done for the patients who came to the outpatient departments of general surgery and podiatry. All chronic diabetic foot ulcers of size less than or equal to 5 cm² were included in the study. After attaining reasonable glycemic control, the patients were posted for debridement in the operation theatre under the coverage of systemic antibiotics, and bone cultures were sent. Culture-specific antibiotics were started later.

Antibiotic beads were used in the 'bead' group and oral antibiotics in the 'no bead' group. Intravenous antibiotics were given empirically in both groups. Amoxicillin-clavulanic acid and cefoperazone-sulbactam were the most commonly used ones. Patients in both groups required hospitalization of about a week, after which patients were discharged. Patients were assessed based on their time taken for healing days. The wound was considered healed when there was complete epithelialization of the ulcer.

In the 'bead' group, after debriding the wound, the antibiotic beads were prepared based on the culture and sensitivity report and were placed over the ulcer with underlying osteomyelitis. Beads were made by mixing the required antibiotic concentration with synthetic implant-grade calcium sulfate dihydrate- stimulant rapid cure (biodegradable and biocompatible). After proper mixing, a smooth paste was formed, and it was applied uniformly with the paste applicator to the bead mat. It was then kept undisturbed for setting. The bead mat was then flexed to release the beads. These were then placed onto the ulcer, and sterile gauzes were placed over it and were replaced once in 3 days by the patient or his/her caregiver (Figure 1).



Figure 1: Technique of antibiotic beads placement.

Patients were reviewed in our outpatient department once in 3 weeks, and wounds were re-assessed. In case of slough or residual infection of the tissue, debridement

was done, followed by the reloading of the antibiotic beads till the wound heals.

In the 'no bead' group, patients were discharged with oral antibiotics based on the culture and sensitivity reports. Patients in this group required daily dressing from the outpatient department or local hospitals. Review and re-assessment of the wound once in 3 weeks were mandatory. All patients were reviewed for six months, and ulcers not healing within six months were taken as failed therapy.

Statistical details

Statistical analysis was done using IBM SPSS 20. (SPSS Inc, Chicago, USA). The results are given in Mean \pm SD for all the continuous variables and categorical variables as numbers and percentages. The chi-square test was applied to obtain the association of categorical variables and to compare the mean difference of numerical variables between groups an independent two-sample t-test was applied. A p value <0.05 was considered statistically significant.

RESULTS

Our study had 60 patients with 30 in each group with ages ranging from 37 to 84 years, with a mean age of 59 years in the 'bead' group and 60 years in the 'no bead' group. Among these, 13 patients were females, and 47 were males, showing a male predominance for diabetic foot osteomyelitis. There was no statistically significant difference in the mean age, body mass index, random blood sugar, and HbA1c values among the two groups (Table 1).

Table 1: Demographics, laboratory and wound characteristics of the study population.

Features	No bead group (n=30)	Bead group (n=30)	P value
Mean age (years)	60 (37-84)	59 (38-76)	0.436
Sex			
Male	24	23	0.287
Female	6	7	0.239
BMI (kg/m ²)	38.12 \pm 2.01	39.46 \pm 1.87	0.352
Random blood sugar (mg/dl)	189.92 \pm 15.67	195.01 \pm 13.69	0.185
HbA1c	8.78 \pm 0.57	7.99 \pm 1.21	0.485
Wound size at presentation (cm ²)	3.78 \pm 2.79	4.03 \pm 1.24	0.12
Duration of wound at presentation (days)	22.31 \pm 3.56	24.37 \pm 2.89	0.173
Wound healing			
Yes	23	28	0.145
No	7	2	
Mean duration of wound healing (days)	74.70 \pm 30.25	81.18 \pm 30.80	0.454

In our study, the healing of the ulcer was compared between the two groups, and it was found that among the 60 patients in both groups, 51 patients showed healing, and nine did not heal.

Out of the nine which did not heal, 7 (23.2%) belonged to the no bead group and 2 (6.7%) to the bead group. Out of 51 who showed healing, 23 (76.7) belonged to the no bead group and 28 (93.3%) to the bead group. The

healing association was statistically insignificant, with a p value of 0.145. The mean healing duration in the no bead group was 74.70 ± 30.25 and 81.18 ± 30.80 in the bead group, with a p value of 0.454, which was not statistically significant (Table 1). The healing duration in no bead group (n=23) was 11 (47.8%) within 60 days, 9 (39.1%) within 60-120 days and 3 (13%) within 120-180 days and in bead group (n=28) was 7 (25%) within 60 days, 20 (71.4%) within 60-120 days and 1 (3.6%) within 120-180 days.

The microbiological profile in both the study groups were 23 (38.3%) *Staphylococcus aureus*, 15 (25%) *Enterococcus*, 14 (23.3%) *Klebsiella*, 10 (16.7%) *Pseudomonas*, and 8 (13.3%) *E. coli*. The most typical organism among both the groups in our study was *staphylococcus aureus*. *Enterococcus*, *Klebsiella*, and *Pseudomonas* followed this. Polymicrobial status was seen in 27 out of 60 patients in both groups (Figure 2).

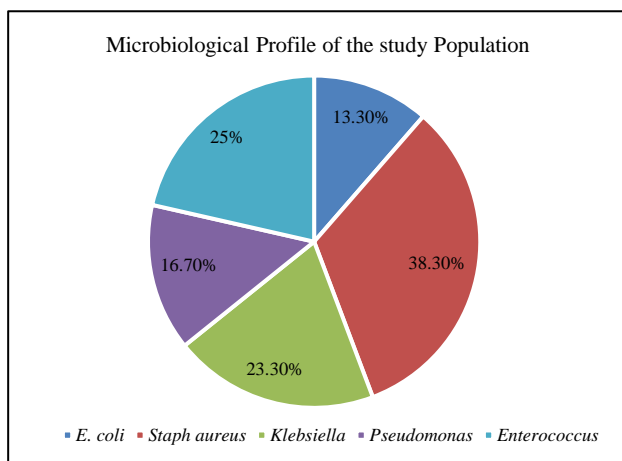


Figure 2: Microbiological profile of the study population (n=60).

DISCUSSION

Treating diabetic foot infections is always challenging, especially with underlying osteomyelitis. Foot ulceration and infections are significant causes of high morbidity in patients. The lifetime risk of diabetic foot patients is 25%, which is one of the leading causes of lower limb amputation and prolonged hospital stay.¹

Our study had 60 patients, with 30 in each group with ages ranging from 37 to 84 years, with a mean age of 59 in group 1 and 60 in group 2, of which 13 were females and 47 were males, showing a male predominance for diabetic foot osteomyelitis.

In a study done at multi-disciplinary foot clinic at Royal Darwin Hospital, Northern Territory Australia, from 2003 to 2017, 513 patients with diabetic foot ulcers were included. The mean age was 59.9 ± 12.3 years, and 62.8% were males.¹¹ Our study also showed a male predominance for diabetic foot osteomyelitis.

In our study, the number of days for healing was compared in the two groups, and it was found that among the 60 patients in both groups, 51 patients showed healing, and nine did not heal. Out of the nine which did not heal, 7 (23.2%) belonged to the 'no bead' group and 2 (6.7%) to the 'bead' group. Out of 51, 23 (76.7%) belonged to the 'no bead' group and 28 (93.3%) to the 'bead' group.

Even though the association of healing among groups was statistically insignificant with a p value of 0.145, the 'bead' group showed a healing rate of 28 (93.3%). In comparison, the healing was only 23 (76.7%) in the 'no bead' group. The number of patients who failed in 'no bead' therapy was 7 (23.3%), almost twice the number in the 'bead' group, which was 2 (6.7%). The mean healing duration in the 'no bead' group was 74.70 ± 30.25 and 81.18 ± 30.80 in the 'bead' group, with a p value of 0.454, which is not statistically significant. The healing duration in 'no bead' group (n=23) was 11 (47.8%) within 60 days, 9 (39.1%) within 60-120 days and 3 (13%) within 120-180 days and in 'bead' group (n=28) was 7 (25%) within 60 days, 20 (71.4%) within 60-120 days and 1 (3.6%) within 120-180 days. The maximum number of wounds healed in the 'no bead' group was within 60 days, and for the 'bead' group, it was from 60-120 days. Our study's most commonly used antibiotic beads include colistin, followed by meropenem and gentamycin. Among the 30 patients for whom antibiotic beads were used, colistin beads were placed for 18 patients.

In a study conducted in the department of diabetes, University hospitals of Leicester, NHS Trust, UK, by Kong and Jogia, 20 patients who had diabetes with nonhealing foot ulcer and with forefoot osteomyelitis were treated with debridement and antibiotic beads (vancomycin and gentamycin) using HPS calcium sulfate. They were observed for 18 months. Osteomyelitis was confirmed in these patients with bone culture and x-ray foot. Calcium sulfate was mixed with 1gm vancomycin and 80mg gentamycin. All patients healed with a median time of 5 weeks and did not have a recurrence for 12 months. No adverse reactions were noted for any of these patients.¹²

A study by Van et al, department of endocrine and diabetology in France compared the healing rate of those treated with antibiotics alone and those treated with conservative surgery. The healing in the first group was 57%, while in the other group, it was 78%.¹³

Based on a study done in Toronto by Israeli surgeons from Rambam medical center, 15 patients were diagnosed with diabetic foot osteomyelitis. All these patients were treated with local antibiotic therapy. One patient among 15 required amputations and others healed with local antibiotic treatment in an 11-month follow-up study.¹⁴ They did not have a comparison group in their study.

In our study, the microbiological profile in both groups were 23 (38.3%) *Staphylococcus aureus*, 15 (25%) *Enterococcus*, 14 (23.3%) *Klebsiella*, 10 (16.7%) *Pseudomonas*, and 8 (13.3%) *E. coli*. The most typical organism among both the groups in our study was staphylococcus aureus. This was followed by *Enterococcus*, *Klebsiella*, and *Pseudomonas*. Polymicrobial was seen in 27 out of 60 patients in both groups.

In a study published in the European journal of clinical microbiology and infectious diseases 2016, it was found that the most typical organism detected in the bone samples was Staphylococcus which was the same as ours.⁸ It was detected in 89.6% (26 of 29) of the sequenced samples, with a high contribution to the total bacterial population. Corynebacterium followed this. Mixed genera were present in 83.3%.¹⁵

Hospital stay was compared between the 'bead' and 'no bead' groups. No of the days of hospital stay was more in the 'bead' group which required one week of empirical antibiotic and debridement with a culture-based local antibiotic bead application in the operation theatre. The patients were observed for two days and discharged. This was done as an outpatient procedure in a few. The other group was also managed the same way, except they were discharged with oral antibiotics and daily dressings.

The majority of our study findings corroborated with the studies done in other centers, as mentioned earlier. Antibiotic bead treatment can be used in patients whose systemic condition does not allow the use of oral or intravenous intake of antibiotics. We have seen that antibiotic beads reduce the frequency of hospital visits and the burden of daily dressings. It was easier to apply by the surgeon and was well tolerated by the patients. In our study, the duration to heal was more in the antibiotic 'bead' group, but a maximum number of patients with healed wounds belonged to this group. The placement of beads was comfortable and quickly done by the surgeon after debriding the wound under nerve block and was well tolerated by the patient. The 'no bead' group required daily wound inspection and dressing. Most of the patients had difficulty accessing hospitals every day. The healing percentage was less compared to the other group.

Limitations of this study are the study included only those with small ulcers (within or equal to 5 cm²). The economic aspects of both treatments were not compared.

CONCLUSION

In our study, we have found a male predominance of diabetic foot infections with a mean age of 60. The usage of antibiotic beads improves patient convenience by reducing hospital visits and the need for daily dressing without compromising the healing rate. The 'no bead' group had difficulties accessing hospitals daily, and few

even skipped their daily dressings due to personal inconveniences. Local delivery of antibiotic beads increases the local tissue concentration of the antibiotic with low serum levels, thus reducing the systemic side effects. Intravenous use of antibiotics for osteomyelitis, which was used earlier, is being replaced by oral antibiotics with the highest bioavailability and antibiotic beads, increasing the tissue concentration without systemic toxicity. This has significantly improved patients' quality of life and reduced the duration of hospital stays.

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Dr. Anjali Krishna L and Dr. Ashwin Vinod contributed equally to the article and hence needs to be considered as co-first authors. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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