

# Stimulan® Antibiotic Impregnated Beads for the Treatment of Diabetic Foot Infection

## Abstract

**Context:** Limited evidence has been found on the effectiveness of Stimulan® antibiotic beads for the treatment of diabetic foot ulcer. **Aims:** The aim of the study was to evaluate the safety and efficacy of Stimulan® antibiotic beads in treating diabetic foot infection and review the healing rate, infection recurrence rate, and the length of postoperative hospital stay. **Settings and Design:** It was a retrospective review of patients implanted with Stimulan® antibiotic beads at a district general hospital in England from 2017 to 2019. **Subjects and Methods:** Nineteen patients with Wagner Grade 3 and 4 ulcers were included, with a mean age of 62.3 years. Stimulan®, an antibiotic loaded absorbable calcium sulfate biocomposite, was used to treat persistent diabetic foot infection with chronic osteomyelitis. *Staphylococcus aureus* was the most common bacteria isolated. Exclusion criteria consisted of those with Wagner Grade 1 or 2 ulcers and infections that had clinically responded to long courses of systemic antibiotics treatment. **Results:** All patients underwent local wound debridement with the application of Stimulan® beads and received intravenous antibiotics for 48 h postoperatively. The average postoperative hospital stay was 2 days. After 1 month of follow-up, 16 wounds (84%) fully healed, two wounds (11%) had partially healed, and one wound (5%) showed no sign of healing. Two patients (11%) had shown recurrence of diabetic foot infection in a different foot after 24 months. Amputation rate was 0% over 24 months. **Conclusions:** This study recorded the clinical efficacy of Stimulan® antibiotic beads by demonstrating 0% amputation rate after two years and shortened hospital stay. With a low recurrence rate (16%), Stimulan® beads could be considered as one of the alternative treatments in managing diabetic foot infection.

**Keywords:** Antibiotic beads, diabetic foot infection, diabetic foot ulcer

## Introduction

There is a paucity of evidence on the effectiveness of Stimulan® antibiotic beads for the treatment of diabetic foot infection. Approximately 4.7 million people in the UK suffer from diabetes mellitus in 2019 and between 70,000 and 90,000 people go on to develop a diabetic foot ulcer.<sup>[1]</sup> In the UK, more than 8500 diabetic-related amputations occur each year. With diabetic foot infection being one of the most common reasons for diabetic-related hospitalization, many patients proceed to have lower limb amputations.<sup>[2]</sup> Around 50% of patients die within 24 months after a major amputation.<sup>[1]</sup> Diabetic foot infections are mostly polymicrobial, especially in chronic infection, with causative organisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis* being the ones that are commonly found on the wound

surfaces. The former is typically seen in the early stages of infection, whereas the latter is found in the final stages of infection.<sup>[3]</sup>

The prevalence of this infection highlights the need for an effective treatment that can increase the rate of healing, decrease the length of hospital stay, and reduce the chance of potential amputations.

The traditional treatment options for diabetic foot infection encompass conservative management with the use of long-term intravenous broad-spectrum antibiotics, wound debridement, and amputations. However, long-term use of antibiotics can be harmful with consequential side effects and drug-to-drug interactions, especially in those who were on multiple medications due to underlying medical conditions. For this reason, a different approach has been taken to treat these infections. Recent studies evaluating the use of Stimulan® antibiotic impregnated beads in orthopedic

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**Received:** 07-04-2020

**Revised:** 18-05-2020

**Accepted:** 17-06-2020

**Online Published:** 21-08-2020

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### Access this article online

**Website:** www.arabjir.com

**DOI:** 10.4103/AJIR.AJIR\_9\_20

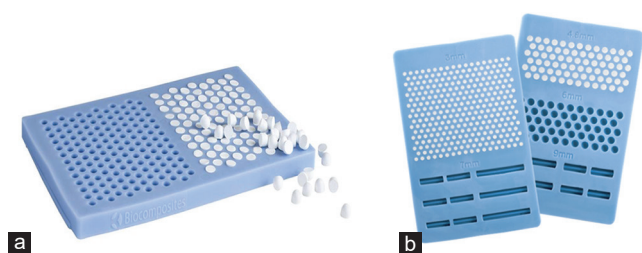
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**How to cite this article:** Wai Chon HT, Hamish M, Kirupananthan P, Gmati A, Abdalla H, Hicks R. Stimulan® Antibiotic impregnated beads for the treatment of diabetic foot infection. Arab J Interv Radiol 2020;4:73-8.

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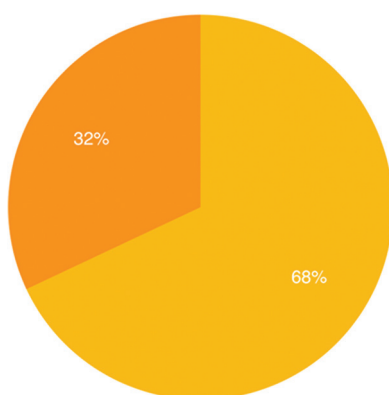
**Figure 1: Stimulan antibiotic impregnated beads (a) and the size of the beads ranging from 3 mm to 9 mm (b)**

**Table 1: Major amputation in 1 year for various stages of amputation risk**

WIFI risk of amputation in one year (stage)	Major amputation in one year		
	No	Yes	Total
1: Very Low	4	0	4
2: Low	12	0	12
3: Moderate	2	0	2
4: High	1	0	1
			19

**Table 2: Patients with diabetic foot infection subdivided into two groups**

- 1st subgroup: DFI+chronic OM+failed conservative tx
- 2nd subgroup: DFI+require debridement/amputation



related infections have shown promising results, offering 90% healing rates in diabetic foot osteomyelitis with a mean healing time of 12 weeks and the diminished need for systemic antibiotics.<sup>[4,5]</sup>

Stimulan® antibiotic impregnated beads are bioabsorbable beads consisting of calcium sulfate, gentamicin, vancomycin, and tobramycin.<sup>[6]</sup> Calcium sulfate acts as a delivery agent of the antibiotics and ensures 100% antibiotic load delivery directly to the wound. Aminoglycosides were used in these beads as they are effective in treating staphylococcus species mentioned above.<sup>[7]</sup> They were initially evaluated in orthopedic cases such as prosthetic joint infection and chronic osteomyelitis as they offered higher loads of antibiotics locally and provided a reduction

in inflammatory responses.<sup>[8]</sup> Patients who acquired diabetic foot infection will receive local wound debridement, insertion of Stimulan® beads, and wound closure. After receiving a full wound debridement, patients' wounds will be closed. Images of the stimulan antibiotic beads and the size of the beads have been displayed in Figure 1.<sup>[6]</sup>

Considering the increasing prevalence of diabetic foot infection and the advantages of Stimulan® beads mentioned above, this study had chosen the evaluation of the safety and clinical efficacy of Stimulan® antibiotic beads in treating diabetic foot infection as its main purpose, while reviewing the healing effect, the rate of infection eradication, and the length of postoperative hospital stay. The cohort in question has acquired diabetic foot infections and received insertion of Stimulan® antibiotic beads with debridement and wound closure.

## Subjects and Methods

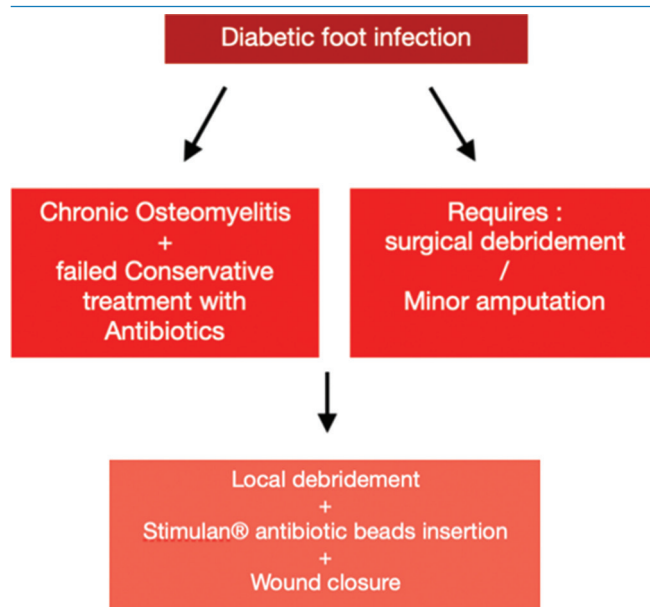
A retrospective study was performed on a group of 19 patients who had severe diabetic foot infection at the same time period in the vascular surgery unit of a district general hospital in England from 2017 to 2019. Inclusion criteria consisted of both outpatients and inpatients whose ulcers were classed as Grade 3 and 4 in the Wagner Ulcer Classification System and those who had failed to heal with long-term use of antibiotics and required surgical debridement. Exclusion criteria were patients who had ulcers graded as Wagner 1 or 2 and those who responded to 4–6 weeks of systemic antibiotics.

The study group consisted of 19 patients with a mean age of 62.3 years. The postoperative outcome of the wound and the duration of healing and follow-up were evaluated in this study. In the study cohort, there were 3 females and 16 males. Various data have been collected including patient demographics, date of admission, clinical presentation, comorbidities, diagnosis, patency of blood supply in the affected area, endovascular interventions, initial and further debridement, length of postoperative stay in hospital, and duration of intravenous broad-spectrum antibiotics used before surgery. Data such as the healing duration, follow-up duration, and the healing effect in follow-up clinics after 1 month of the operation have also been taken into account. The WIFI classification system was used to estimate the risk of amputation after 1 year. Table 1 showed the estimation of the risk of amputation after 1 year using the WIFI classification system.

In the hospital, two major groups of patients were selected for Stimulan® antibiotic beads implantation. Group 1 ( $n = 13$ ) refers to patients with diabetic foot infection who have been diagnosed with chronic osteomyelitis and failed to improve with long-term use of broad-spectrum antibiotics clinically. Group 2 ( $n = 6$ ) refers to those with diabetic foot infection who required surgical debridement or minor amputation. Both the

groups had antibiotic therapy for diabetic foot infection preoperatively to cover different types of microorganisms such as Gram-negative species, Gram-positive species, and anaerobic bacteria. Table 2 above showed the proportion of patients in each group. Group 1 received antibiotics as follows: co-amoxiclav 625 mg TDS Three times a day in

**Table 3: The indication of Stimulan® antibiotic beads**



**Table 4: Characteristics of the study group**

Characteristic	The Study Group
Infected foot	19
Site of infection (Left)	10
Age	62.3 (45 - 82)
Sex (Female)	3
Mean duration of pre-op antibiotic use (days)	13.6 (4 - 28)
Wagner Ulcer classification system	
Grade 3	14
Grade 4	5
Co-morbidities	
Hypertension	12
Ischaemic heart disease	4
Peripheral vascular disease	4
Hypercholesterolaemia	2
End-stage renal failure	1

5 patients (38%), flucloxacillin 1 g QDS Four times a day in 5 patients (38%), and a regimen of flucloxacillin 1 g QDS and metronidazole 400 mg TDS in 3 patients (23%). Group 2 received antibiotics as follows: a regimen of flucloxacillin 1 g QDS and metronidazole 400 mg TDS in 4 patients (67%) and a regimen of tazocin 4.5 g TDS and vancomycin (dose dependent on the renal functions of patients) in 2 patients (33%). The average duration of preoperative antibiotics was 13.6 days, ranging from 4 to 28 days. Patients were started on antibiotics

in general practice and follow-up appointments in the diabetic foot clinic and vascular surgery clinic.

Patients received local debridement, insertion of Stimulan® antibiotic beads, and wound closure. At first, necrotic tissue and infected bones were removed from the wounds. This was followed by the preparation of antibiotic beads. One thousand milligram of vancomycin powder and 240 mg of gentamicin liquid was mixed into the Stimulan® rapid cure powder. The mixed powder was then applied onto a bead mat containing the mold of a specific size of beads. The beads used in this study were 3 mm in length. After the mixture had settled, antibiotic beads were released from the bead mat with a mixture of calcium sulfate, vancomycin, and gentamicin. They were then directly applied to the dead space of the wound. Afterward, the wounds were sutured and closed with no tension. Table 3 demonstrated the indications of Stimulan antibiotic beads in patients with diabetic foot infection.

The healing process of a wound is multifactorial, and this study had taken into account certain factors such as diabetic control, wound care, and perfusion status of the foot. Patients received clinical care from the diabetic foot team, which consisted of a diabetic foot nurse and a diabetologist. Blood glucose monitoring, tailoring footwear, and arranging outpatient follow-up appointments were provided. Preoperative mean HbA1c was 8.1 (6.2–11.3). Three vascular specialist nurses were responsible for wound care management and regular dressing changes for inpatients. Perfusion status of the foot was assessed by initial duplex in vascular study unit on admission, followed by endovascular intervention if needed.

The diagnosis was made with three main components taken into account: clinical history from the patient, duplex report, and angiogram outcome. Seven patients were presented late to the vascular surgery department due to social issues and noncompliance hence failed to attend follow-up appointments from the previous admission. Six patients had an absence of leg pulses on the initial presentation. Within those who had absences of pulses, two patients had occlusions in superficial femoral arteries and the remaining had multifocal stenoses in arteries. All six patients received treatment from endovascular intervention, such as angioplasty. Five patients had successful outcomes from the angioplasties, with one patient having unsuccessful angioplasty due to failure in re-entry.

All patients in the cohort had multiple medical comorbidities. Twelve patients had hypertension. Four patients had ischemic heart disease and four had peripheral vascular disease. Two patients had hypercholesterolemia and one had end-stage renal failure. An overview of the characteristics of the study group can be seen in Table 4.

As per the local hospital guideline of Northamptonshire NHS trust, for those who had received insertion of

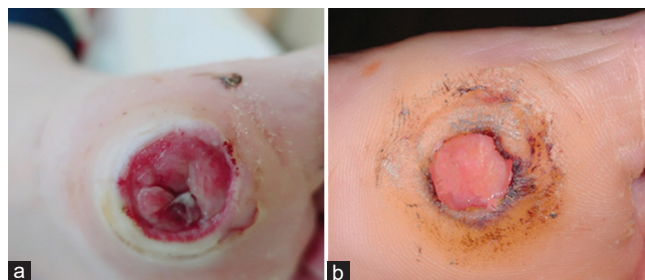


Stimulan® antibiotic beads, they would receive antibiotics within 48 h postoperatively. The antibiotics of choice depended on what the patients received during admission. The aim of utilizing the Stimulan® antibiotic beads was to reduce the use of systemic antibiotics and its duration in general. If the surrounding cellulitis coexisted, postoperative antibiotics would be continued for another week as per the trust guidelines. Figure 2(a) showed the photo of an 82 year old male patient's diabetic foot ulcer before debridement. Figure 2(b) showed the appearance of the ulcer 48 hours after wound debridement and insertion of Stimulan beads.

After the operation, patients were offered their first follow-up appointments in the vascular surgery outpatient clinic in 4 weeks from the discharge date. The healing effect was assessed in the follow-up outpatient clinics. This study defined wound healing as the presence of complete epithelialization or a marked reduction in ulceration to a superficial skin level of less than 1 cm,<sup>[2]</sup> with the absence of infection.<sup>[9]</sup> Nonhealing wounds include those with a persistent infection which required further surgical debridement or antibiotics. Recurrence of infection was assessed by the existence of bone infection at the original wound site or new site of a same or different foot in clinics after 24 months.

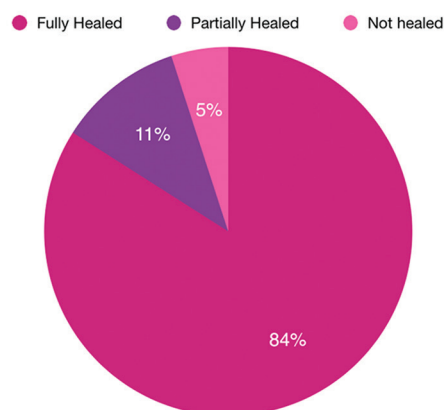
## Results

All 19 patients within the study group met the inclusion criteria. Sixteen patients (84%) fully healed after 1 month, two patients (11%) had partially healed wound, and one patient's (5%) wound showed no signs of healing. Table 5 demonstrated the proportion of patients with different stages of healing over 1 month. All patients' wounds healed after 6.3 months, with a mean healing duration of 3.3 months in Group 1 and 3.1 months in Group 2. Sixteen (84%) patients showed no signs of recurrent infection after 24 months. Table 6 demonstrated the recurrent infection rate after insertion of Stimulan beads over 24 months. Three patients from Group 1 had a recurrence of infection: Two patients (11%) had developed an infection in a new site on the different foot and one patient (5%) had a recurrence of infection in the same wound. None of the patients from Group 2 had a recurrence of infection. The average length of postoperative hospital stay for patients who had Stimulan® bead inserted was 2.2 days in Group 1 and 2.7

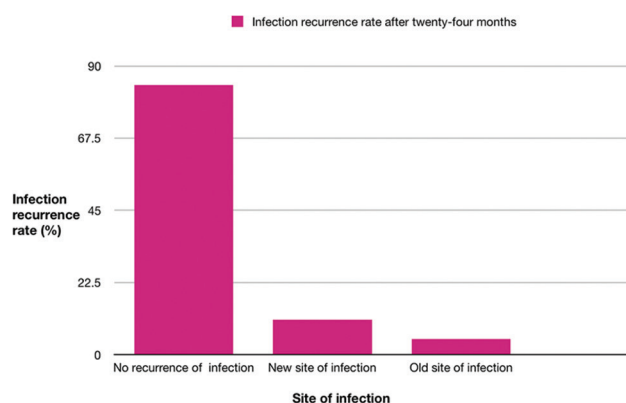


**Figure 2:** An 82-year-old male patient with a diabetic foot ulcer before wound debridement (a) and 48 h after insertion of Stimulan® antibiotic beads (b)

**Table 5: Proportion of patients with different stages of healing over 1 month**



**Table 6: Recurrent infection rate after insertion of Stimulan® beads over 24 months**



**Table 7: The follow-up outcomes of two groups**

	Group 1 (Chronic osteomyelitis)	Group 2 (Surgical debridement/minor amputation)
Number of patients	13	6
Pre-operative antibiotics duration (days)	14.8 (4 - 20)	12.6 (6 - 28)
Mean post-operative hospital stay (days)	2.2 (2 - 4)	2.7 (2 - 5)
Post-operative healing rate after one month	84.6% (11/13)	83.3% (5/6)
Mean healing duration (months)	3.3 (2 - 6.3)	3.1 (1.2 - 4.5)
Recurrence rate after twenty-four months	23% (3/13)	0.0% (0/6)
Amputation rate after twenty-four months	0.0% (0/13)	0.0% (0/6)

in Group 2. The mean follow-up duration was 15.8 months. Table 7 showed the follow-up outcome of both groups. During the follow-up period of 24 months, there was no mortality, and no amputations were required.

## Discussion

Diabetic foot infection is associated with a high rate of morbidity and mortality.<sup>[2]</sup> Approximately 20%–60% of patients who suffer from diabetic foot infection will develop diabetic foot osteomyelitis, and this can be challenging to treat. Chronic osteomyelitis is one of the complications of diabetic foot infection, and it is associated with gangrenous tissue, nonhealing ulcers, and necrosis in soft tissues. Therefore, the treatment of chronic osteomyelitis must cover these associated conditions.<sup>[10]</sup> Patients with chronic osteomyelitis received long courses of antibiotics, which could result in potentiating adverse drug reaction of long-term use of antibiotics with their regular medications and drug-induced nephrotoxicity and hepatotoxicity. Long-term use of antibiotics promotes the development of bacteria that can become antibiotic resistant. These make the option of prolonged use of antibiotic less favorable.<sup>[10]</sup>

An alternative method such as direct application of antibiotic beads to the wound was used to evaluate whether a shortened duration of intravenous antibiotic use and lowered amputation rate could be achieved.<sup>[11]</sup>

The high healing rates in using Stimulan® antibiotic beads demonstrated in this study were corroborated by Qin *et al.*,<sup>[10]</sup> who studied diabetic foot osteomyelitis management using calcium sulfate antibiotic beads in those who had resections of infected bone. The study has demonstrated that those with calcium sulfate beads inserted had a 90% healing rate with a mean healing duration of 13.3 weeks, which was similar to the results in this study, compared to 78.6% healing rate in patients with debridement of bone only.<sup>[10]</sup> Similarly, Rajesh *et al.* showed a 100% healing rate in twenty patients with diabetic foot osteomyelitis who received surgical management of wound debridement with the insertion of calcium sulfate antibiotic beads. Their median healing duration was 5 weeks. There was no recurrence recorded after 12 months.<sup>[12]</sup> A retrospective study by Noman *et al.* reviewed the effectiveness of using adjuvant calcium sulfate antibiotic impregnated beads and debridement on seventy patients with diabetic foot osteomyelitis showed a 90% infection eradication rate and 81% healing rate after a follow-up of 10 months.<sup>[4]</sup> The result of high healing rates recorded in these studies could be explained by more residual microorganisms being eradicated by the delivery of a higher concentration of antibiotics directly to the wound.

Traditional methods of treating diabetic foot infection include conservative management with antibiotics and surgical debridement. Krause *et al.* compared the clinical

outcomes of transmetatarsal amputation (TMA) in diabetics using antibiotics beads ( $n = 60$ ) with a control group of surgical debridement only ( $n = 16$ ). About 8.2% revision rate after amputation was recorded in beads group, while the control group recorded 25%, concluding antibiotic beads to be a useful adjuvant for TMA by preventing longer hospital stay and cutting cost.<sup>[13]</sup> Similarly, Dekker *et al.* evaluated the efficacy of antibiotics beads in the healing of neuropathic foot ulcers with osteomyelitis undergoing surgical debridement. They showed an average hospital stay for those treated with beads to be 10 days compared to 16 days in the control group.<sup>[14]</sup> However, the percentage of patients healed in 12 months between the beads group and control group was similar (76.9%, 72.4%). The mean healing time in both the groups (5.8 months in the beads group; 5.5 months in the control group) showed no statistically significant difference either.<sup>[14]</sup> Lázaro-Martínez *et al.* carried out a randomized comparative trial on treating diabetic foot osteomyelitis with antibiotics versus surgery. At the 12<sup>th</sup> week follow-up, the study showed that 19 of 24 patients in the antibiotic group had healed, with two patients showing reulceration; in the surgical debridement group, 15 of 22 patients had fully healed, with four patients showing reulceration. The study concluded that there were no differences found in healing rates and minor amputation rates between the two groups. Median healing time in the antibiotic group was 7 weeks. The mean healing time in the surgical group debridement group was 6 weeks.<sup>[15]</sup> Although the mean healing duration from their study was shorter than this study, they had failed to demonstrate the severity of the diabetic foot infection in each group. Moreover, the antibiotic group did not have definite diagnostic confirmation of diabetic foot osteomyelitis from histopathological investigations despite X-ray reports. The antibiotic regimen used in Lázaro-Martínez *et al.* study was also different from this study.<sup>[15]</sup>

The indications of antibiotics impregnated beads were not limited to treating diabetic foot infection and chronic osteomyelitis. Studies on treating prosthetic vascular graft infection with calcium sulfate antibiotic beads showed 100% graft preservation with no signs of recurrent infections and 80% of healing rate in 2012–2014. Their mean follow-up was 8.3 months. No amputation was required over the period of follow-up.<sup>[8]</sup> A study reviewing the use of traditional surgical methods on managing prosthetic vascular graft infection has shown a 55% of amputation rate and 16% death rate over 2007–2011. The mean follow-up for this study was 2 years.<sup>[3]</sup> Studies on using aggressive wound debridement for attempted graft preservation have an 82% rate of infection persisting in the wound, resulting in a 40% amputation rate, and some patients required complete removal of the graft.<sup>[16]</sup>

This study, however, had a few limitations. It was limited by the small study group and the absence of a control group for data comparison. Nevertheless, the study had

recorded the clinical efficacy of Stimulan® antibiotic beads on the control of infections related to diabetic foot infection when there was no suitable alternative option. Patients selected for this study had multiple comorbidities, and some suffered from long-term illness hence restricted the time frame of follow-up period. Moreover, the study has yet to compare the outcome of the use of Stimulan® antibiotic beads in diabetic foot infection against those who received surgical debridement only.

## Conclusions

Application of Stimulan® antibiotics beads during surgical debridement may play an important role in the treatment of diabetic foot infection. It can be regarded as safe and efficacious in achieving a high healing rate and shortened hospital stay. A follow-up study is required to compare the clinical outcomes with a control group who received surgical debridement only.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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