Research

Effects of local antibiotics in calcium-sulphate granules for the treatment of diabetic forefoot osteomyelitis: a propensity-matched observational study

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ABSTRACT

Background To assess the effects of a local antibiotic delivery system on the incidence of post-surgical infective complications after surgical procedures in patients with diabetic foot osteomyelitis (DFO).

Methods A retrospective study was carried out on patients with forefoot DFO associated with soft tissue infection undergoing minor amputations using local antibiotics in calcium-sulphate granules. Patients were matched with a historical series using propensity-score matching. The principal endpoint was a composite of relapse/recurrence/new onset of DFO, infection/dehiscence at the surgical site, re-intervention for abscesses drainage, and major amputation. Direct costs were analysed as a secondary endpoint.

Results Composite endpoint occurred in 19% and 36.4% (p=0.17) of cases and controls, respectively. Only three patients in the control group had recurrent DFO. After adjusting for ulcer duration, the risk of infective complications and major amputation was significantly lower (Hazard Ratio [HR] 0.20 [0.04;0.95], p=0.047) and the 90-day healing rate was significantly higher (HR 4.44 [1.03;19.07], p=0.045) in cases than in controls. The median direct healthcare costs for cases and controls during the 90-day follow-up were €2,050 [1,829;3,946] and €1,731 [1,028;14,817] per patient, respectively (p=0.072). Median costs for antibiotics were lower for cases than controls (p<0.001).

Conclusions The use of calcium-sulphate granules as an add-on therapy to surgical treatment of DFOs reduces post-surgical infections and complications, without increasing direct costs.

INTRODUCTION

Diabetic foot ulcers (DFUs) are a major complication of diabetes mellitus (DM) and are associated with a high risk of major amputations and mortality[1–3]. In patients with DM, the incidence of lower extremity amputations (LEA) ranges from 70 to 700 per 100,000 person-years[4] and 5-year survival after an amputation appears to be similar to that of patients with malignancies (around 60–70%)[5]. Moreover, DFUs have a detrimental effect on quality of life and disability[6]. Last but not least, DFUs have a relevant economic impact, with estimated mean yearly costs ranging from US$650 million to over US$1 billion[7–13].

Diabetic foot osteomyelitis (DFO) further increases the risk of major amputations and mortality in patients with DFU, with relevant consumption of economic resources[14]. Moreover, DFO often requires prolonged antibiotic therapy and extensive surgical debridement with a relevant risk of perioperative complications, possibly delaying healing[15,16]. Patients with

DFO are often affected by multiple comorbid conditions such as peripheral artery disease, which can limit the efficacy of systemic antibiotic therapy for insufficient tissue penetration[17], as well as renal or liver insufficiency which may contra-indicate a prolonged antibiotic therapy. Moreover, antibiotic-resistant bacteria can prevent the use of many antibiotics[18,19].

Recently, several devices capable of releasing antibiotics at local level have been developed to overcome some of these criticisms, thus reducing the risk of post-surgical infections, possibly accelerating healing processes; however, clinical reports are still scarce and related to limited experiences[20–22]. The assessment of the economic impact of this approach is also lacking.

The aims of the present cohort study are the assessment of the incidence of post-surgical infective complications, healing rates and time-to-healing, and direct healthcare costs in patients with forefoot DFO undergoing surgical procedures and treated with local antibiotics in calcium-sulphate granules,

as compared with a propensity-matched historical control sample.

PATIENTS, MATERIALS AND METHODS

Patients

The present analysis was retrospectively performed on a consecutive series of patients with diabetes and forefoot DFO who underwent minor amputation (i.e. toe amputation, metatarsal-phalangeal osteoarthrotomy and/or metatarsal osteotomy) using local antibiotics in calcium-sulphate granules (Stimulan®, Biocomposites Ltd, UK) at the Diabetic Foot Unit of Careggi Hospital, Florence, Italy, between 1 June 2021 and 1 June 2022. Patients were included if they fulfilled the following criteria:

- Diagnosis of DM.
- Texas 3B or 3D[23] forefoot DFO and clinical infection of deep tissue.
- TcPO2 (transcutaneous oximetry) measured on the dorsum of the affected foot before surgical procedure ≥30mmHg.
- Follow-up of at least 90 days.

Cases were compared with an historical cohort of patients undergoing the same procedures with the exception of the antibiotic-loaded calcium-sulphate granules inception.

A propensity score using variables that might have affected treatment assignment or outcomes was developed, following the protocol used by Kosiborod and colleagues[24]. Candidate variables used in the development of the propensity score were: age, sex, duration of diabetes, and site of DFO. Matching was performed by randomly selecting (the first patient in the historical dataset) at least one patient with the same propensity score (with a ratio of at least 1:1) ± 1SD.

The study protocol was approved by the local ethical committee (Protocol number: 22331_OSS), and informed consent was obtained from all patients before inclusion in the analysis.

Baseline data collection

Demographic and clinical data were collected from clinical records, including a medical history with detailed information on the duration of diabetes, complications and concomitant medical conditions, current pharmacological treatment, cardiovascular risk factors, self-reported smoking habits, and any other relevant medical conditions. At the first visit, following an established standard procedure of the Clinic, all patients underwent a physical examination, during which their weight, height and blood pressure were recorded. Results of laboratory determinations (HbA1c, creatinine, LDL cholesterol calculated with Friedewald formula[25]) performed within 3 months prior to the first visit were recorded.

Pain at the first visit was assessed using a visual analogue scale (VAS) ranging from 0–100mm. As per local standard of care, transcutaneous pressure of oxygen (TcpO2; Radiometer Medical ApS; Brønshøj, Denmark) at the basis of the first toe and/or ankle-brachial index (ABI) were measured, and arterial duplex-scanning of lower limb arteries was performed. Diagnosis of diabetic neuropathy was performed by measuring both vibratory perception threshold (VPT)[26] with a biothesiometer (METEDA, San Benedetto del Tronto, Italy) and a 10g monofilament; diagnosis of neuropathy was performed in case of non-sensitivity of 10g monofilament on at least one

of the application points and/or VPT ≥25 volts at the hallux or malleolus. DFU were classified according to the University of Texas score[23], which ranges from 0=no lesions to 3=lesions deep to bone and joints, and graded from A=no infection and no ischaemia to D=infection and ischaemia. When more than one lesion was present, only the largest ulcer was taken into account (index lesion). Diagnosis of DFO was made using the probe-to-bone test using a sterile metal probe (considered positive when the probe met the hard surface of the bone at the base of the wound) in conjunction with a plain X-ray of the foot, which was performed in all patients and considered positive for DFO when it showed bone destruction, cortical reabsorption, periosteal reaction, or a sequestrum.

In all patients, a tissue biopsy with a scalpel or punch biopsy instrument, following Levine technique[27], was taken for bacteriological analysis and culture.

Renal failure was defined as a reported previous diagnosis of renal failure, or as serum creatinine >1.5mg/dl. Ischaemic heart disease (IHD) and cerebrovascular disease were diagnosed when patients reported previous myocardial infarction/ angina or stroke/transient ischaemic attack. Comorbidity was assessed through the calculation of Charlson's comorbidity score (CCS)[28].

DFU treatment

All patients underwent minor amputations following the standard of care of our unit; amputations were performed using loco-regional anaesthesia in an ambulatory setting.

Necrotic tissues, pus and infected soft tissues were removed until exposing healthy bleeding tissue. If DFO was located in the diaphysis, devitalised bones at the base of DFU were exposed and excised to the level of healthy cancellous and cortical bone. If possible, the bases of the metatarsal and phalangeal bones were preserved for healthy tendons attaching. When infection was located in interphalangeal or metatarsophalangeal joints, both the joints and partial distal and proximal bones were excised. Fibrous tissues, fascia and tendons nearby were also completely removed. Following bone resection, irrigations with a solution of iodopovidone were performed. Antibiotic-impregnated calcium-sulphate was then prepared. Vancomycin and/or tobramycin, on the basis of the results of the antibiogram, was mixed into the synthetic calcium-sulphate (Stimulan®, Biocomposites Ltd, UK) with the manufacturer-recommended ratio: 0.5g vancomycin with 5ml calcium-sulphate or 120mg tobramycin with 5ml calcium-sulphate. Then they were dissolved in a sterile saline solution and injected into the void space created by bone resection.

Further treatments

According to the Global Vascular Guidelines[29], patients with critical limb ischaemia underwent percutaneous or surgical revascularisation prior to minor amputation. Local medications were performed following the International Working Group on Diabetic Foot (IWGDF) guidelines[30]. Empiric systemic antibiotic therapy was prescribed for up to 4 weeks and eventually modified on the basis of antibiogram[30] in all patients. In all cases antibiotic therapy was stopped when clinical signs and symptoms of infections were resolved. Antibiotic therapy was continued after surgical procedure only in case of persistence of signs and/or symptoms of infection.

Therapeutic shoes (with pressure-relieving insoles) were used in all patients with plantar DFU, for pressure relief, as per the standard procedure of the Clinic.

Follow-up data

During the 90-day follow-up, re-infections, new surgical procedures for DFO recurrence, the total number of visits, duration of systemic antibiotic therapy, laboratory and instrumental exams, and hospital admissions were monitored.

Plain X-ray was repeated in all patients at 90 days to evaluate the eradication of DFO.

For patients with missing information on 1 October 2022, an attempt to retrieve information (including vital status) was made via telephone.

Endpoints

The primary endpoint of the study (within 90 days) was a composite of:

- Recurrence of DFO.
- New onset of DFO in other sites.
- New onset of tissue infection/dehiscence at the surgical site.
- Re-intervention for abscesses drainage or recurrence of DFO
- Major amputation.

New DFO or DFO recurrence was diagnosed if radiological signs of DFO were detected in the surgical site or in adjacent sites within 90 days. Dehiscence was defined as any infective process (PEDIS >1[31]) in the surgical site within 7 days from surgical procedures.

Infective complications were defined as any infective process (PEDIS >1) in the surgical site that occurred between 7 days after surgical procedure and the end of the study.

Re-intervention was defined as the need for a new surgical intervention at the site of previous DFO in case of abscesses drainage or relapse of DFO.

Major amputation was defined as an amputation proximal to the ankle joint.

The choice of individual components of the primary endpoint were made in order to explore the putative protective effects of local antibiotics in calcium-sulphate granules on post-surgical infective complications.

Secondary endpoints were:

- Healing rate.
- Time to healing.
- Total number of visits.
- Major amputation rate.
- Re-intervention rate.
- Severe adverse events (SAE).
- Direct costs.

Healing was defined as complete epithelialisation of the wound with the absence of drainage, confirmed at two follow-up visits (the first one was taken as referral to calculate time to healing).

SAE were defined as any event or adverse reaction which corresponds to one or more of the following criteria: a) fatal outcome; b) life–threatening; c) requires hospitalisation or determines a prolongation of it.

Economic assessment

The economic assessment was performed taking the local health system perspective into account. Thus, only direct healthcare costs were considered, and costs associated with healthcare resource use for the duration of follow-up were extracted from clinical records. In detail, direct costs included specialists' visits, diagnostic procedures, hospital admissions (related to diabetic foot), major and minor amputations, antibiotic therapy, grafts, and off-loading orthesis (Tables 1&2).

Costs for hospitalisations were estimated on the basis of established regional tariffs (https://www.salute.gov.it/portale/temi/p2_6.jsp?id=3662&area=programmazione SanitariaLea&menu=vuoto), i.e. tariffs established for the diagnosis-related group (DRG) associated with each episode for hospital admissions (either day-hospital or full-length stay) and recorded in clinical records; similarly for costs related to specialistic visits and outpatient procedures performed (e.g. RX, MRI, laboratory exams, etc.). The cost of antibiotic therapy was estimated considering ex-factory prices (https://www.salute.gov.it/portale/temi/p2_6.jsp?id=3662&area=programmazione SanitariaLea&menu=vuoto),while current market prices were used to value costs for orthopaedic shoes/orthesis. The health economic analysis performed tried to estimate costs born to the healthcare system, mainly using tariffs related to different healthcare services over 1 year. All costs were referred to 2020.

Table 1. Microbiological findings in two groups

	Case (n= 21)	Control (n= 34)
Staphylococcus aureus	16	14
Enterococcus faecalis	1	2
Pseudomonas aeruginosa	4	10
Staphylococcus epidermidis	1	2
Corynebacterium striatum	3	2
Proteus mirabilis	0	5
Staphylococcus lugduniensis	2	0

Table 2. Costs (€) for hospital admission for foot-related conditions

Diagnosis-related group (DRG) code and description of procedure	Hospital length	
	>1 day	1 day
114 Toe amputation for vascular diseases	8,962	731
205 Lower limb amputation for metabolic or endocrinological and/or vascular disease	13,431	482
130 Peripheral revascularisation with multiple comorbid conditions	4,904	390
131 Peripheral revascularisation without multiple comorbid conditions	3,398	390
556 Peripheral revascularisation with drug-eluting stent	10,097	731
418 Post-surgical infection	3,862	453
238 Osteomyelitis	5,974	379
575 or 576 Sepsis	6,974	453

Statistical analysis

Statistical analysis was performed on SPSS 25.0 (SAS Institute, Cary, Ill). Data were expressed as mean ± standard deviation, or as median (25–75th percentile), depending on their distribution. Costs were reported considering both mean ± standard deviation and median (25–75th percentile). Comparisons between groups were performed using Student's t-test for independent samples or Mann–Whitney U test when appropriate. Chi-square and Fisher exact test were used for between-group comparisons of categorical variables when appropriate. Kaplan–Meier method was used to derive the probability of healing over time. Conditional logistic regression was used for multivariate analysis, in order to adjust for duration of ulcer; no other adjustments were made, as cases and controls had been matched for the other potential confounders.

RESULTS

The study enrolled 21 patients, compared with 34 matched controls, with a ratio 1:1.6. No significant differences were observed between cases and controls, except for duration of ulcer (Table 3). Microbiological findings in cases and controls are summarised in Table 1. All patients were followed for 90 days (or until they died or underwent major amputation) after the surgical procedure. No patient was lost to follow-up. Two patients in the control group, and none among cases, died (after major amputation) during follow-up. Four more patients in the control group, and none among cases, underwent a hospitalisation during follow-up (three for revascularisation and one for sepsis). The mean duration of follow-up was 75±21 days.

The 90-day composite endpoint was achieved by four cases (19.0%) and 15 controls (45.5%) as reported in Figure 1 (p=0.057). Information on individual components of the primary endpoint are reported in Table 3: dehiscence (within 7 days from surgical procedure) and re-infection (after 7 days) occurred in 19.0% and 36.4% (p=0.17) of cases and controls, respectively. Only three patients (9.1%) in the control group had a recurrence of DFO (p=0.15) and underwent a new surgical operation; no episode of new onset DFO was observed. No major amputations occurred within 90 days.

Healing rate within 90 days for cases and controls was 61.9% and 45.5% (p=0.18), with time-to-healing of 78 (45;90) and 90 (73;90) days (p=0.26), respectively.

At conditional regression analysis, after adjusting for ulcer duration, the risk of post-surgical re-infection (recurrence of DFO, new onset of DFO, new onset of tissue infection/ dehiscence and re-intervention) and major amputations (primary endpoint) was significantly lower in cases than in controls (HR 0.20 [0.04;0.95], p=0.047); in addition, the 90-day healing rate was significantly higher in cases than in controls [HR 4.44 (1.03;19.07), p=0.045].

Direct healthcare costs for hospital admission for foot-related conditions and for ulcer management are listed in Tables 2&4. The mean and median direct healthcare costs per-patient for cases during the 90-day follow-up were €2,360±602 and €2,050 [1,964;2,563], respectively. The same figure for controls was €3,386±3,875 and €1,731 [1,278;3,156]. No statistically significant differences were observed for overall costs (all p>0.05).

Table 3. Main anthropometric and demographic characteristics of the enrolled cohort and of observed ulcers

	Case (n=21)	Control (n=34)	p
Demographics			
Age (years)	71.5±13.0	73.3±9.2	0.23
Gender (women, %)	9 (56.3%)	7 (43.8%)	0.089
Body mass index (kg/m^2)	25.8±4.8	27.5±4.2	0.18
Diabetes duration (years)	19.6 [11;80]	18.0 [9.9;30.7]	0.78
Medical history and risk factors (n, %)			
Diabetes mellitus type 1	2 (9.5%)	1 (3.0%)	0.31
Charlson's score index	6.0 [5.0–7.0]	5.0 [5.0–7.0]	0.57
Peripheral artery disease	19 (90.5%)	27 (81.8%)	0.38
Neuropathy	19 (90.5%)	23 (69.7%)	0.073
Retinopathy	10 (47.6%)	20 (60.6%)	0.35
Chronic renal insufficiency	12 (57.1%)	21 (63.6%)	0.63
Dialysis	1 (4.8%)	1 (3.0%)	0.74
Ischaemic cardiopathy	8 (38.0%)	17 (51.5%)	0.17
Heart failure	5 (23.8%)	12 (36.4%)	0.33
Ictus	3 (14.3%)	5 (15.2%)	0.93
Charcot disease	4 (19.0%)	5 (15.2%)	0.78
Connective tissue diseases	1 (4.8%)	0 (0.0%)	0.21
Malignancies (<5 years)	1 (4.8%)	2 (6.1%)	0.83
Cognitive impairment	2 (9.5%)	8 (24.2%)	0.17
Laboratory parameters			
HbA1c (%)	54.4±19.3	54.1±14.4	0.69
Creatinine (mg/dl)	1.2 [1.0;2.3]	1.5 [0.8;1.9]	0.63
LDL-cholesterol (mg/dl)	59.0±29.5	72.2±32.8	0.57
Pharmacological treatment (n, %)			
Insulin	10 (47.6%)	23 (69.7%)	0.10
Glucose-lowering agents	13 (61.9%)	18 (54.5%)	0.059
Anti-aggregants	19 (90.5%)	28 (84.8%)	0.47
Anticoagulants	6 (28.6%)	7 (21.2%)	0.50
Statins	18 (85.7%)	29 (87.9%)	0.81
Main ulcer's characteristics			
Duration (days)	199 (97;418)	113 (50;278)	0.048
Area (cm^2)	1.98 (0.47;5.14)	2.36 (0.63;6.57)	0.62
Texas grade 3B	9 (42.9)	13 (39.4)	0.38
Texas grade 3D	12 (57.1)	20 (60.6)	0.49
Gangrene (%)	7 (33.3)	11 (33.3)	1.0
Number of visits	9.8±3.7	10.3±4.1	0.71
Individual components of 90-day principal endpoint			
Recurrence of osteomyelitis (n, %)	0 (0.0)	3 (9.1)	0.15
New onset of osteomyelitis	0 (0.0)	0 (0.0)	–
Dehiscence/re-infection	4 (19.0)	12 (36.4)	0.17
Re-intervention	0 (0.0)	3 (9.1)	0.15
Major amputation (n, %)	0 (0.0)	0 (0.0)	–

Table 4. Costs (€) associated with procedures and laboratory examinations

Diagnosis-related group (DRG) code and description of procedures		Costs (€)
88.28	Foot/ankle x-ray	21
88.38.7	Foot/ankle computed tomography	173
88.77.2	Lower limbs ecocholordoppler	49.5
88.94.1	Foot/ankle nuclear magnetic resonance	254
89.65.4	Transcutaneous oxygen monitoring	18.6
90.16.3	Creatinine	1.2
90.28.1	Glycated haemoglobin	10.6
90.27.1	Glycaemia	1.30
90.14.3	Total cholesterol	1.1
90.14.1	HDL cholesterol	1.8
90.43.2	Triglycerides	1.3
90.72.3	C-reactive protein	3.6
86.11	Cutaneous biopsy	13.9
90.85.2	Swab with antibiogram	12.2
99.24.2	Antibiotic infusion (cost for antibiotics not included)	3.1

Costs (median) during the 90-day follow-up for antibiotics were significantly lower in cases, whereas costs for exams were significantly lower in the control group. A non-statistical trend toward reduction of costs for hospital admission was also observed in favour of cases (Table 5).

DISCUSSION

We show here for the first time a comparison between patients with DFO treated with antibiotic-impregnated calcium-sulphate granules, and control patients, matched for propensity score. The principal endpoint (a composite of infection and amputation) was reduced by 80%, and healing showed a more than four-fold increase in comparison with controls, after adjusting for the duration of DFUs.

These results are of interest considering the high risk of major amputation in patients with DFO. In fact, DFO treatment is particularly challenging for several reasons. The penetration of antibiotics at bone level is difficult, usually achieving insufficient therapeutic concentrations, mainly because of concomitant peripheral vascular disease. Moreover, the presence of many comorbidities, such as renal insufficiency, limits the long-term use of many antibacterial compounds.

Several different local delivery systems have been explored as adjunctive therapies in order to overcome these problems, such as antibiotic-impregnated collagen sponges which have been demonstrated in randomised clinical trials to significantly improve the DFO prognosis[32–34]. An alternative approach is represented by antibiotic-impregnated calcium-sulphate granules, despite the scarce evidence mainly derived from retrospective uncontrolled studies[35,36]. The putative advantages of calcium-sulfate granules in comparison with other local delivery systems (e.g., carriers with protein or synthetic polymers, grafts[37] etc.) include biodegradability, predictable elution characteristic osteoconductivity, and ability to fill void space after bone resection[38]. All these favourable characteristics could have positive effects on healing and amputation rates, as suggested by retrospective studies. However, available studies are affected by a number of limitations, such as heterogeneity of DFO (for site, concomitant deep-tissue infection, etc.), small sample sizes, and heterogeneity of surgical techniques used in combination with antibiotic-impregnated calcium-sulphate granules. There is only one other case control study on this device, reporting a reduction of DFO recurrence, without increasing the healing rate[22]. In our study, we observed a similar reduction of post-surgical infective complications, but with a higher proportion of patients healed at 90 days. Since outcomes are largely affected by the characteristics of enrolled samples, results obtained with this treatment should be compared with those of a control group.

In our study, we decided to use propensity score matching, a technique capable of minimising the distortion determined by prescription bias in observational studies[24]. With this approach, the cohort of patients receiving treatment is compared with a cohort of control patients selected within the same reference population, matched for a score that summarises the chance of receiving the investigated treatment. Although this technique can improve the reliability of results, in comparison with traditional adjusted analyses of cohort or case control studies, the possibility of residual confounders
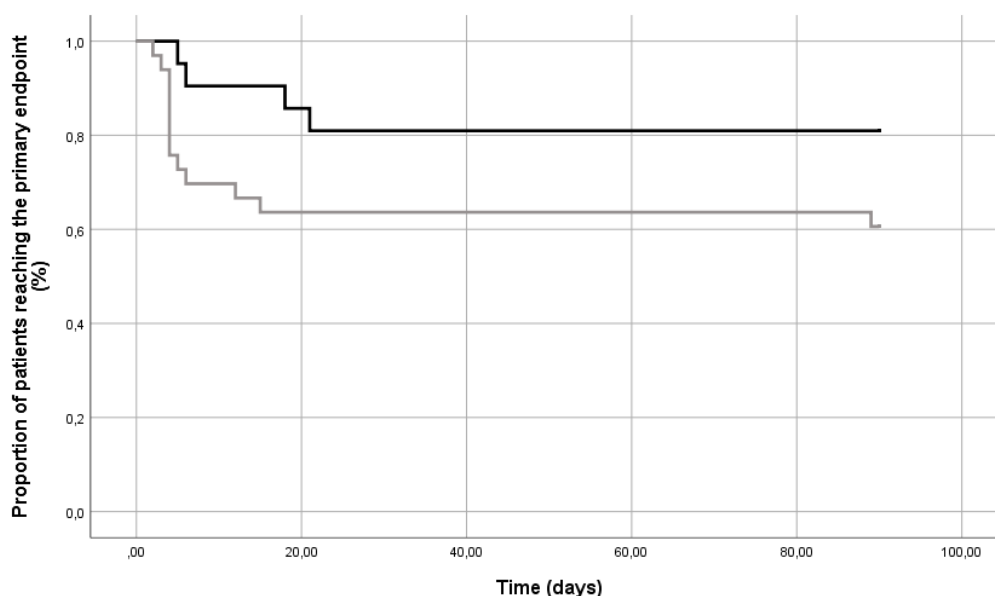

Figure 1. Proportion of patients (%) reaching the primary endpoint during the follow-up. Black line: cases; grey line: controls

Table 5. Average costs (€) per cases and controls over the 90 day follow-up

Healthcare costs (€)	Cases		Controls		p for mean	p for median
	Mean SD	Median [interquartiles]	Mean SD	Median [interquartiles]		
Laboratory exams	212±108	157 [136;284]	145±31	136 [136;136]	0.002	<0.001
Outpatient visits	490±144	500 [375;525]	517±294	400 [300;700]	0.73	0.71
Antibiotics	81±302	0 [0;7]	360±668	109 [54;289]	0.059	<0.001
Granules	776±321	662 [662;662]	–	–	<0.001	<0.001
Surgery	801±220	731 [731;731]	846±286	731 [731;731]	0.40	0.39
Hospital admission for foot-related problems	0 [0;0]	0 [0;0]	1480±3804	0 [0;0]	0.082	0.064
Total costs	**2360±602**	**2050 [1964;2563]**	**3386±3875**	**1731 [1278;3156]**	**0.24**	**0.072**

cannot be completely ruled out. It is therefore possible that the difference in outcome between cases and controls is partly determined by differences in characteristics of the two samples which were not accounted for in the definition of propensity score.

Moreover, a multivariate analysis was performed in order to adjust for the duration of DFUs, which was significantly different between cases and controls. It is well known that the duration of DFUs is associated with a greater severity of DFO, possibly affecting the results obtained. After adjusting for DFU duration, the risk of major adverse lower limb events was significantly lower in patients allocated to the treatment group.

The use of new devices and techniques is often limited by high costs. However, the cost of the device is only a small part of direct costs for the clinical management of DFOs, which also include antibiotics, hospital admission, specialists' visits, laboratory examination, etc. For this reason, we performed an analysis of direct costs recorded in cases and controls, suggesting that the use of antibiotic-impregnated calcium-sulphate granules is affordable and cost-effective. In fact, the cost of the device seems to be balanced by savings for antibiotic therapy and hospital admission.

Despite the limitations of the present retrospective single-centre study, we believe that the use of antibiotic-impregnated calcium-sulphate granules in DFO treatment could be safe and cost-effective; the actual efficacy and safety of antibiotic-impregnated calcium-sulphate granules in DFO should be confirmed by randomised controlled trials.

AUTHOR CONTRIBUTION

BR and MM designed the study and contributed to data collection, interpretation and writing. AP revised the manuscript and contributed to interpretation of data. EM contributed to writing and supervised the data quality control. MM is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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