CLINICAL EVALUATION OF DE MARCO FORMULA AS AN ADJUNCTIVE THERAPY FOR INFECTED ISCHEMIC DIABETIC FOOT: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background
De Marco Formula (DMF) is a novel formulation of procaine and PVP.

Objective
To assess the efficacy and safety of DMF as an adjunctive therapy for infected ischemic diabetic foot in a prospective randomized controlled clinical trial.

Methods
Adult patients, 39 male/ 79 female, were randomly assigned (59 patients/treatment group) to the conventional therapy alone (A) or plus DMF (0, 15 ml/kg .day i.m.) during ten days and them twice a week until healing of the lesions or completion of 52 days (B). The response to the treatment was considered favorable when an amputation was not needed even though a decrease of the wound area or complete healing was not shown. It was considered unfavorable when a major amputation was necessary because of worsening of the lesion (wound spreading to any magnitude greater than the initial one) or the appearance of new wounds in the same leg.

Results
Both groups were comparable with regard to age, sex, level of arterial occlusion, type of lesion, anatomic localization of lesions and previous surgical procedures. The cumulative percentage of unfavorable results was significantly lower after treatment B with respect to treatment A (25.4% vs. 45.8%; p= 0.02), for a reduction of 44.5%. Four slight adverse reactions were associated with DMF: vertigo and nausea at the 7th treatment administration (one patient), and headache and tachycardia at the 12th dose (another patient). Blood hemoglobin and leukocyte counts and serum alanine transaminase were not affected.

Conclusion
The treatment with DMF for 52 days as an adjuvant for the conventional therapy was associated with a lower need for major amputations. It was also well tolerated and safe.

Key words: *Diabetic foot, sepsis, amputation, Procaine, Polyvinylpyrrolidone De Marco Formula*

Diabetic foot is the most threatening complication of Diabetes mellitus.[1-10] For instance, amputation rates from 25% - 29% and mortality rates of 10, 2 to 11, and 8 % have been found among Cuban patients suffering from diabetic foot.[11-13] A combination of ulceration and sepsis, which can lead to in situ thrombosis of the foot's arteries, enhances the risk for gangrene in an ischemic diabetic foot. Such wounds need weeks or months of treatment, and sometimes require major amputation of the damaged extremity.[14,15]

Analysis of the clinical outcomes of patients with the diagnosis of ischemic diabetic foot at the Service for Diabetic Angiopathy of the National Institute for Angiology and Vascular Surgery showed a rate of major amputations of 69 %.[16]

The physiopathology of diabetic foot involves:
1) Long lasting hyperglycemia leading to a low tissue oxygenation and ischemia;
2) Depression of immunity system resulting in an increased susceptibility to infections that in turn provokes a long-lasting inflammatory situation involving the release of leukocyte mediators that induce tissue damage; and
3) Synthesis of acute phase reactant proteins such as fibrinogen and factor VII, which contribute to hyperviscosity, hypercoagulability, local ischemia and thrombosis and tissue damage.[17]

The impairment of patients' quality of life, social cost and the fact that mortality rate rises after amputation[18-20] confirms the need for new therapeutic alternatives to lower the rate of major amputations among patients with infected ischemic diabetic foot.

The granulocyte colony-stimulating factors and systemic hyperbaric oxygen therapy have been proposed as possible therapeutic options for severe infections or for those that have not adequately responded to conventional therapy.[21-23] The mechanisms of action proposed for these agents are the stimulation of antimicrobial defense[22] and of angiogenesis[23], respectively. Procaine is an old and well-known drug. Some of its biological properties may be crucial for the treatment of infected ischemic diabetic foot, namely, the tissue protecting[24-29], antiphlogistic[30-34], immunomodulating[35], fibroblast cell division[36] and protein synthesis[37-39] stimulating, antimicrobial[40] and vasorelaxant[41] actions.

De Marco Formula (DMF) is a new chemical combination of procaine HCl and polyvinylpyrrolidone. Two uncontrolled studies, performed at the National Institute for Angiology and Vascular Surgery, have suggested that this drug may be useful as adjunctive treatment to prevent amputation to patients with diabetic foot (unpublished results). The first study included 31 patients suffering from any kind of diabetic foot, and showed a 67% probability of favorable responses (prevention of leg amputation) after the addition of a treatment consisting of intramuscular injections of 0.15 mL of DMF /kg every 8 h (about 400 mg of procaine/dose) for seven days to the conventional therapy. The second study included 35 patients with infected ischemic diabetic foot, and assessed the effect of the addition of a treatment with 15 DMF mol/kg per day i.m. to conventional therapy for ten days and then twice a week until healing of the lesions or completion of a six-week period of treatment. This latter study showed that major amputation was not needed for 27 patients (81.8%). We therefore designed a study to assess the efficacy and safety of DMF as an adjunctive therapy for infected ischemic diabetic foot in a prospective randomized controlled clinical trial.

METHODS

Adult patients admitted to the Service for Diabetic Angiopathy of the National Institute for Angiology and Vascular Surgery due to the diagnosis of ischemic diabetic foot were enrolled in this prospective, randomized, controlled clinical study. The need to treat number of patients (N =58 per group of treatment) was calculated.[42] It was based on the hypothesis that at least a 30% reduction of the need of major amputations would be associated with the addition of DMF to conventional therapy. A 70 % probability of unfavorable responses after the conventional treatment alone was expected, according to the previous experience of the Service for Diabetic Angiopathy. Values of $\alpha = 0.05$ and $\beta = 0.9$ were used in the sample size calculation. Taking into account the possibility of missing data, 118 patients (59 per treatment group) were enrolled in the study.

Diagnosis Criteria

The following diagnosis criteria were used when identifying potential participants for this study: patients suffering from infected ischemic diabetic foot, those who have suffered from amputation of one or more toes, and patients with a history of transmetatharsal amputation.

The following characteristic features of the wounds were evaluated:

- Extent: The lesion areas were measured with a double-sided nylon .The side in contact with the lesion was discarded and the other one was used to determine the two longer perpendicular diameters. The superficial areas were calculated as cm^2 and the percentages with respect to pre-treatment values were calculated.
- Characteristics of the bottom: Presence (or not) of secretion, granulation tissue or bony exposure.

- Edges: Possible existence of regular or ischemic edges was evaluated.
- Characteristics of adjacent tissues: Classified as normal, infiltrate or edematous.
- Inclusion criteria were as follows: accomplishment of the diagnosis criteria; 30-75 years of age; risk of amputation of the damaged leg; serum alanine transaminase and blood hemoglobin within the normal reference ranges; and ability to provide informed consent to participate in the study.

Exclusion criteria were as follows: need for major amputation of the damaged leg in the following seven days; known hypersensitivity to Procaine; neoplasia; pregnancy; puerperium; lactation; psychiatric disorders; hepatic or renal dysfunction; unmanageable pain and use of immunosupressor treatments.

Strategy for Inclusion of Patients

Patients who met the inclusion criteria were hospitalized until the end of the treatment period and randomized to one of the two following treatment groups.

Treatment A

Conventional therapy that consisted of:

- Careful debridement of soft tissue to remove the septic foci, and local cleaning with sterile.
- Water, disinfection with saline solution and removal of necrotic tissues whenever required.
- Antihyperglycemic treatment with s.c. injections of insulin 0.2 to 0.9 IU/kg per day. Seventy per cent of the daily dose of insulin consisted of a fast-acting recombinant human insulin (Actrapid^{r}HM, Nordik, Denmark), divided into three doses (each dose 30 minutes before breakfast, lunch and dinner). The remaining 30 % of the daily dose consisted of a slow-acting recombinant human insulin (Insulatard ^{R} HM, Nordik, Denmark) administered between 10:00 and 11:00 p.m. The daily dose of insulin was adjusted according to the individual needs for a good glycemic control. Glycemic control was classified as good, acceptable or poor according to fasting blood glucose concentrations (4.4 to 6.1; 6.2 to 7.7 and > 7.7 mmol/L, respectively) and glycohemoglobin HbA1c (<8.0; 8.0 to 9.4 and ≥ 9.5 %, respectively).
- Antibiotic therapy (Penicillin, Chloranphenicol, Amikacine or Ciprofloxacin), according to the results of microbiological studies of the lesions.

Treatment B

Conventional therapy plus DMF (Gen Cell Research, USA). DMF was administered by deep intramuscular injections in the glutei region. The dosing schedule was 0.15ml/kg body weight per day (average dose of procaine = 400 mg) for ten days, then twice a week (on Tuesdays and Thursdays) until healing of the lesion or completion of a six–week period of treatment.

Patients were assigned to each treatment according to a central randomized list generated at the Center for Coordination of Clinical Trials and based on the randomized blocks method. The therapeutic schemes were used until wound healing or need for amputation was determined. Concomitant therapy consisted of antiplatelet (Acetyl salicylic Acid), hemorrheologic (Pentoxifylline) and analgesic (Dipirone) drugs. All patients consumed a balanced diet adjusted to their need for proteins and calories supply according to the body mass and clinical situation.

Follow-up

Foot lesions were evaluated at enrollment, after 10-24 days (equivalent to 14 applications of DMF) and at 52 (equivalent to 22 applications of DMF) days of treatment. The evaluations were performed by a Vascular Surgeon who was blinded to the patient's treatment allocation; therefore avoiding the influence of subjective factors on the physician's decision (blind measurement). The analysis included the characteristic features of lesions, appearance of new wounds, need for amputation or remission and/or adverse reactions.

The extent and bottom characteristics of the lesion, existence or not of regular or ischemic edges, secretion, agony, granulation tissue, or bone exposure, as well as the characteristic feature of adjacent tissues (normal, infiltrate or edematous) were considered as main factors to determine the need for amputation. The initial extent of the lesion was measured with double-side nylon. The side in contact with the lesion was discarded and the other one was used to determine

its mean diameter and calculate the superficial area in cm^2.

Patients were classified according to the anatomic foot zones affected, as follows:

Group I: One toe or another zone of the foot
Group II: Two toes or one toe and another zone of the foot
Group III: Heel or whole forefoot
Group IV: Broader extent of lesions

Other measurements performed at the enrolment included: general physical check up, hemodynamic (ankle brachial indexes), radiologic and routine clinical laboratory studies. Blood glucose concentrations were determined daily.

Efficacy Criteria

The response to the treatment was considered favorable when an amputation was not needed, even though a decrease to the wound area or complete healing was not shown. It was considered unfavorable when a major amputation was necessary because of worsening of the lesion (wound spreading to any magnitude greater than the initial one) or the appearance of new wounds on the same leg. Major amputations were those performed at the level of the ankles or the legs (below or above the knees). The decision to perform an amputation was supported by the following clinical parameters: further reduction of the limb pressure indexes and collateral circulation degree, as well as pathologic arteriography results, anemia or hypoproteinemia.

Assessment of DMF Tolerability and Safety

The occurrence of adverse reactions was checked along the treatment period. They were classified according to their intensities as follows: slight (pharmacological treatment is not needed), moderate (responds to pharmacological treatment), severe (does not respond to pharmacological treatments and very severe (may be threatening to patient's life). Possible relations of adverse events with the treatment were assessed by the use of the Karch and Lasagna's decision table.[43] Blood hemoglobin and leukocyte count, as well as serum alanine transaminase were quantified at baseline and at the end of the treatment to assess DMF undesirable side effects.

Ethics

This study was performed according to a research protocol previously approved by the Committee for Inspection and Ethics of the National Center for the Coordination of Clinical Trials of Cuba, which coordinated and supervised the assay as well as for the Ethics Committee and the Scientific Council of the National Institute for Angiology and Vascular Surgery. The use of placebo injections was considered unjustified from the ethical point of view for this study with patients that are frequently exposed to invasive medical treatments. The objective and characteristics of the assay were explained to the patients and their informed consent was obtained before enrollment in the study.

Quality Control of the Trial

Adherence to the protocol, and accomplishment of Cuban Good Clinical Practices regulations were verified by the National Center for the Coordination of Clinical Assays of Cuba during the study.

Statistical Analysis

Researchers from the Center for the Coordination of Clinical Trials of Cuba performed the statistical analysis of the data. Descriptive statistics was applied to continuous variables (age, duration of Diabetes mellitus and lesion area). Wilcoxon`s and Square Chi tests were used for the comparison of continuous and categorical variables, respectively. Differences were considered statistically significant for p values < 0.05.

RESULTS

Characteristics of Patients

The Quality Control assessment demonstrated good protocol adherence. Also, withdrawal of study medication due to side effects was not necessary; thus, there was the necessary number of patients in each treatment group to assess the DMF efficacy as an adjuvant drug for the treatment of infected ischemic diabetic foot. Considering possible missing data, one patient in excess was included in each group (N=59 per group). Both groups were comparable with regard to the demographic characteristics of patients and Diabetes duration (Table 1), clinical characteristics of the diabetic foot (Table 2), anatomic localization of diabetic foot lesions (Table 3) and surgical procedures performed before the inclusion of the patients in the study (Table 4).

TABLE 1 Demographic characteristics of the patients included in the study

	Treatment A	Treatment B	P value
N (Male/Female)	59 (22/37)	59 (17/42)	0.3280 a
Age (years)	62.5 (56.5 to 66.5)	61.8 (58.8 to 64.8)	0.8504 b
Diabetes duration (years)	16.1 (11.6 to 20.6)	19.9 (15.8 to 24.0)	0.1400 a

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. The data corresponding to age and Diabetes duration are the means with the intervals of confidence, in parenthesis. The statistical comparisons between the treatment groups were done by the Square Chi [a] and Wilcoxon's [b] tests.

TABLE 2 Baseline clinical characteristics of the diabetic foots of the patients included in the study

	Treatment A (N= 59)	Treatment B (N=59)	P value
	Level of arerial occlusion N (%)		0.08 [a]
Aorto-Illiac	8 (13.6)	2 (3.4)	
Femoro-popliteal	20 (13.9)	18 (30.5)	
Distal	31 (52.5)	39 (66.1)	
	Type of lesion N (%)		0.356 [a]
Ischemic Gangrene	29 (49.2)	34 (57.6)	
Ischemic Ulcer	30 (50.8)	25 (42.4)	
	Lesion size (cm2)		0.086 [b]
	20.33	27.45	
	10.18 to 30.48	14.25 to 40.85	

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. The data corresponding to the lesions size are the means with the intervals of confidence, in parenthesis. [a] The treatment groups were compared, with regard to the proportions of aorto-illiac, femoro-popliteal and distal lesions, as well as with regard to the proportions of ischemic gangrene and ischemic ulcers, by the Square Chi test. [b] They were compared with respect to the lesions size by the Wilcoxon′s test.

TABLE 3 Anatomic localization of the diabetic foot lesions of the patients included in the study

Group[a] N (%)	Treatment A (N= 59)	Treatment B (N=59)
I	32 (54.2)	34 (57.6)
II	12 (20.3)	16 (27.6)
III	14 (23.7)	9 (15.6)
IV	1 (1.7)	0 (0)
P value	**0.7995[b]**	

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. [a] The patients were classified, according to the anatomic foot zone affected, as follows: Group I (One toe or another zone of the foot), Group II (Two toes or one toe and another zone of the foot), Group III (The heel of whole forefoot) and Group IV (Broader extent of lesions). [b] The treatment groups were compared, with regard to the proportions of patients from each anatomic foot lesion group, by the Square Chi test.

TABLE 4 Minor surgical procedures performed to the patients before the inclusion in the study

Surgical Procedure N (%)	Treatment A (N=59)	Treatment B (N=59)
Surgical toilette	9 (15.3)	7 (11.9)
Amputation of phalanxes	1 (1.6)	0 (0)
Amputation of toes	17 (28.8)	17 (28.8)
Transmethatarsal amputation	11 (18.6)	5 (8.5)
Other [c]	3 (5.0)	4 (6.7)
No procedure	18 (30.5)	26 (44.0)
P value	**0.7995** [a]	

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. [a] The treatment groups were compared, with regard to the proportions of the surgical procedures performed, by the Square Chi test. [c] Different types of minor surgery.

The characteristic features of patients enrolled in this study were: older than 50 years, majority of female gender and diabetes duration longer than ten years (Table 1), predominant distal arterial occlusion (Table 2) and ischemic gangrene and ulcer were similarly prevalent among the patients (Table 2). The lesions at one toe or another zone of the foot were the most frequent (Group I), followed by two toes or one toe and another zone of the foot (Group II) and heel or whole forefoot (Group III). Only one patient from the control group (conventional treatment alone) had broader extent of lesions (Group IV) (Table 3). Surgical procedures were performed to 66 % of patients before their inclusion in the study, with surgical toillete and toe and transmethatarsal amputations the most frequent (Table 4).

Assessment of the Glycaemic Control of the Patients in the Study

As could be expected - a low proportion of patients were found in the category of good control at the enrollment and increased to about 70 % at the end of the treatment in both groups (Table 5). There were no statistical difference between the groups with respect to the glycemic control along the treatment period; therefore, the possible influence of this variable on the results of this assay is discarded.

TABLE 5 Glycaemic control along the treatment period

	Glycaemic Control[a]			
Treatment (N)	**Good N (%)**	**Acceptable N (%)**	**Poor N (%)**	**P value** [b]
		BASELINE		0.399
A (59)	12 (20.3)	23 (39.0)	24 (40.7)	
B (59)	10 (16.9)	26 (44.1)	23 (39.0)	
		11 to 24 days		0.421
A (35)	14 (40.0)	15 (42.9)	6 (17.1)	
B (44)	16 (36.4)	19 (43.2)	9 (20.5)	
		25 to 52 days		0.398
A (24)	18 (75.0)	3 (12.5)	3 (12.5)	
B (30)	23 (69.0)	4 (13.3)	3 (10.0)	

[a] Glycaemic control was classified as good, acceptable and poor according to fasting blood glucose concentrations (from 4.4 to 6.1; 6.2 to 7.7 and > 7.7 mmol/L, respectively) and glycohemoglobin HbA1c (<8.0; from 8.0 to 9.4 and ≥ 9.5 %, respectively)
[b] The statistical comparisons between the treatment groups were done by the Square Chi test.

TABLE 6 Effect of DMF, as an adjuvant of the conventional therapy on the rate of unfavourable responses among the patients include in the study

	Unfavourable Response N (%)		
Treatment Period (days)	**Treatment A (N = 59)**	**Treatment B (N = 59)**	**P value**
0 to 10	21 (35.6)	11 (18.6)	
11 to 24	2 (3.4)	1 (1.7)	
25 to 52	4 (16.8)	3 (5.1)	
Total	27 (45.8)	15 (25.4)	0.020 [a]

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. [a] The treatment groups were compared, with regard to the cumulative percentages of unfavorable responses (need for amputation of the damage leg), by the Square Chi test.

Assessment of Treatment Efficacy

The majority of unfavourable responses were found within the first ten days of treatment in both treatment groups. However, the rate of amputations was significantly lower among patients who were treated with DMF, with a reduction of 44.5 % with respect to the conventional therapy (Table 6). The results included in the Table 4 show that there were no statistical differences between the treatment groups with respect to the rate of minor surgical procedures performed before the inclusion in the study. Therefore, an influence of this variable on the lower rate of unfavourable responses in the group treated with DMF with respect to the control group is unlikely. The duration of the treatment period had a similar effect for obtaining a favourable response for both treatment groups, i.e., prolonged treatment increased the probability of a favourable response which was independent of the treatment (Table 7).

TABLE 7 Effect of the period of treatment needed to prevent the amputation of the damaged leg to the patients included in the study

	Favourable Response N (%)	
Treatment Period (days)	**Treatment A**	**Treatment B**
0 to 10	3 (9.4)	4 (9.1)
11 to 24	9 (28.1)	13 (29.5)
25 to 52	20 (62.5)	27 (61.4)
Total	32 (100)	44 (100)
P value	**0.5225[a]**	

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. [a] The treatment groups were compared ,with regards to the distribution of the favorable responses (no need for amputation of the damaged leg) among the treatment periods, by the Square Chi test.

This study included patients at high risk for a major amputation in the next few days after hospitalization due to the combination of infection, arterial ischemia and previous minor surgeries; that may explain the occurrence of the majority of amputations during the first ten days of treatment (Table 7). Nevertheless, the reduction of unfavourable responses associated with the combined treatment in this period of time (Table 6) suggests the utility of this therapeutic approach to prevent amputations during the early stage of treatment of the infected ischemic diabetic foot.

The influence of the duration of the treatment on the favourable responses in both treatment groups (Table 7) may be related to the improvement of the glycaemic control over time (Table 5). No minor amputations were performed on the patients during the follow-up period. A failure of the treatment was an indication for a major amputation in correspondence with the high risk at enrollment.

Assessment of Safety

No significant clinical abnormalities were reported during the study. Two patients (3.4%) in treatment group B reported slight adverse reactions. One of them suffered from vertigo and nausea at the 7th DMF administration and the other one suffered from headache and tachycardia at the 12th dose. These adverse reactions occurred once along the treatment period and did not require medication.

According to the protocol, the period of treatment for each patient finished when healing of the ulcer or need for amputation was determined; though, the 52-day treatment scheme planned was not finished. Therefore, the number of patients under study diminished progressively within each treatment group over time. Thus, the N values corresponding to the laboratory measurements done from 0 to 10, 11 to 24 and 25 to 52 days were 59, 35 and 24, respectively for treatment A and 59, 44 and 30, respectively for treatment B.

This study did not find statistical differences between conventional therapy alone or plus DMF with regard to blood hemoglobin and leukocyte counts or serum alanine transaminase (Table 8 - Table 10).

TABLE 8 Effect of DMF, as an adjuvant of the conventional therapy, on blood hemoglobin (g/L) along the treatment period

Treatment Period (days)	Treatment A	Treatment B	P value
0 to 10	110 (100 to 120)	112 (95 to 127)	0.0638 [a]
11 to 24	110 (90 to 130)	110 (92 to 128)	0.2550[a]
25 to 52	111 (90 to 132)	112 (97 to 127)	0.2302 [a]

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. N values corresponding to 0 to 10, 11 to 24 and 25 to 52 days of treatment were 59, 35 and 24, respectively for treatment A and 59, 44 and 30 for treatment B, respectively. The data are the means and intervals of confidence. Normal reference range: ≥ 100 g/L. [a] The statistical comparisons between the treatment groups were done by the Wilcoxon′s test.

TABLE 9 Effect of DMF, as an adjuvant of the conventional therapy, on blood leukocyte count (Number x 10 9 /L) along the treatment period

Treatment Period (days)	Treatment A	Treatment B	P value
0 to 10	9.6 (6.6 to 12.6)	8.9 (6.7 to 11.1)	0.0960 [a]
11 to 24	7.8 (6.6 to 9.0)	8.1 (6.3 to 9.9)	0.0766 [a]
25 to 52	8.6 (6.6 to 10.9)	7.7 (5.6 to 9.8)	0.1692 [a]

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. N values corresponding to 0 to 10, 11 to 24 and 25 to 52 days of treatment were 59, 35 and 24, respectively for treatment A and 59, 44 and 30 for treatment B, respectively. The data are the means and intervals of confidence. Normal reference range: 5 to 10 9/L. [a] The statistical comparison between the treatment groups were done by the Wilcoxon′s test.

TABLE 10 Effect of DMF, as an adjuvant of the conventional therapy on serum Alanine transaminase activity (IU/L) along the treatment period

Treatment Period (days)	Treatment A	Treatment B	P value
0 to 10	18 (11 to 25)	22 (17 to 27)	0.7238 [a]
11 to 24	20 (12 to 28)	19 (11 to 27)	0.8801 [a]
25 to 52	17 (11 to 23)	20 (11 to 29)	0.8313 [a]

Treatments A and B correspond to the conventional therapy alone and with DMF, respectively. N values corresponding to 0 to 10, 11 to 24 and 25 to 52 days of treatment were 59, 35 and 24, respectively for treatment A and 59, 44 and 30 for treatment B, respectively. The data are the means and intervals of confidence. Normal reference range ≤ 35 IU/L. [a] The statistical comparison between the treatment groups were done by the Wilcoxon′s test.

DISCUSSION

This prospective, randomized, controlled clinical trial with patients suffering from infected ischemic diabetic foot demonstrated that treatment with DMF, as adjuvant of the conventional therapy for 52 days, was associated with a lower need for major amputations. Furthermore, the product was well tolerated and safe, as evident by the low rate of slight adverse reactions and no evidence of hematopoietic and hepatic damage.

The equivalent dose of procaine received by our patients through the administration of DMF was lower than the average usual dose for anaesthetic purposes; suggesting that the result was unrelated to the local anaesthetic action of procaine. Though infected diabetic ischemic foot is a high risk factor for low extremity amputations, disability and depth among diabetic patients[1-20], the studies devoted to assessing new therapeutic options for this clinical condition are scarce.[21-23] There are no previous reports on the use of a procaine formulation for the treatment of diabetic foot; therefore, the present work has provided the first scientific evidence supporting this use. Further prospective randomized controlled clinical trials should be done to elucidate DMF mode of action.

CONCLUSION

The treatment with De Marco Formula for 52 days as an adjuvant for the conventional therapy for infected ischemic diabetic foot was associated with a lower need for major amputations. It was also well tolerated and safe.

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