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Lower Limb Salvage using Regenerative Therapy in Patients with Diabetic Foot Ulcers: A Controlled Randomized Trial

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Abstract

Background: Treatment modalities that promote wound healing are warranted.

Objectives: To assess the efficacy and safety of regenerative therapy (MEBT/MEBO) as compared to standard treatment with wet-to-moist saline dressings (controls) regarding healing of chronic diabetic foot ulcers (DFUs), development of new ulcers, amputation rates, and survival of patients.

Subjects and Methods: 109 Patients (with 139 ulcers) were randomized for treatment with MEBT/MEBO (Group 1, n=56 with 71 ulcers) or saline solution dressing (Group 2 controls, n=53 with 68 ulcers). Data collected prospectively included demographics, patient features and ulcer characteristics. Ulcer surface area (SA) and healing index (HI) were calculated at two-week intervals for 12 weeks. Secondary amputations and development of new ulcers were recorded at 12 months, and patient survival at 24 months after initiation of therapy. Adverse effects or hypersensitivity reactions to the topical agent, if any, were also recorded.

Results: Patients in both groups had similar demographic, clinical and ulcer characteristics. There was a significant increase in HI and reduction in ulcer SA on weeks two and four respectively, that was maintained through 12 weeks in patients treated with MEBT/MEBO ($P<0.01$). More than half of ulcers (59.2%) treated with MEBT/MEBO had complete healing (HI=1) by 12 weeks, as opposed to only 25% of those treated with saline ($P=0.000$). None of the patients receiving MEBO had a HI of <0.5 by 12 weeks as compared to 27.4% of those receiving saline ($P=0.0001$). At 12 months post-treatment, 23 patients (21.1%) had undergone various amputations with only two (3.6%) belonging to the MEBT/MEBO Group ($X^2= 7.22$, $P=0.008$). No major amputations were required for patients receiving regenerative therapy as compared to 9.4% (5/53) of those receiving saline dressings ($X^2=4.71$, $p=0.03$). Two patients in each group developed a new ulcer by 12 months ($X^2= 0.21$, $P>0.647$). No difference in patient 2-year survival was noted, and no adverse effects or allergic reactions of MEBO were encountered.

Conclusions: (1) In addition to its safety, regenerative therapy with MEBT/MEBO significantly promotes the healing of chronic DFUs with significant increase in HI of any given ulcer as early as two weeks following initiation of treatment, and significant reduction of ulcer SA starting at 4 weeks, with complete healing of approximately 60% of ulcers by 12 weeks, and (2) No major amputations were required and significantly fewer overall amputations were needed by 12 months in patients treated with MEBT/MEBO.

Keywords: Regenerative therapy; MEBT/MEBO; Moist environment; Diabetic foot; Ulcers; Healing index; Wound healing; Amputation.

Introduction

The total number of people with diabetes mellitus (DM) worldwide is expected to rise from 171 million patients in 2000 to 366 millions in 2030 [1]. Diabetic foot complications are the most frequent reason for hospitalization in patients with DM [2, 3]. Approximately, 60-70% of those with DM will develop peripheral neuropathy [4], and up to 25% will develop diabetic foot ulcers (DFUs) [5], more than half of which will become infected, requiring hospitalization, and 1 in 5 will require an amputation [6]. Diabetic foot is the main cause of non-traumatic lower extremity amputation (LEA) Worldwide [7], as the risk of LEA is 15 to 46 times higher in people with diabetes [8, 9]. In fact, it is reported that every 20 seconds, somewhere in the world, a limb is lost as a consequence of diabetes [10]. After a major amputation, 50% of patients will have their other limb amputated within 2 years [11-13]. Moreover, the 5-year mortality rate (MR) after limb amputation is 68%, being second only to lung cancer (86%) [5, 14]. People with a DFU have a 40% greater 10-year mortality than people with diabetes alone [15] and having a DFU immediately doubles one's chances of dying at 10 years compared to those without diabetes [16].

Early detection and appropriate treatment of DFUs may prevent up to 85% of amputations and help to reduce the personal and social burden of diabetes-related amputation [17]. The effectiveness of any recommended practice needs rigorous assessment. Amputation rate alone may not be a good marker of the quality of clinical care and better endpoints are required. Effectiveness can be judged in terms of outcomes relating to the ulcer, limb, and the patient, and all three should be considered together. The most appropriate endpoint is complete healing without amputation, but this is often not achieved [18].

The present controlled randomized trial (CRT) was conducted to assess the efficacy and safety of regenerative therapy using Moist Exposed Burn Therapy / Ointment (MEBT/MEBO – Julphar Gulf Pharmaceutical Industries, UAE, and SanTou MEBO Pharmaceutical Co, Ltd, China)) as compared to standard treatment with wet-to-moist saline dressings (controls) regarding healing of chronic DFUs, development of new ulcers, minor and major amputation rates, patient survival.

Subjects and Methods

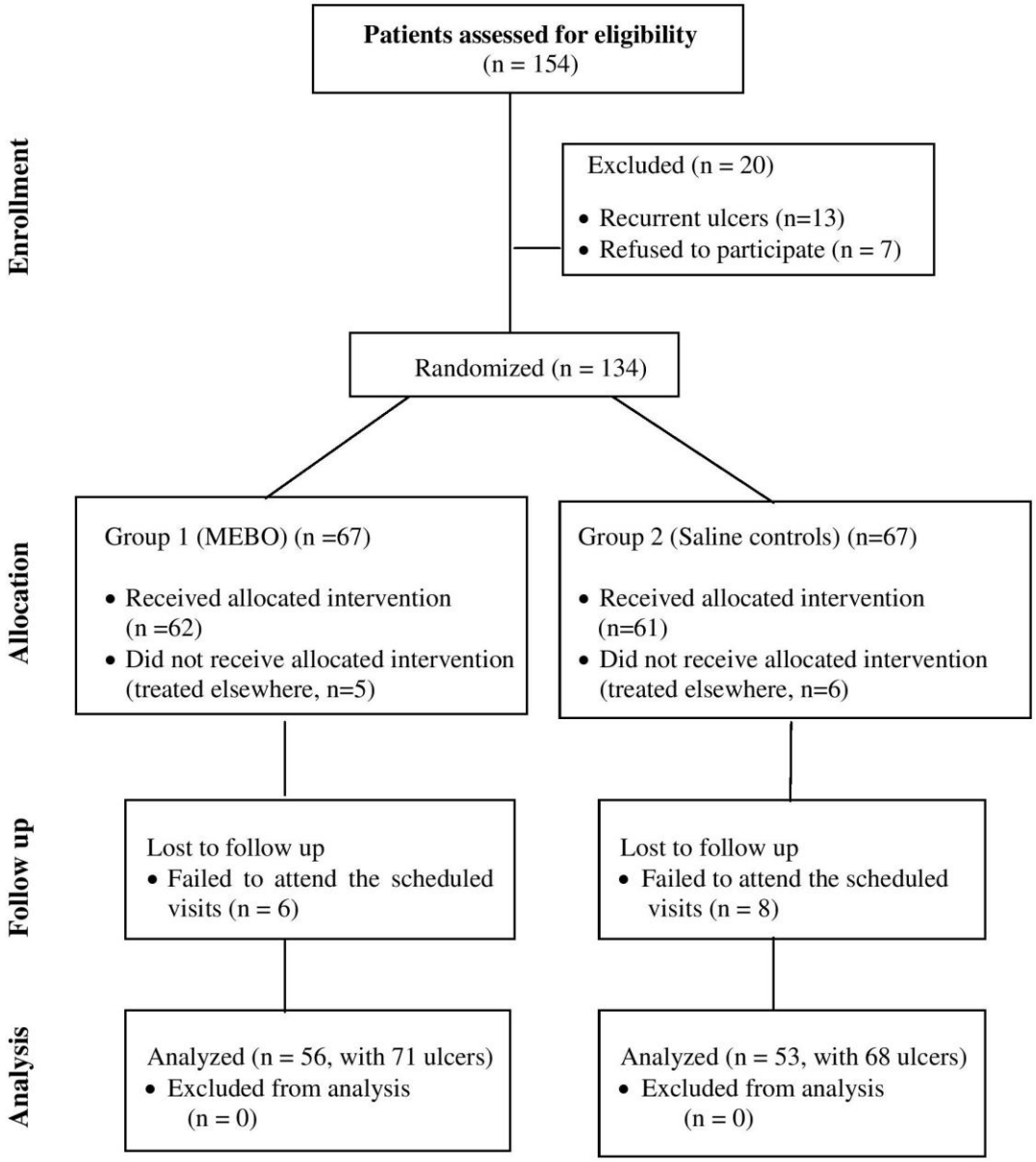
Study Design

The protocol of this single-blind, prospective, CRT was approved by the Ethics Committees of the Faculty of Medicine, Egypt, and Ahmadi hospital, Kuwait, prior to commencement of the trial. Patients were randomly assigned to receive local treatment with MEBT/MEBO dressing or saline solution (wet-to-moist dressing), and were blinded as to the type of dressing used. Randomization was performed in the outpatient department according to a computer-generated schedule with individual assignments concealed in sequentially numbered closed envelopes that were opened in order when assignments were made.

Study Population

All consecutive patients with DFUs (n=154) seen between January 2010 and January 2014 were assessed for eligibility. Patient disposition is shown in Figure 1. As may be seen, 109 Patients (with 139 ulcers) who completed the study and were analyzed represent the study population of this CRT. They were randomized for treatment with MEBT/MEBO (Group 1, n=56 with 71 ulcers) or saline solution dressing (Group 2 controls, n=53 with 68 ulcers). There were 88 males (80.7%) and 21 females (19.3%). Their ages ranged between 31-72 years with a mean of 56±11.7 years.

Figure 1: Patient flow chart



Data Collection

In addition to demographics, data collected prospectively, included type and duration of DM, hypertension, and other co-morbidities. Ankle /brachial index (ABI) was measured for all patients whose laboratory investigations included complete blood count, hemoglobin level, liver and renal function tests, serum electrolytes, blood glucose levels, and HbA1c level. Ulcer characteristics included number, type, duration, size, site and Wagner grade [19]. Plain X-ray and other appropriate imaging studies were conducted as indicated. Adverse effects or hypersensitivity reactions to the topical agent, if any, were also recorded.

Management Protocol

Clinical Assessment: At presentation in the diabetic foot clinic, the site of the ulcer was noted, and a *photograph* with a digital camera was taken. After adequate surgical *debridement*, the *surface area* (SA) of each ulcer was measured using a wound-mapping chart (3M Health Care, Loughborough, UK). Each ulcer was *graded* from 1 to 5 using the Wagner wound classification system [19]. Ulcers were considered *infected* if a purulent discharge was present with two other local signs including warmth, erythema, lymphangitis, lymphadenopathy, edema, and tenderness [20]. *Osteomyelitis* was diagnosed by the ability to probe the bone with the presence of infection and suggestive imaging features [21], and lower extremity *vascular insufficiency* was diagnosed by absence of pedal pulse and/or an ABI of <0.9 [22]. The presence of significant sensory *neuropathy* was assessed using the nylon monofilament test [23].

Systemic Treatment: Whenever indicated, nutritional deficits were corrected, and effective antibiotics were chosen according to the wound status and the results of drug sensitivity tests. Blood glucose level was controlled within the normal range (fasting blood glucose below 7.1 mmol/L or HbA1c below 7%).

Local Wound Management: After removal of all necrotic tissue, a thick layer of MEBO (1-2 mm) was applied at 6-hourly intervals using a tongue depressor after gently removing the previously applied layer. Dry sterile gauze and dressing then covered the wound and pressure relief was provided with a Scotshcast. Swabs for culture were taken only whenever it was clinically indicated. Wound dressing change was carried out in a standardized procedure following the "three timely principles" i.e. timely removal of liquefied products, timely removal of necrotic tissue and timely application of MEBO, as well as the "three NO principles" i.e. no pain, no bleeding and no further injury to viable tissue [24]. Patients in the control groups received saline dressings applying the "wet-to-moist" technique. Local wound reconstruction was not considered in any patient of both groups.

Clinical Outcomes (Endpoints): ulcer – limb - patient

All patients were followed-up every two weeks for a period of 12 weeks. Upon each visit, clinical evaluation of the ulcer was done, photographs were taken, SA was measured, and HI calculated (first end-point). Development of new ulcers and the need for amputation was recorded at 12 months post-treatment (second end-point). Major amputations mean those proximal to the tarso-metatarsal joint [18]. Patient vitality was documented at 24 months (third end-point).

Healing index (HI) was calculated by dividing the difference in ulcer size between "day 0" (initial day of assessment) and any given "day x" by ulcer size at "day 0".

Healing Index (HI) = (ulcer size day 0 - ulcer size day x) / ulcer size day 0.

The HI thus ranges between 0-1, where 0 means no healing, and 1 means complete healing, irrespective of ulcer size. Accordingly, treatment was considered to be:

1. ***Healing (cure):*** Wounds healed completely and covered with epidermis i.e. HI = 1
2. ***Effective:*** Reduction of SA by 50% or more i.e. HI > 0.5 and new grown granulation tissue with less local effusion, and actively growing epidermis at the edges of the ulcer. Cure rate and effectiveness add up to *"total effective rate".*
3. ***Ineffective:*** HI < 0.5 and slowly growing granulation tissue and epidermis on the wound edge, or no new grown granulation tissue.

Statistical Analysis

The target sample size was a minimum of 50 patients, which an initial power calculation suggested would be required to detect a 20% change in HI with a power of 80%, at the 5% significance level. Data were analyzed using the Statistical Package for Social Sciences Version 20 software (SPSS Inc, Prentice-Hall, Chicago, IL). Continuous variables were expressed as mean values ± standard of deviation and were compared using the student's t test. Variables of HI and SA over time were expressed as mean values ± standard error of the mean (X ± SEM). Differences in ulcer SA between the 2 groups were compared using the Menn-Whitney test due to wide range, and proportions were compared using the Chi-square (X^2) test or Fisher Exact Probability Test when the expected cell frequencies were smaller than 5. Probability value of <0.05 was considered to be statistically significant. A linear regression analysis calculating r^2 values was performed to indicate that the change in SA and HI can be attributed to dressing application. Values of r^2 >0.4 indicate that the 2 parameters are in correlation with each other whereas values <0.4 indicate that other variables may have contributed to the observed changes in wound size.

Results

Patients in both groups had similar baseline demographic details and clinical features regarding their age, gender, hypertension, hyperlipidemia, as well as type and duration of DM prior to ulcer formation. Moreover, patients did not differ significantly regarding their ABI, HbA1c, hemoglobin and albumin levels (Table 1). Baseline Ulcer characteristics at first presentation were also similar (p>0.05) between both groups with respect to their number, site, size, duration, Wagner grade and infection. The majority of DFUs, in both groups, belonged to Grades 2-3 and was most commonly seen in the forefoot (Table 2).

Table 1: Baseline Patient Characteristics (n=109)

Patient Characteristics	MEBT/MEBO (Group 1, n=56)	Saline Solution (Group 2, n=53)	p Value
Age (years)*	57.3 ± 7.2	55.4 ± 10.1	NS
Gender (M/F)	45/11	43/10	NS
DM (Type1/Type2)	10/46	8/45	NS
Duration of DM (months)*	27.4 ± 5.7	24.1 ± 6.3	NS
Hypertension	37(66.1%)	38 (71.7%)	NS
Hyperlipidemia	29 (51.8%)	31 (58.5%)	NS
HbA1c (%)*	8.4 ± 1.1	8.7± 1.3	NS
General Laboratory Tests*			
- Hemoglobin (g/dl)	10.5 ± 1.3	11.2 ± 0.9	NS
- Albumin	31 ± 2.4	30 ± 3.7	
ABI (mmHg) *	0.8 ± 1.7	0.9 ± 2.1	NS

* Data presented as mean and standard deviation of the mean (X±SD), NS = non-significant

Table 2: Ulcer Characteristics in Both Groups (n=139).

Ulcer Characteristics	MEBT/MEBO (Group 1, n=71)	Saline Solution (Group 2, n=68)	P Value
Type of Ulcer			
- Neuropathic	42 (59.2%)	40(58.8%)	NS
- Neuro-ischemic	27 (38.0%)	26 (38.2%)	
- Ischemic	2 (2.8%)	2 (3.0%)	
Duration (months)	2.7 (2-4.6)	2.3 (2-4.5)	NS
Size (cm^2)	6.7 (0.6 – 13.9)	5.9 (1-15.6)	NS
Infection	29 (40.8%)	25 (36.8%)	NS
Wagner Grade			NS
- Grade 1	9 (12.7%)	10 (14.7%)	
- Grade 2	33 (46.5%)	34 (50.0%)	
- Grade 3	23 (32.4%)	19 (27.9%)	
- Grade 4	6 (8.4%)	5 (7.4%)	
- Grade 5	0	0	
Site (Location)			NS
- Forefoot	54 (76.1%)	51 (75.0%)	
- Midfoot	9 (12.7%)	10 (14.7%)	
- Hindfoot	8 (11.2%)	7 (10.3%)	

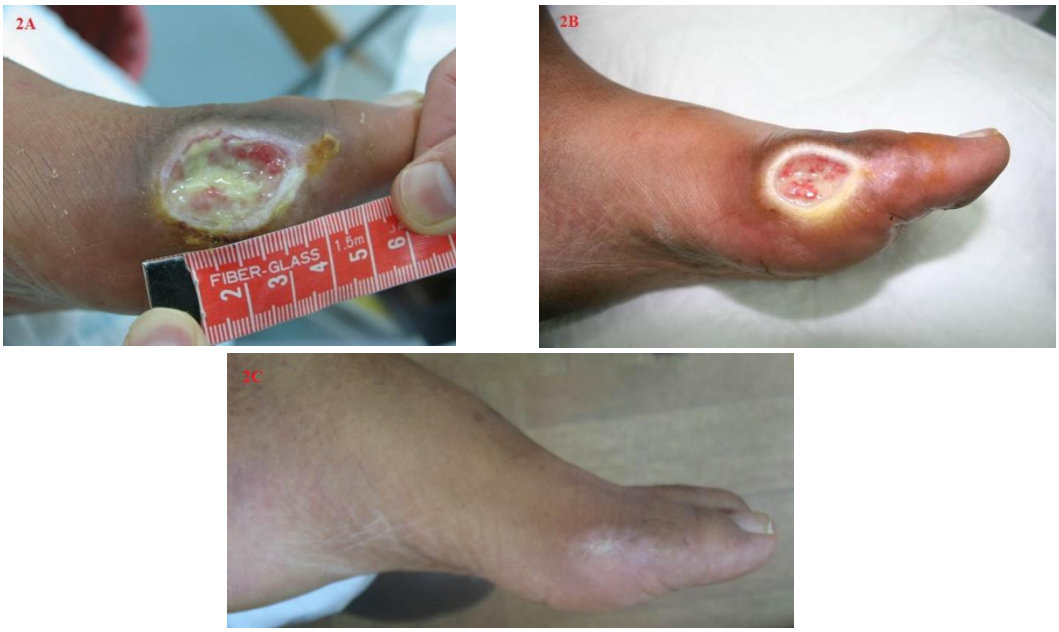
NS = non-significant

The main clinical outcomes are shown in Table 3. Of all ulcers (n=139), 59 (42.4%) were cured i.e. healed completely (HI=1) by 12 weeks; 42 (59.2%) treated with MEBO (Figure 2), and 17 (25%) with saline solution (X^2= 15.22, P=0.000). None of the patients receiving MEBT/MEBO had a HI of <0.5 (ineffective) by 12 weeks as compared to 27.4% of those receiving saline (X^2=20.6, P=0.000) (Figure 3). Adding the cure rate to the effective rate resulted in a "total effective rate" of 100% (71/71) among patients receiving regenerative therapy with MEBT/MEBO as compared to 72.1% (49/68) among controls (X^2=22.9, p=0.000) (Figure 4). As seen in Figure 5, the higher the Wagner grade at presentation, the less likely it was for that ulcer to heal within the study period irrespective of treatment received. All grade 1-ulcers in patients belonging to both groups healed completely by 12 weeks. On the other hand, none of grade 4-ulcers in the saline group healed completely by 12 weeks as opposed to 33.3% (2/6) of those treated with MEBT/MEBO). Moreover, significantly more grade 2- and 3-ulcers healed completely by 12 weeks with regenerative therapy (X^2= 17.6, P=0.000, and X^2= 3.92, P=0.049, respectively).

Table 3: Main Clinical Outcomes in Both Groups

Clinical Outcome (time after initiating treatment)	MEBT/MEBO (Group 1)	Saline Solution (Group 2)	P Value
Ulcer			
- Cure i.e. HI=1 (12 w)	42/71 (59.2%)	17/68 (25%)	0.000
- Effective i.e. HI>0.5 (12 w)	29/71 (41.8%)	32/68 (47.1%)	0.252*
- Ineffective i.e. HI<0.5 (12 w)	0	19/68 (27.4%)	0.000
- Total Effective Rate (12 w)	71/71 (100%)	49/68 (72.1%)	0.000
- Development of New Ulcer (12 m)	2/56 (3.6%)	2/62 (2.6%)	0.647*
Limb			
- Major amputation (12 m)	0	5/53 (9.4%)	0.030
- Minor amputation (12 m)	2/56 (3.6%)	7/53 (13.2%)	0.237*
- Total amputations (12 m)	2/56 (3.6%)	12/53 (22.6%)	0.008
Patient			
- Mortality (24 m)	4/56 (7.1%)	4/53(7.5%)	0.778*

W = week, m = month, * = Non-significant (P>0.05)



Figures 2 (A-C): A 54-year-old gentleman with a DFU in the left forefoot on admission (Figure 2A), after treatment with MEBO for 2 weeks (Figure 2B), and complete healing (Figure 2C) by 6 weeks.

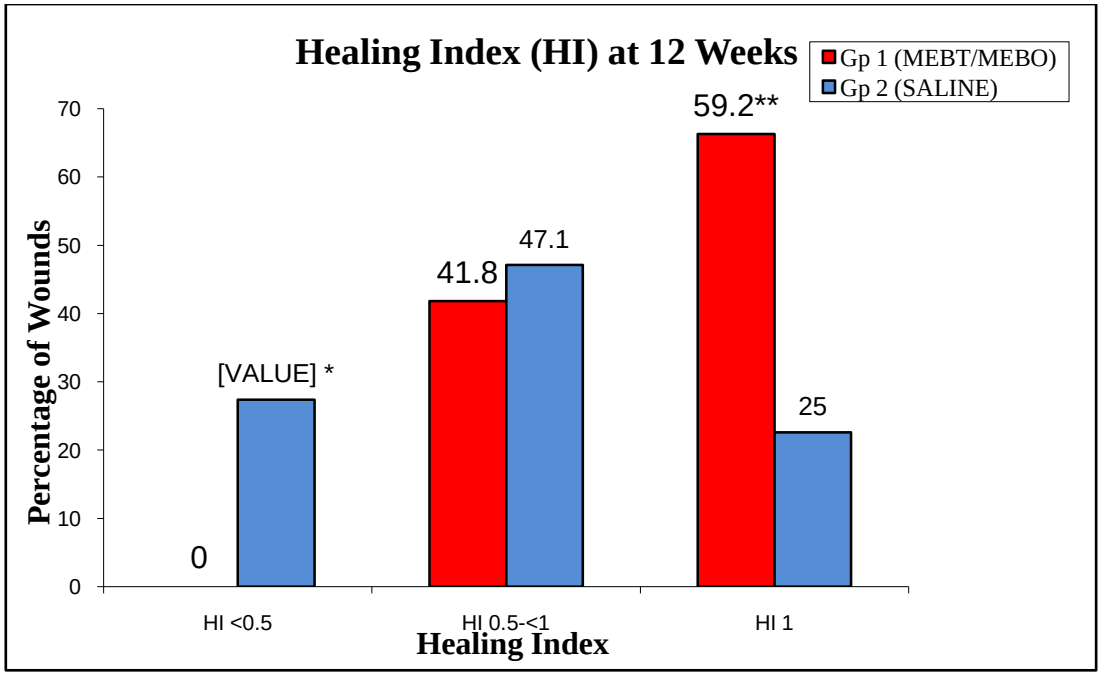


Figure 3: Proportion of healing DFUs in both groups after 12 weeks of initiation of topical therapy. Note complete healing (HI=1) of >50% of ulcers in patients treated with MEBO. *(Yates X^2 = 24.49, P=0.0001), **(Yates X^2 = 11.93, P=0.0006)

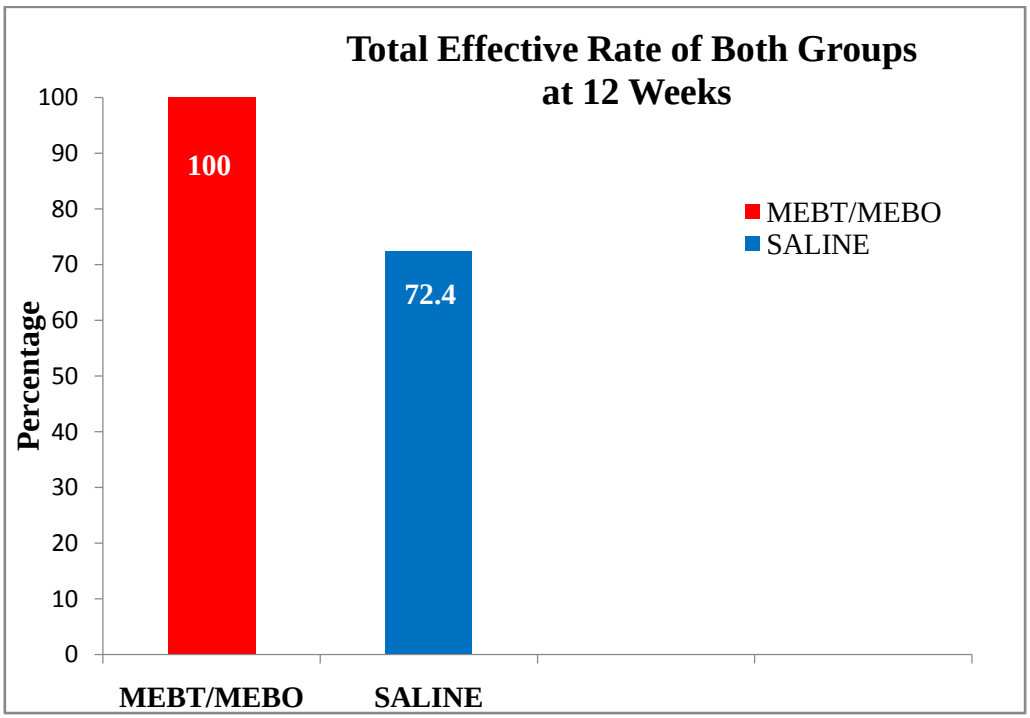


Figure 4: Total effective rate of both groups at 12 weeks after initiation of treatment showing significant increase of MEBT/MEBO over controls (X^2 = 87.9, p=0.000)

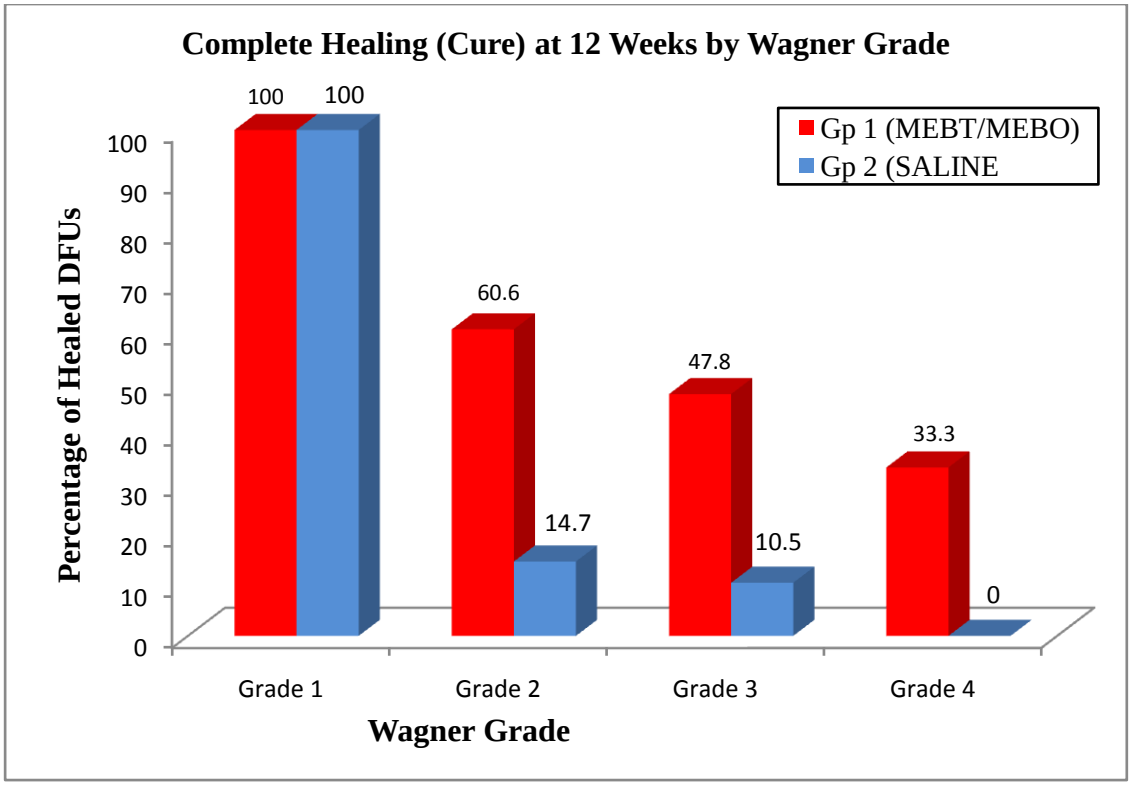


Figure 5: Complete healing (cure, HI=1) of DFUs in both groups at 12 weeks post-treatment according to Wagner grade. Note significant increase with MEBT/MEBO for grade 2 (X^2 =12.5, p=0.000), and grade 3 (X^2=4.01, p=0.043).

In general, there was a significant (P<0.01) increase in healing index (HI) (Figure 6) and reduction in ulcer surface area (Figure 7) on weeks two and four respectively, that was maintained through 12 weeks in patients receiving MEBT/MEBO as compared to those receiving saline dressing. Linear regression analysis showed that the change in ulcer size and HI can be attributed to ointment application (r^2 > 0.4). No adverse effects or hypersensitivity reactions of the ointment were encountered.

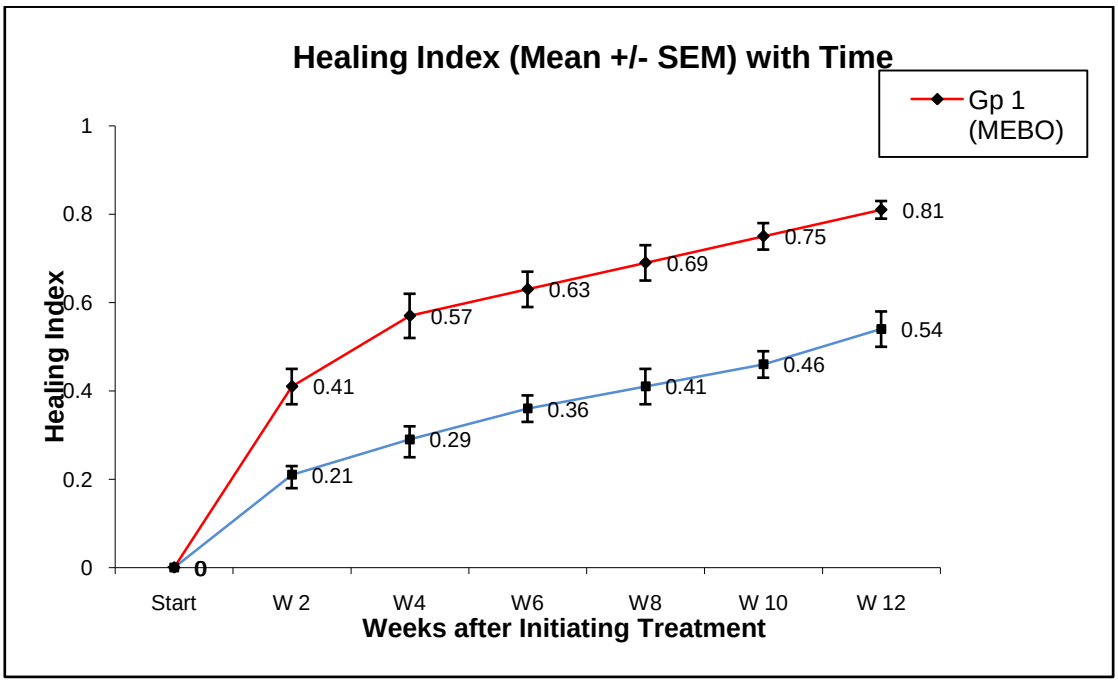


Figure 6: Mean healing index (HI) of chronic DFUs in both groups with time showing significant increase in HI in patients receiving MEBO starting 2 weeks after initiation of therapy.

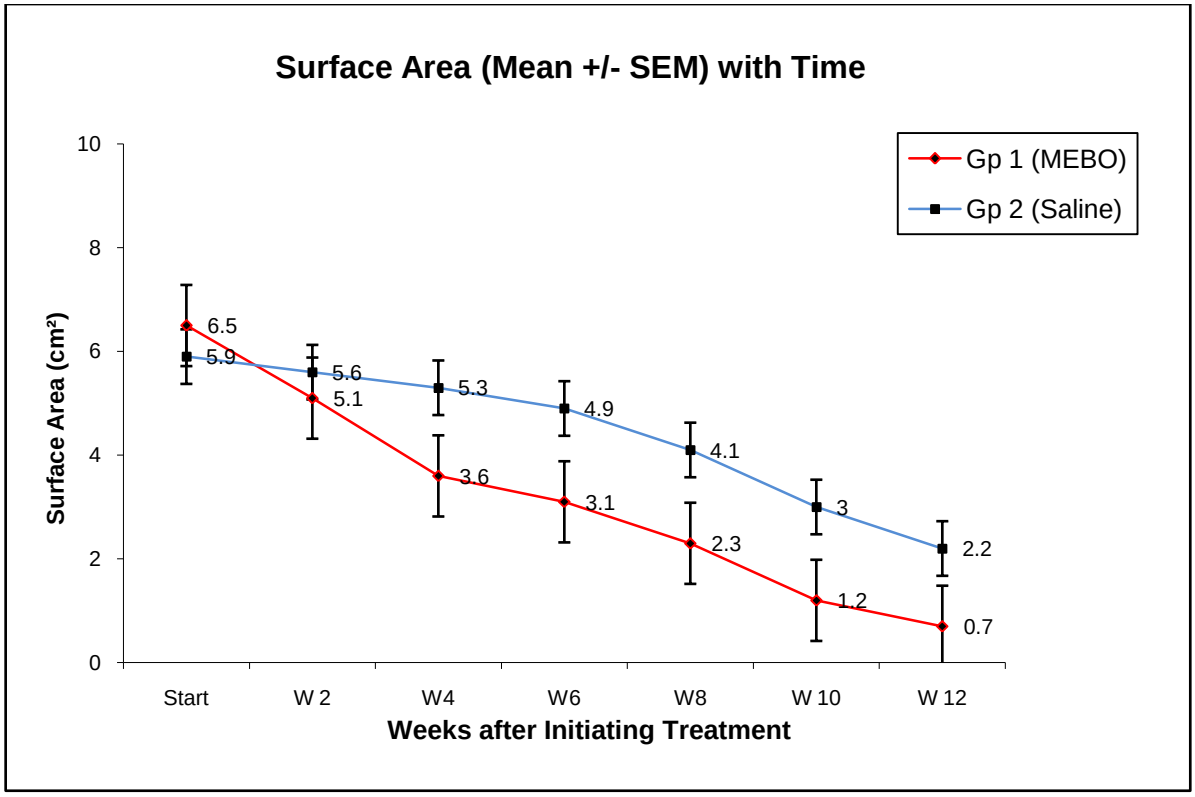
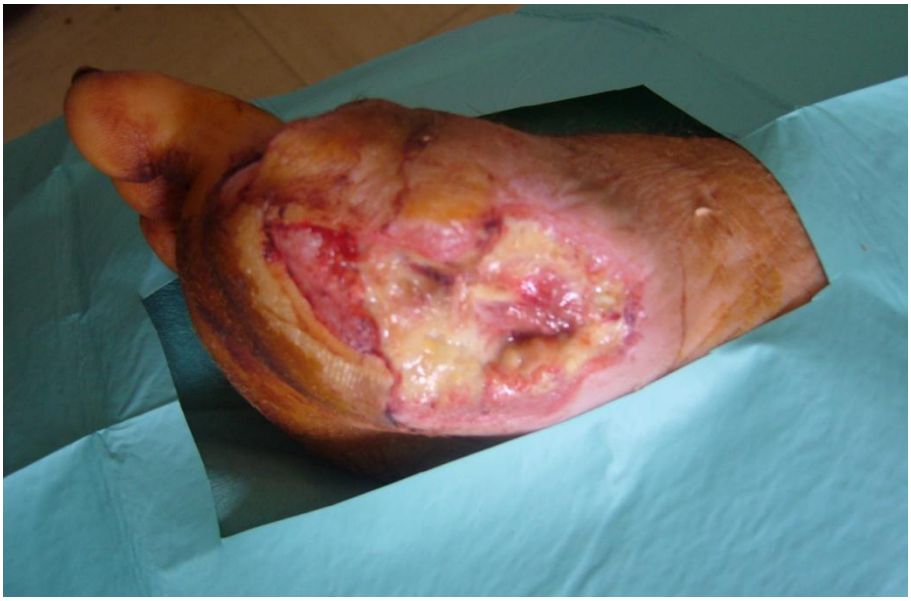


Figure 7: Mean surface area (SA) of chronic DFUs in both groups with time showing significant reduction of ulcer size in patients treated with MEBO starting 4 weeks after initiation of therapy.

At 12 months post-treatment, a total of 23 patients (21.1%) had undergone various amputations because of development of gangrene. Of those patients, only two (3.6%) belonged to the MEBT/MEBO Group (X^2= 7.22, P=0.008). They underwent ray amputation and the open wounds left behind healed completely with MEBO dressings (Figure 8). As may be seen in Figure 9, no major amputations were required for patients receiving regenerative therapy as compared to 9.4% (5/53) of those receiving saline dressings (X^2=4.71, p=0.03). However, differences between both groups regarding minor amputations were non-significant (X^2= 2.19, P=0.0.139). Likewise, two patients in each group developed a new ulcer by 12 months (X^2= 0.21, P>0.647).

(A)



(B)

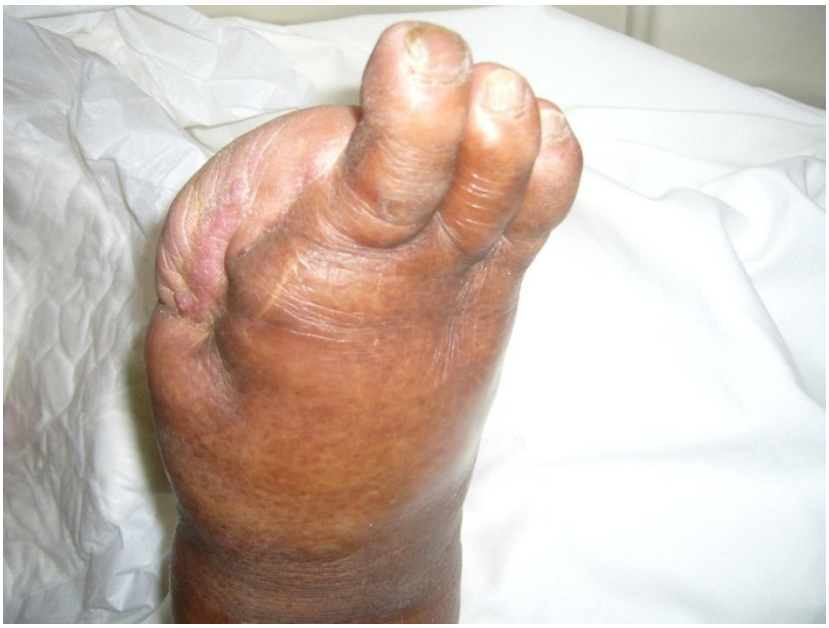


Figure 8: A 60-year-old gentleman with a ray amputation of the medial two toes. The wound was left open (A) and healed completely with MEBT/MEBO for 4 weeks (B).

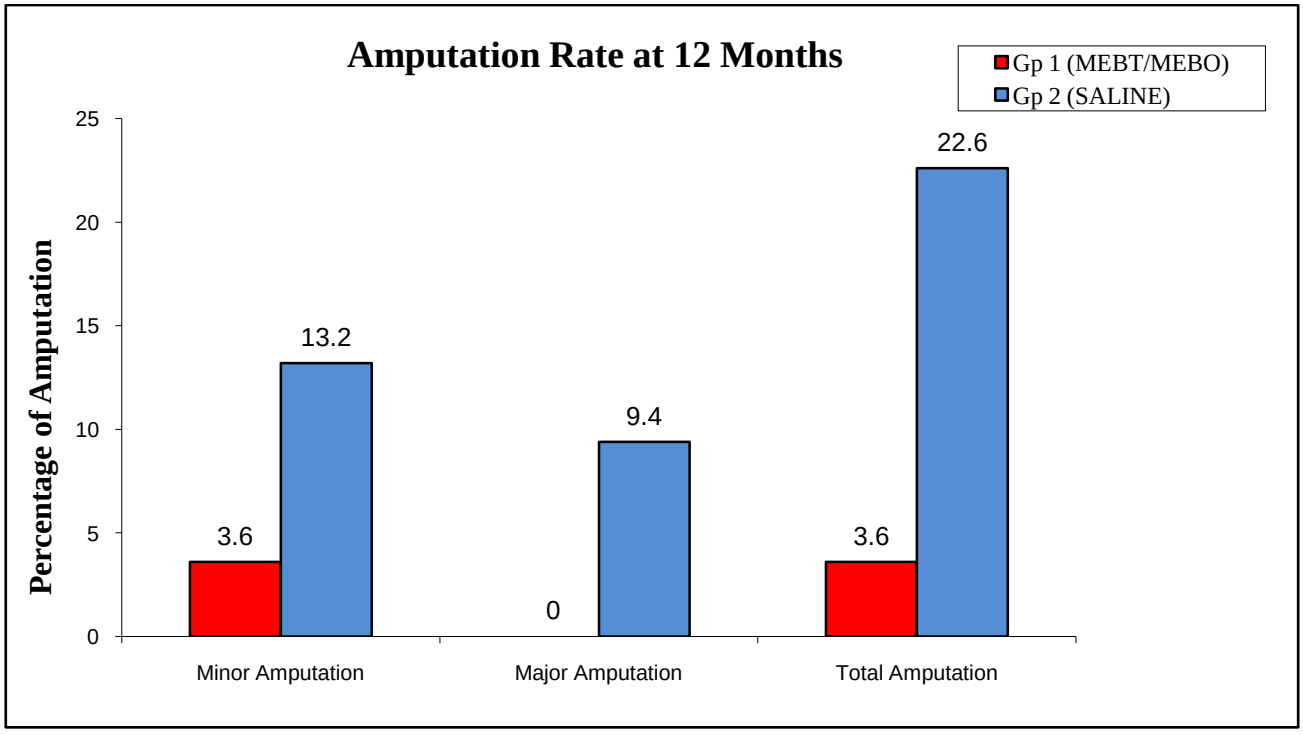


Figure 9: Amputation rate in both groups at 12 moths post-treatment. Note significant drop in major and totsl amputation rates with MEBT/MEBO (X^2=4.71, p=0.03, and X^2=7.22, p=0.008, respectively).

Four patients died in each group after 13-22 months of their enrollment in the study, which did not affect the data gathered regarding the outcome of their DFUs. The patients who died were older at presentation compared with the rest of the group (Mean age 70.4±15.7 years versus 56.4±10.3 years, P=0.037). The deaths were due to myocardial infarction (n=3), stroke (n=2), pneumonia (n=2), and septicemia (n=1).

Discussion and Conclusion

Diabetic foot ulcers precede 85% of non-traumatic LEAs [25] causing significant health and socioeconomic problems, with adverse effects on the quality of life and imposing a heavy economic burden on the patient and country. They can lead to prolonged hospitalization and the need for rehabilitation and home care services [26, 27]. Management of DFUs is largely determined by its severity (grade), vascularity, and infection [28]. For ulcer healing and limb salvage, a multidisciplinary approach that does not only include wound control but also microbiological, mechanical, vascular, metabolic, and educational control should be employed. The general management strategies implemented herein included relief of pressure, restoration of skin perfusion, debridement, and metabolic control, treatment of infection and co-morbidity, and intensive local wound care. Patients in both groups differed only in the type of local wound dressing applied.

The rapid development of topical wound dressings during the last 3 decades has left the physician with a confusing number of choices. Conventional dressings however, have such disadvantages as prolonged healing course, difficult dressing change, and time, money and energy consumption. On the other hand, the standard application of MEBT/MEBO in the treatment of various open wounds, together with comprehensive systemic treatment have been reported by several authors to achieve regenerative healing in situ even when blood glucose level has not been controlled in diabetics [29-32].

Wound healing in diabetic patients is generally impaired by deficiencies in local growth factors, changes in the extracellular matrix, diminished fibroblast function, and reduced antimicrobial activity of leukocytes and disturbances in the macro- and micro-circulation [33]. The present CRT showed the simplicity, safety and efficacy of MEBT/MEBO as part of the local management of chronic DFUs. Significant increase in HI of any given ulcer is to be expected as early as two weeks following initiation of treatment, yielding a cure rate by 12 weeks of approximately 60% and a total effective rate of 100%, as opposed to only 25% and 72.1%, respectively of those treated with saline dressings. Similar superior results of MEBT/MEBO in the management of chronic pressure ulcers [29] and DFUs [30, 34-37] were previously reported. Atiyeh et al. [36] reported in their multi-center prospective clinical trial that 80% of their DFUs reached 0.25 HI by the second week, and 65% reached 0.75 HI by the fourth. They added that application of MEBO can be continued for prolonged periods of time without leading to the emergence of resistant bacterial strains. Moreover, Margolis et al. [38], in their meta-analysis of healing of DFUs receiving standard treatment with saline, reported a mean healing (cure) rate of 24% at 12 weeks post-treatment, which matches our results (25%). It is established that MEBO is the basis of MEBT (moist environment burn therapy) popularized 3 decades ago by Xu Rongxiang [39] of the Beijing Burn Center in China. The key role is played by MEBO, which can isolate the necrotic tissue from the viable and vital tissues [40], liquefy and discharge the necrotic tissues completely through a serial of biochemical reactions and consequently show the healthy pink granulation tissue within 7-10 days of treatment [41]. Meanwhile, MEBO activates potential regenerative cells (PRCs) at the deep wound to transform into K-19 stem cells, so as to promote regeneration of new skin tissue in-situ. Furthermore, MEBO provides the appropriate moist environment and nutritional substances necessary for neocapillary formation and nerve fiber regeneration [42]. After wound healing, MEBO should be applied continuously as a protective skin cream to assure physiological structural and functional recovery of skin tissue.

Despite comprehensive wound management, however, there remains a cohort of patients with non-responding wounds, often resulting in amputation, which reached in some reports up to 38.1%-75% [43]. Patients treated with MEBT/MEBO in this study had significantly fewer overall amputations than those treated with saline by 12 months of initiation of treatment. Likewise, Chuan-ji et al. [44] cured all 15 cases with necrotic DFUs with MEBO without one case of amputation, while Xin [45] reported that only 3 of their 30 patients with DFUs received amputation under MEBT/MEBO. Similar results were also reported by An-lin [46] who treated 31 DFUs with MEBO and toe amputation was required in only three. Several authors reported that history of a previous amputation in either foot may predict another amputation [47]. Thus, the reduced rate of major amputations with MEBT/MEBO reported herein is conceivably reflected not only with improvement in the quality of life of patients but also with fewer future contra-lateral amputations. Moreover, the 5-year mortality rate after amputation is as high as 68% [15]. The present study did not show such a high mortality in either group, obviously due to the shorter follow-up of patients.

The enhanced ulcer healing and improved limb salvage observed herein could be attributed not only to the healing and regenerative power of MEBT/MEBO, but also to its anti-inflammatory (β-sitosterol constituent) and anti-microbial effects (berberine constituent) in addition to the improvement of circulation. It has been reported that MEBO can inhibit proliferation rate of bacteria, induce microbial dissociation, and lower the quantity of bacteria and production of endotoxins [46].

Furthermore, MEBT/MEBO can improve the growth of blood vessels of living tissues of the deep wound layer and improve the blood flow to the diabetic ulcer, gangrene area or wound surface, resume the blood flow in the blocked microcirculation of the basal site, and provide the tissue cells on the wound surface with nutrition and oxygen again. Meanwhile, it helps promote the regeneration of epidermis cells, suppress the rehabilitation of fibrous tissue and keep the growth of epidermal cells and collagenous fiber near to a normal proportion [34].

It is noteworthy that the standard procedures of MEBT/MEBO with no accumulation of necrotic tissue, no accumulation of liquefied product, and no accumulation of excessive drug should be followed strictly so as to achieve optimum ulcer healing and significant limb salvage.

Alternative or complementary therapy such as MEBT/MEBO, although widely used in China and some Middle East countries, has hitherto not been subjected to the rigors of properly conducted CRTs. Some authors have suggested that double standards exist in judging alternative or complementary medicine [45-47]. We believe that the only correct way of promoting evidence-based complementary medicine is by the conduct of more CRTs [48-51].

Based on the results of this study, it may be concluded that for patients with chronic DFUs (1) MEBT/MEBO dressing can be applied with simplicity and safety, (2) Regenerative therapy with MEBT/MEBO significantly promotes healing with significant increase in the HI of any given ulcer irrespective of its size, site or grade starting two weeks after initiation of treatment, (3) With the use of MEBT/MEBO, the SA of any given ulcer is significantly reduced with complete healing of approximately 60% of the ulcers achieved by 12 weeks, and (4) Patients with DFUs treated with MEBT/MEBO undergo no major, and significantly fewer overall amputations, by 12 months than those treated with saline. Another comparative study between this topical treatment modality of chronic DFUs and other existing practices merits further investigation.

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