A New Approach to Local Burn Wound Care: Moist Exposed Therapy. A Multiphase, Multicenter Study

Bishara S. Atiyeh, John Ioannovich, Gilberto Magliacani, Michele Masellis, Michel Costagliola, Ruwayda Dham, Kusai A. Al-Musa

Division of Plastic & Reconstructive Surgery, American University of Beirut Medical Center, Beirut, Lebanon, Department of Plastic Surgery and Burns, General State Hospital of Athens, Athens, Greece, Department of Plastic Surgery and Burn Center Region Piemonte, Torino, Italy, Department of Plastic Surgery and Burn Center, Palermo, Italy, Department of Plastic Surgery, University of Toulouse, Toulouse, France, Drug Research Center, Dubai, UAE

Published October 10, 2003

The effect of a moisture retentive ointment (MEBO – Moist Exposed Burn Ointment) has been tested experimentally proving its beneficial potential on wound healing. A series of clinical studies have been conducted in multiple centers to demonstrate its validity in clinical practice. The ointment was tested on healing of split thickness skin graft donor sites and compared to semi-open (Sofra Tulle) and a semi-occlusive (Tegaderm) dressing. Healing with the ointment was observed within 5-8.9 days versus 10-13 days for the other dressings. Scar assessment scores demonstrated significantly better scars for MEBO at 1 month (p<0.001) as compared to Tegaderm. The difference was significant (p<0.05) at 2 and 6 months. Subsequently, two clinical trials on burn patients were conducted. MEBO application resulted in a statistically significant (p<0.001) decrease in overall treatment costs as compared to other topical treatment modalities. The most significant cost reduction was observed in the utilization of medical facilities (p<0.0001). The trials elaborated the practicality of moist exposed burn therapy and its effectiveness in preventing burn wound sepsis. Initial swab cultures were positive in 29% of the immediately treated patients and 92% in patients treated on the third post burn day. By the second week, bacterial colonization dropped to 5% and 23% respectively.

Introduction

Increasingly aggressive surgical approach with early tangential excision and wound closure is probably the most significant change in recent years leading to improvement in mortality rates of burn victims at a substantially lower cost.1-4 By shortening the hospital stay, early burn wound closure reduces the infective complications. Faster healing decreases the severity of hypertrophic scarring, joint contractures, stiffness, and promotes quicker rehabilitation.2 Despite these major advances in management observed in recent decades, local burn wound care continues to be a significant component of the overall burn management and sometimes, due to lack of proper facilities or adequate resources, may be the major modality of burn
management. Local burn wound care involves application of topical antibiotic creams, ointments or solutions with or without an overlying dressing until re-epithelialization of superficial burns is completed or the eschar overlying deeper burns separates uncovering granulation tissue that is subsequently grafted.

Though burn injuries have traditionally been considered as special types of wounds requiring specialized management protocols, healing of burn wounds does not differ in any way from healing of any other type of wound. It is only logical that general principles of wound healing apply to burn wounds as well. It is widely accepted now that good hydration is the single most important external factor responsible for optimal wound healing. Allowing traumatized or ischemic tissues to dehydrate, produces further tissue loss by transforming the "zone of stasis" adjacent to the zone of injury into a "zone of necrosis". Possible mechanisms explaining the observed improved healing under moist conditions include easier migration of epidermal cells over the moist wound surface instead of under a dry scab, increased partial pressure of oxygen, and the preservation of growth factors and proteinases present in fluid exudates that are hence allowed to exert their potentiating effect on wound healing. The clot-inducing environment caused by increased precipitation of fibrinogen and fibronectin observed under moist conditions helps in promoting re-epithelialization.

Dressings with controlled permeability provide a protective barrier, prevent dry eschar formation, reduce the dermal necrosis seen in wounds that have been allowed to dry, and significantly accelerate wound re-epithelialization. Enthusiasm generated by these results has been tempered by concerns over tissue maceration and infection following prolonged cutaneous water exposure. These concerns may not be justified. Despite mounting evidence and appreciation of the biologic beneficial factors of moist environments the advantages of water-impermeable occlusive dressings on wound healing are often offset by their impracticality particularly when applied to large split thickness donor site areas or extensive burns.

Widely used topical antimicrobial agents for local burn wound management have been developed to reduce the incidence of burn wound sepsis and its associated morbidity and mortality. This goal has been largely attained, however, without much concern regarding burn wound healing. Reduction in burn wound sepsis has been associated with prolongation of healing time because of delayed eschar separation by liquefaction necrosis. Contrary to other topical burn creams or ointments, the moisture retentive ointment under investigation offers the advantage of addressing both issues of burn wound sepsis and burn wound healing at the same time. It acts like other medicated preparations as an effective antibacterial agent and, at the same time, acts like an occlusive or semi occlusive dressing promoting rapid autolytic debridement and optimal moist wound healing.

Material and Methods

All phases of the study have been conducted in accordance with the indicated guidelines and ethical standards. Signed consent was obtained from all patients participating in any phase of the study.

Phase I: Clinical study 1

15 consecutive patients with no underlying medical conditions requiring split thickness skin grafts were included in a prospective clinical study. All patients were Caucasians with Fitzpatrick skin types II and III with an age range of 5 to 65 years. A skin graft 0.012 in. thick was harvested with a Padgett Electric Dermatome from the thigh. Moisture retentive ointment was applied in a thick layer on half of the split thickness skin graft donor site and covered by a thin non-occlusive semi open dressing. It was reapplied and the dressing changed daily until full re-epithelialization. On the other half, the standard conventional dressing was applied intra-operatively consisting of an antibiotic impregnated Vaseline gauze, Sofra Tulle, covered by a bulky gauze dressing held in position by an elastic
bandage. Twenty four to forty eight hours later, the bandage was removed and the now adherent gauze was kept uncovered and undisturbed in place until spontaneous separation occurred. Parameters evaluated included speed of re-epithelialization, analgesia, and cosmetic appearance of resultant scars. Photographic documentation at regular intervals was performed. The longest follow up was eighteen months.18,30-32

Phase II: Clinical study 2

20 STSG donor sites in 13 adult patients requiring skin grafts were included in the study. 0.012in thick skin grafts were harvested uniformly in all patients by the same investigator using the Padget electric dermatome. Donor sites were assigned randomly for MEBO (10 fields) or Tegaderm (10 fields) application. The ointment was applied daily in a thick layer and covered by a simple semi-open dressing. Tegaderm layer, on the other hand, was changed whenever indicated. Ointment or Tegaderm application was continued until anatomical healing was observed. Healing was evaluated qualitatively by clinical assessment and, quantitatively by measuring the wound transepidermal water loss (TEWL) by Dermalab 900 (Denmark). In order to avoid the wide variation in TEWL due to ambient temperature and humidity, a TEWL index was calculated by computing the ratio of wound or subsequent scar TEWL measurement over TEWL of the adjacent normal skin on any given day. Due to the relatively small number of study fields included in the study, only non-parametric statistical analysis using the Mann Whitney test was possible. Resultant scar quality was evaluated using the Visual Analogue Scale described by Beausang et al.26 Total recorded scores as well as scores of each parameter (Color, contour, distortion, texture, and aspect) were analyzed independently. Variations over time (at 1, 2, & 6 months) within each group were analyzed statistically using non-parametric repeated measures ANOVA, the Friedman test followed by Dunn’s multiple comparison test which compares any two particular time points within a particular treatment group. On the other hand, differences between the two treatment groups at any one particular time point (months 1, 2, or 6) were analyzed statistically using non-parametric test, the Mann-Whitney test, followed by Dunn’s multiple comparison test.18,19

Phase III: Clinical trial 1

A prospective multicenter clinical trial was conducted between December 1999 and November 2000. 52 patients of both sexes with burn injuries (30 flame burns, 18 scalds and 4 patients with other causes of thermal injury) with an age range of 12 to 80 years (mean 40.5 y) were entered in the study according to strict inclusion and exclusion criteria. All patients were seen at the out patient department. The burned areas were cleansed with physiologic saline solution along with debridement of blisters. The lesions were subsequently dried before the application of a thick layer of MEBO ointment (1-2 mm). Whenever it was more convenient, dry sterile gauze with an elastic bandage were applied. Ointment application was performed once or twice daily after gently removing the previously applied layer. A total of 100 burn sites with a TBSA of 0.5% to 15% were evaluated by physical examination, recording of patients’ satisfaction, and assessment of pain by the visual analogue scale VAT of Choiniere et al.33 Transepidermal water loss and moisture were measured at regular intervals. Swab cultures was also done regularly.

Descriptive statistics and non-parametric ANOVA tests were used to analyze the changes in VAT pain scores over days 0-12 of MEBO application. The Dunn's Multiple Comparison Test and the Mann-Whitney Test were used to analyze the changes in pain scores over two specified days. Changes in TEWL and moisture values on days 0-12 were analyzed with the one-way ANOVA test. TEWL changes over two specified tests were analyzed with the Tukey-Kramer Multiple Comparison Test. Since the population analyzed falls under a Gaussian distribution, the unpaired t-test was also used to confirm the difference between two specified days. Statistical significance was evaluated using two-tailed probability levels. For all analyses
P<0.05 was considered statistically significant, P<0.001 very significant and P<0.0001 extremely significant.

Phase IV: Clinical trial 2

Forty patients of both sexes between the ages of 5 and 54 years presenting with superficial partial thickness burns 5–20% TBSA in adults and 5–15% TBSA in children greater than 5 years of age sustained <24 hrs prior to presentation over a period of 3 months were included in the study. The study was conducted in five different centers in Egypt where medical care is largely under government control in order to minimize accounting discrepancies. All patients were admitted to the hospital and assigned randomly to two comparable study groups. Twenty patients were managed with the moist exposed method and 20 other patients received the standard local therapy utilized at the given center. Overall cost of therapy was evaluated by estimating both direct and indirect costs. Direct cost included actual cost of the topical agent, i.v. fluids, concomitant antibiotics, analgesics and other pharmaceutical agents and preparations, such as gloves, catheters and dressing materials. Direct cost also included the cost of hospitalization as fixed by authorities as well as the cost of all the laboratory tests. Indirect cost was estimated by computing time spent by the treating physicians and nurses in attending to the various needs of the patients, such as dressing changes, debridement and bathing. Total cost of treatment as well as individual components (hospitalizations duration and cost, physician/nurse time, topical treatment, systemic antibiotics, analgesics, other medications, laboratory services and medical materials) were recorded, calculated (as per course of treatment or per day) and analyzed statistically using unpaired t-test or where appropriate unpaired t-test with Welch correction.5

Results

Phase I: Clinical study 1

Wounds treated by the moisture retentive ointment were completely re-epithelialized within 5-6 days while the conventionally treated areas required 10-12 days to re-epithelialize and were markedly less hyperemic and pigmented. Final cosmetic appearance as documented photographically, as well as patient's satisfaction and preference were much superior for the MEBO treated areas.18,30-32. In one adult male patient, hair growth in the MEBO treated area was observed to proceed at a much faster rate than the control area.

Phase II: Clinical study 2

Anatomical healing time for MEBO was 8.9 ± 2.846 days and 13.133 ± 2.258 days for Tegaderm (significant difference p=0.0185). 3 fields of the Tegaderm group developed local wound complications. Though initially in the first three days TEWL values in the MEBO treated group increased sharply from initial base line values, average TEWL at the time of anatomical healing was 10.58 and 11.93 times greater than normal for MEBO and Tegaderm respectively. On the other hand, average functional barrier recovery time was 67.4 ± 13.368 days for MEBO and 150 ± 46.476 days for Tegaderm (extremely significant difference p=0.0005). Significantly better scar quality was also observed in the MEBO group compared to Tegaderm as evidenced by photographic documentation and scar assessment scores at 1, 2, and 6 months. The score difference at 1 month was extremely significant (p<0.001). At 2 and 6 months it was only significant (p<0.05). On the other hand, decrease of total scores over time from month1 to month 6 reflecting scar quality improvement was statistically extremely significant (p<0.001) for MEBO and very significant (p<0.01) for Tegaderm. Separate score analysis of the various parameters investigated indicates that contour, texture, and other aspects of the MEBO group did not change significantly over time indicating that for these parameters the good results were reached at the first month in contradistinction to the Tegaderm group. Changes in color scores with time were statistically extremely significant (p<0.001) in the MEBO group and very significant (p<0.01) in the Tegaderm group. Although both treatment modalities induced a decrease in color scores over time, MEBO acted faster than Tegaderm.18,19
Phase III: Clinical trial 1

Most burn wounds when first examined were dry. Upon initiation of topical treatment with the moisture retentive ointment, the wounds became wet with a red to white base and swollen margins. As treatment progressed in time, the wounds became red in appearance without an overlying eschar. There was minimal exudation and the margins looked healthy. At day 6 of treatment, the residual none healed red and wet surface as compared to the initial surface area decreased significantly in size (p<0.001). After the application of MEBO, a rapid and progressive reduction of edema and clinical inflammation was noticed. It was also observed that topical ointment application contributed to the debridement of the wound facilitating rapid epithelialization within 2 to 6 days.

Prior to MEBO application, the mean value of the pain scores was 6.92 ± 5.50. Pain scores decreased gradually following treatment. At day three, with the non-parametric ANOVA test, the decrease was not statistically significant (p>0.05). However, it was extremely significant with the Mann-Whitney test (p=0.0001). During the following assessments at days 6, 9 and 12 the changes in the pain scores became statistically extremely significant (p<0.001) (non-parametric ANOVA test) and extremely significant (Mann-Whitney test). During the follow up period, no analgesic drugs were required even during dressing changes.

The measured TEWL values every three days were compared using the parametric ANOVA test. Immediately after the injury the mean value of TEWL of the wound was high (58.65 ± 22.8 g/m2/h) as compared to that of intact skin (8.12 ± 7.37 g/m2/h). TEWL of partial thickness burns decreased on day 3, but the decrease was not statistically significant. However, from the 6th day post-treatment, the decrease in TEWL became very significant (p=0.01 for day 6, p<0.001 for day 9 and p<0.001 for day 12). On the other hand, full thickness burn wounds exhibited no change of TEWL on day 3, but very significant decrease on days 6 and 12, though there were no differences between these two consecutive measurements. Moisture measurements were significantly increased during the first five post-burn days as compared to the low values of intact skin. As re-epithelialization of the wound progressed there was a net decrease in moisture paralleling TEWL.

Swab cultures were regularly taken in all 52 patients. 3 patients were excluded from the statistical analysis because they were treated by systemic antibiotics. 21 patients were seen immediately following their injury and were treated with moist exposed therapy. 15 patients were started on ointment application on the first or second post-burn day whereas 13 patients were started on MEBO on the third post-burn day or later. Positive initial swab cultures were obtained in 6 patients (29%) of the immediate group (21 patients) and in 12 out of 13 patients (92%) of the late group. After one week of MEBO treatment, bacterial wound colonization decreased to 10% in the immediate group and to 61% in the late group. By the second week, colonization dropped to 5% and 23% respectively. All patients with positive swab cultures progressed to complete healing. Though MEBO exhibited frank antibacterial activity, persistent bacterial colonization in some patients did not prevent full re-epithelialization. During the relatively short period of follow-up (2-4 months), the resulting scars in healed burn wounds appeared normal colored in 68% of patients. The scar was soft in 44 patients and hypertrophic in one. Scar contracture was observed in three patients, one of whom ended with a deformity.

Phase IV: Clinical trial 2

19 patients in the MEBO study group and 17 patients in the control group had adequate data for statistical analysis. A very significant (P <0.01) reduction in hospital stay for the moist exposed therapy group was demonstrated. The observed decrease in the average time spent by the treating physicians with patients treated by the moisture retaining ointment as compared
to time spent with patients treated by other modalities is significant ($P < 0.05$). On the other hand the decrease in average time spent by nurses between the two groups was very significant ($P < 0.01$) in favor of the moist exposed therapy. MEBO application resulted in a statistically very significant decrease ($P < 0.001$) in overall direct treatment costs though this decrease per day of treatment was only significant ($P < 0.01$). When various parameters responsible for direct costs are examined separately, the observed differences between the two groups in cost of systemic antibiotics as well as other medicaments and cost of haematological, biochemical and microbiological tests were not significant. On the other hand, MEBO-treated patients required less analgesics ($P < 0.05$). The most extremely significant reduction in cost, however, was observed with the medical materials utilized ($P < 0.0001$) which reflects the great savings that can be made by adopting the moist exposed method of burn wound management as compared to the classical semi-open dressings with topical antimicrobial agents.

**Discussion**

Multiple topical anti-microbial creams and ointments have been described for local burn wound care. Their usage is primarily aimed at prevention or delay of burn wound colonization by specific pathogens (mainly *Pseudomonas aeruginosa*), and the reduction of bacterial population to the level at which invasive sepsis becomes unlikely. Although, no particular agent is universally used, 1% Silver Sulfadiazine cream is the initial topical agent of choice in many burn centers. It is a good antibacterial prophylactic agent, however, it has limited diffusion into the burn eschar and may be associated with transient neutropenia. Mafenide acetate cream (*Sulfamylon*) has a good bacteriostatic activity for gram positive and gram negative organisms with excellent eschar penetration. It is, however, painful on application and in a high proportion of patients, associated with metabolic acidosis. 0.5% Silver Nitrate is a highly effective antibacterial agent though it may affect the patient’s electrolyte and water balance. Its use, however, is extremely impractical because of the black staining it produces on the skin, clothing, and furniture. None of these agents have been described to provide the necessary moisture for optimal re-epithelialization and wound healing.

The moisture retentive ointment under investigation MEBO (Moist Exposed Burn Ointment) (Julphar Gulf Pharmaceutical Industries, UAE) is a USA patented formulation since 1995. Its main active component is β-sitosterol C$_{29}$H$_{50}$O at a concentration of 0.25%. It is extracted from Philodendron amurense (Amur Cork tree). The ointment comprises 17 amino acids, 14 fatty acids, 4 polysaccharides as well as various vitamins and trace elements in a base of beeswax and sesame oil. Clinical and experimental studies reported in the Chinese literature have demonstrated that MEBO markedly reduces evaporation from the wound surface (27). It has an inhibitory effect on smooth muscle cells and has no evident effect on the humoral and cellular immune defense mechanisms. Though the ointment does not have any demonstrable in vitro bacteriostatic and bactericidal activity (probably due to its oily composition that does not allow proper diffusion in a watery culture medium), it has been shown in vivo to have similar action to Silver Sulfadiazine in controlling burn wound sepsis. Moreover, rabbit skin burns healed at a much faster rate with better quality scars when treated with moisture retentive ointment. In a recent report, MEBO has been found to be a useful alternative for the treatment of partial thickness facial burns because of its convenient method of application, which allows easier assessment of healing progression.

Two decades ago, Xu Rongxiang from the Beijing Chinese Burn Center has popularized MEBT (Moist Exposed Burn Therapy) outside China. Chinese traditional medicine (CTM) is quite different from the type of medicine and approach to disease as practiced in the west. It is wrong, however, to totally disregard CTM and its empirically time proven practices and remedies. It is difficult to accept CTM without
somehow adapting it to our ways of scientific analysis and documentation. Having realized the negative impact of currently applied methods of local burn wound care on wound healing, and after having demonstrated the beneficial effect of the ointment on healing of laser induced burns in experimental animals, a multiphase, multicenter investigation of the moisture retentive ointment has been carried out between 1999 and 2001. Results of each phase of the investigation except of phase III have been already published independently. This report, however, combines all the phases stressing the rational progression in the investigation of a product totally unknown to us from experimentation on an animal model to clinical testing and trials.

It is not conceivable to abandon products and methods currently in use for local burn wound care whose benefits have been well documented unless additional benefits of the new product can been well elaborated. Our first concern was to demonstrate that the new moisture retentive ointment has a good antibacterial effect. Second, it was important to prove its moisture retentive capacity and its positive impact on wound healing as it applies to burn wounds. Third it was crucial to determine whether the use of this ointment could be practical and cost-effective.

Though it is not an antibiotic, adequate local antibacterial action of the ointment has been demonstrated in a previously reported experimental study as well as in clinical trial 1. In a parallel study it was shown that prolonged use of MEBO does not seem to lead to the emergence of resistant strains. Improved healing potential of the ointment has been demonstrated in clinical studies 1 and 2. The clinical value of the moisture retentive ointment in autolytic debridement and healing of burn wounds has been elucidated in clinical trial 1. Clinical trial 2, on the other hand, stressed the practicality and cost-effectiveness of the ointment in local wound care. Adverse side effects to the ointment was observed in clinical trial 1 in only one female patient who developed itching and presented with flushing of her face following the second day of application. All symptoms subsided as soon as application was discontinued.

We believe that this step-by-step investigation of the new moisture retentive ointment has well documented its potential benefits for local treatment of burn wounds as well as its potential advantages over products currently in use. It could be the basis for a more ambitious study on more extensive burn injuries as well as for a comparative study between the moisture retentive ointment and other products like Silver Sulfadiazine, which is considered the gold standard for local burn wound care.

References

1. Linn BS, Stephenson SE, Bergstresser PR, Smith J. Do dollars spent relate to outcomes in burn care? Med Care 1979; 17: 835


21. Jonkman MF, Hoekema EA, Nieuwenhuis P. Accelerated epithelialization under a highly vapor-permeable wound dressing is associated with increased precipitation of fibrin(ogen) and fibronectin. J Invest Dermatology 1990; 94: 478


31. Atiyeh BS, Ghanimeh G, Kaddoura IL, Al Amm C, Ioannovich J. Split Thickness Skin Graft Donor Site Dressing: Preliminary Results of Controlled Clinical Comparative Study of MEBO and Sofra-Tulle.


35. Li L: Experiment on inhibiting constriction of the ileum from a white mouse. Chinese J Burns Wounds Surf Ulcers 1990; (1): 50


38. Xing D: Experimental study on the actions of the moist burn ointment on promoting healing of skin wound and anti-infection. Chinese J Burns Wounds Surf Ulcers 1989; (1): 75


