INTRODUCTION

Cutaneous ulcers affect mainly the lower extremities and are classically subdivided into venous stasis ulcers, pressure ulcers and diabetic ulcers and remain one of the most costly unsolved problems in health care today. Moreover, non-healing foot ulcers associated with peripheral vascular disease mainly in the elderly or in diabetic patients constitute a major morbidity and represent a prominent cause of

The efficacy of moisture retentive ointment in the management of cutaneous wounds and ulcers: A multicenter clinical trial

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ABSTRACT

Local management of chronic wounds and ulcers remains one of the most costly unsolved problems in health care today. With proper clinical management, most chronic wound healing problems can be resolved and healing expected, though recurrence may be common. The recent logarithmic growth in our knowledge about wound healing and the appreciation of the importance of a moist environment in optimal wound healing has led to the introduction of new and exciting therapeutic modalities. In view of the many practical disadvantages as well as the serious complications of currently available moisture retentive dressings when applied to chronic contaminated wounds, a prospective multicenter clinical trial was conducted from December 1999 to November 2000 to evaluate the safety and efficacy of a newly introduced moisture retentive ointment (MEBO: Moist Exposed Burn Ointment) (Julphar – Gulf Pharmaceutical Industries, UAE) in the local wound care of problematic non-healing wounds. The active component of the ointment is β-sitosterol in a base of beeswax, sesame oil and other components. Though it was not a comparative study, the ointment was found to induce rapid reduction in ulcer size even after a prolonged stagnant state with other therapeutic modalities without complications such as skin maceration, unmanageable excessive exudation, and wound infection. As expected with such chronic wounds, the healing potential of local ointment application is limited by the mere size of the original defect and the underlying pathologies and associated diseases. However, the safety and practicality of simple ointment application was found to be a valid alternative treatment for local management of chronic wounds.

KEY WORDS

Chronic ulcers, Cutaneous ulcers, Optimal wound healing, Moist wound healing.
amputation,\textsuperscript{2} which is viewed as the first stage of a “creeping death”.\textsuperscript{3} Foot ulceration with infection is one of the leading causes for hospitalization of patients with diabetes mellitus,\textsuperscript{4} with an annual health care cost in the USA greater than $1 billion.\textsuperscript{1} Preventing foot ulceration takes on major significance when survival data after lower limb amputation are considered. The three and five year survival rates are approximately 50% and 40% respectively; the major cause of death being cardiovascular disease. Following one lower limb amputation, there is a 50% incidence of serious contralateral foot lesion within 2 years and a 50% incidence of contralateral amputation within 2-5 years.\textsuperscript{5} Diabetes is a contributing factor in 50% of all lower extremity amputations in the United States, and the relative risk of amputation is forty times greater in diabetic individuals.\textsuperscript{2,6} On the other hand, approximately 60% of patients with spinal cord injuries will develop pressure ulcers at some point of time. If the elderly population with pressure ulcers is added to the spinal cord injury population, then the figure for the care of all chronic ulcers is enormous. The care for venous stasis ulcers is also very costly.\textsuperscript{7} The triad of minor trauma, skin ulceration, and wound healing failure (often with gangrene and infection) precede in 72% of all lower limb amputations. 84% of the amputations could be partly attributed to skin ulceration, 81% to defective wound healing, 81% to initial minor trauma, 46% to ischemia, 55% to gangrene, 59% to infection and 61% to neuropathy.\textsuperscript{8} In that perspective, local wound management becomes an essential component in the overall management protocol aimed at limb salvage of patients suffering from lower limb ulcerations.

Wound healing is a complex series of events characterized by inflammation; however, it does not culminate in tissue regeneration but rather in tissue restoration.\textsuperscript{8} Healing involves three processes: epithelialization, connective tissue deposition, and contraction. The contribution of each process varies according to the type of wound.\textsuperscript{9} Factors adversely affecting wound healing include advanced age of patients, poor nutrition, smoking, diabetes, anemia, obesity, cancer, ischemia, uremia and denervation. Chemotherapeutic agents as well as the administration of corticosteroids and tissue irradiation also lead to delayed wound healing. Local wound factors such as infection and prolonged periods of pressure greater than tissue perfusion pressure results in delayed healing as well\textsuperscript{8,10,11} and shifting of the gain in tensile strength curve to the right signifying chronicity. There is, however, more recent evidence in literature that good hydration is the single most important external factor responsible for optimal wound healing.\textsuperscript{12-25} Ever since Winter\textsuperscript{26} has proposed his classical hypothesis that the optimum environment for epithelialization is a moist environment, few have challenged him. However, some have proposed that the optimum environment would be an intermediate gelatinous environment between moist and dry such as seen under highly vapor-permeable dressings,\textsuperscript{27,28} and others have demonstrated accelerated healing of full-thickness skin wounds in a wet environment in contradistinction to a moist environment.\textsuperscript{12} Irrespective of this apparent controversy, allowing traumatized or ischemic tissues to dehydrate produces further tissue loss and transforms the “zone of stasis” adjacent to the zone of injury into a “zone of necrosis”.\textsuperscript{12,19,22} In the natural course of events, dermis or deeper subcutaneous tissues devoid of epidermal protection lose water to the atmosphere. The uppermost layers become dehydrated and incorporated in the scab trapping some of the leukocytes that crowd to the wound surface.\textsuperscript{29}

Moist Exposed Wound Ointment (MEBO) (Julphar Gulf Pharmaceutical Industries, UAE) is the basis of MEBT (Moist Exposed Burn Therapy). It has been popularized two decades ago by Xu Rongxiang\textsuperscript{10} from the Beijing Chinese Burn Center. It offers the advantages of a moist environment for wound healing in addition to those of the open treatment technique avoiding cumbersome, bulky, and expensive dressings. MEBO is a USA patented formulation since 1995. Its active component is β-sitosterol in a base of beeswax, sesame oil and other components. Clinical and experimental studies reported in the Chinese literature have demonstrated that the ointment markedly reduces evaporation from the wound surface.\textsuperscript{31} It has an inhibitory effect on smooth muscle cells, which is dose related\textsuperscript{12} and has no evident effect on the humoral and cellular immune defense mechanisms.\textsuperscript{33} Though MEBO 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 that in vivo it had similar action to Silver Sulfadiazine in controlling burn wound sepsis and systemic infection with P. aeruginosa. It has also been demonstrated experimentally that it exhibited a statistically significant wound healing potential on rabbit corneal epithelium as compared to saline, homologous serum, Vitamin A and dexamethasone. Moreover, rabbit skin burns healed at a much faster rate with better quality scars when treated with the ointment than similar burns treated with Vaseline, with demonstrable histological differences on repeated serial biopsies. 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. It has also been found to be extremely beneficial in the treatment of split thickness skin graft donor sites and for the healing of experimentally induced CO2 laser burns in experimental animals.

In order to investigate the safety and efficacy of the moisture retentive ointment in local wound care and its capacity to induce healing of cutaneous wounds and ulcers, a multicenter prospective clinical trial was conducted from December 1999 to November 2000.

MATERIAL AND METHODS

Protocol
A prospective clinical trial was conducted from December 1999 to November 2000 in multiple centers from Italy, France, Greece, and Lebanon in order to evaluate the effect of a newly described moisture retentive ointment (MEBO) on healing of chronic ulcers affecting mainly the lower extremity. Abiding by the regulations applied in the various countries that guide experimentation of novel medications on human subjects, and after obtaining their consent, patients of both sexes seen within the study period with wounds or ulcers failing to heal for more than 1 month were included in the study. 5 additional cases with problematic wounds of less than one month were also included. Some ulcers affecting other anatomical areas fitting the definition of chronicity were also included. Age and sex of patients as well as their phototype were noted. Chronic ulcers were classified under vascular, venous or arterial, and neurotrophic. Wounds of miscellaneous etiologies such as trauma, gunshot injury, shrapnel injury, chemotherapy extravasations and wound dehiscence were also included in the study. The underlying predisposing diseases were noted as well. These included diabetes, peripheral vascular disease, central nervous system, spinal cord or peripheral nerve injuries, associated malignancy, connective tissue diseases, renal insufficiency, endocrinopathy or chronic osteomyelitis. Previous radiotherapy was also noted as well as concomitant corticosteroids or chemotherapy administration. Other demographic data recorded included the employment status of the patient as well as his mobility and nutritional status. Enrollment in the study of any given patient was terminated whenever requested or whenever she/he developed unwarranted side effects or hypersensitivity reactions to the topical agent being tested or if she/he failed to report for follow-up visits. In such cases only the data gathered prior to their withdrawal was included in the data analysis. Adverse reactions, if any were also reported on a special “adverse experience report” sheet included in the study case record form.

Local wound management was accomplished by daily application of a thick layer of ointment (1-2 mm) using gauze or a blunt instrument (tongue depressor) after gently removing the previously applied layer. Dry sterile gauze and an elastic bandage then covered the wound. All wounds and ulcers were evaluated at weekly intervals whether patients were hospitalized or seen at the out patient department. Whenever healing stagnated other treatment modalities such as surgical debridement and/or soft tissue coverage by skin grafts or flaps were performed as indicated otherwise local therapy was continued until healing of the ulcer was achieved.

Upon each evaluation, a ruler was placed adjacent to the ulcer and a photograph was taken. Wound surface area was subsequently calculated with computerized planimetry (Image Tool 2.0). Edema was assessed by measuring limb circumference 12 cm above and below the knee and 12 cm above the ankle whenever practically feasible. Pain was also evaluated using the
visual analogue thermometer VAT described by Choiniere et al. Clinical evaluation of the wound was performed noting wound margin status with respect to erythema, cellulitis and edema. Hyperpigmentation if present was also recorded. Wound swab for culture was also taken and it was repeated only whenever it was clinically indicated by the deterioration of wound status and the presence of increasing exudation. Laboratory tests recorded included hematocrit, hemoglobin, albumin, globulin, glucose, sodium, potassium and calcium.

**Study Population**

A total of 47 patients with non-healing wounds and ulcers were entered in the study. Underlying diseases as well as the cause of the wound or ulceration are shown in Tables 1 & 2. All were locally managed with moisture retentive ointment application. Adequate surface area measurements were available for 32 ulcers. 27 ulcers were less than 8 cm² and 5 more than 8 cm² ranging from 12.32 cm² to 61.98 cm². Age of patients ranged between 16 and 82 years with an average age of 43.6 years and a median of 47 years. Patients had their ulcers prior to study entry for a median of 86 days, maximum of 3618 days and an average of 358.3 days.

**Healing Index**

Due to the variation in ulcer size between patients (0.4 cm² - 61.98 cm²), which makes comparison rather difficult, a healing index was calculated. It was computed by dividing the difference in ulcer size between day 0 and any given day X by ulcer size at day 0.

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\text{Healing Index (HI)} = \frac{\text{Ulcer size day } 0 - \text{Ulcer size day } X}{\text{Ulcer size day } 0}
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The index ranges between 0 at the initial day of assessment and 1 after completion of healing irrespective of ulcer size (Figures 1 & 2).

**Statistical Analysis**

Descriptive statistics and paired student t-test were used to analyze changes observed in ulcer surface area measurements and in healing index (HI) calculations. Changes over two specific time points were tested in order to quantify the significance of the change. For
all analyses changes with P-values greater than 0.05 were not considered to be significant, whereas change with P-values less than 0.05, 0.01, and 0.001 were considered to be significant, very significant, and extremely significant respectively. A linear regression analysis was also performed calculating r2 values in order to evaluate the change in ulcer size and healing index that can be attributed to ointment application. Since the sample size is relatively small, r2 values more than 0.4 were considered to indicate that the two parameters are in correlation with each other whereas values less than 0.4 indicated that other variables may have contributed to the observed changes in ulcer size. Based on this analysis a 95% confidence interval was calculated which projected the expected healing of ulcers in the population at large.

RESULTS

5 ulcers larger than 8cm² surface area were considered separately because of the extreme variation they would introduce to the statistical analysis. Analysis of surface area v/s time and healing index v/s time of ulcers less than 8 cm² surface area (27 ulcers) revealed some interesting trends. Considering all types of ulcers together, there was an extremely significant reduction in ulcer surface area and increase in healing index over the first 3 weeks of treatment (Figure 3). When separate analysis is conducted for neurotrophic ulcers and for non-neurotrophic ulcers, these changes became more pronounced with less variability particularly for the non-neurotrophic group (Figure 4). Looking at the healing trend of the neurotrophic ulcers may give the impression of no improvement in healing between week one and week two. However, when the same data is analyzed using the paired t-test, significant reduction in surface area and significant increase in healing index between weeks one and two become apparent. The same trends are observed when ulcers of vascular etiology without a neurotrophic component are considered (17 patients).

Cumulative patient sample percentages with 0.25, 0.50, and 0.75 healing indices respectively are shown in Figure 5 for all ulcers grouped together and for neurotrophic and non-neurotrophic ulcers separately. Looking at the 0.25 healing index curves, we can deduce that more than 50% of all ulcers reached 0.25 HI within the first week, more than 80% within the
second week, and more than 90% within the third week. 100% of the non-neurotrophic ulcers reached 0.25 HI by the third week while only 80% of the neurotrophic ulcers reached the same stage of healing. 50% of all ulcers reached 0.75 HI by the second week, and around 80% by the fourth week, while 85% of non-neurotrophic and about 65% of neurotrophic ulcers reached 0.75 HI by the fourth week.

Wound margin appearance is basically a subjective observer dependent clinical observation and was not found to be of value in result analysis. Results of repeated swab cultures available in 26 patients did not seem to influence healing. In the other patients a swab culture was initially taken at the time of inclusion in the study, however, it was not repeated thereafter. None of the patients in the study initially had wound sepsis nor did any patient develop clear signs of wound sepsis during treatment irrespective of the treatment duration, which extended for more than 3 months in few patients for which surgery was not an option either because of the underlying condition or because of their refusal. This is a useful observation indicating that prolonged use of MEBO does not seem to lead to the emergence of resistant strains so dreaded whenever antibiotic ointments are used continuously for prolonged periods of time. Pain score measurements were found not to be relevant as well since most patients with chronic ulcerations had decreased sensation. At the initial assessment 27 out of 46 patients had a VAT score of 0 and 8 patients had moderate pain with a VAT score of 3 to 6. In these patients, pain was not always related to the ulcer itself, but rather due to poor perfusion. Ulcer pain tended to decrease as healing progressed. Skin maceration has not been observed in any of the patients participating in the clinical trial.

**DISCUSSION**

Established practices in topical management of chronic ulcers are often taken for granted and their value in
promoting optimal healing is rarely questioned. Pharmaceutical preparations used include wound cleansing solutions, topical antibacterial and wound debriding agents as well as dressing material and products. The routine use of antiseptic solutions should have little place in wound management. Most antiseptics, particularly those containing cetrimide, have marked cytotoxic properties. Povidone-iodine, acetic acid, hydrogen peroxide, or sodium hypochlorite (Dakin’s solution) are as likely to injure normal tissues, as they are to destroy microorganisms and may delay wound healing (7). Various powders, ointments, creams or solutions available for use as topical antimicrobial agents may control bacterial growth at the wound site for some time, but in most cases, will definitely not cure infection. Indiscriminate use of these agents for prolonged periods of time may predispose to the emergence of resistant strains and several may cause skin hypersensitivity reactions or may have an adverse effect on wound healing. To the exception of 5% Sulfamylon solution, almost all of these preparations inhibit fibroblast growth. Moreover, most topical antibiotic preparations used for local treatment rarely provide the necessary moist environment for optimal healing.

Occlusive dressings prevent surface desiccation greatly enhancing re-epithelialization and wound contraction. They reduce also pain during the healing phase. Early occlusive dressings were quickly abandoned because of the potential of bacterial proliferation and their difficulty of application to areas other than the extremities. Duoderm® (Convatec), a new type of occlusive dressing keeps a moist nonadherent environment over the open wound. Although it appears to be ideal, Duoderm has been associated with the formation of granulomas with increased inflammation and potential scarring. When occlusive dressings are used on large surface areas, the amount of dressing exudate becomes unmanageable and it becomes cost ineffective and labor intensive. Besides, enclosing the wound in a sealed chamber is laborious and requires methodological precision.

Recent advances in cell culture technology has allowed...
the generation of sheets of epithelial cells appropriate for wound coverage\textsuperscript{53} acting simultaneously as a moisture retentive covering dressing and as a definitive treatment. They have been successful in the management of chronic ulcers.\textsuperscript{53} The main problems with this modality, however, are the mechanical instability during the first week after grafting\textsuperscript{54} and the delay required to culture sheets of auto-keratinocytes.\textsuperscript{55} The US FDA approved Epicell ASAProgram generates autologous keratinocytes by the co-culture technique and cell expansion described by Reinwald and Green employing murine fibroblasts as feeder cells.\textsuperscript{56} However, histologic appearance of cultured epithelial autografts long after healing differs greatly from time-matched meshed expanded autografts, which explains the late blister formation in areas covered by cultured autografts.\textsuperscript{57} Problems encountered by the transfer of cultured keratinocytes have stimulated the development of various vehicles for autologous keratinocytes grafting such as Hydroderm, a polyurethane wound dressing,\textsuperscript{56} and cultured skin substitutes consisting of collagen-glycosaminoglycan substrates populated with autologous fibroblasts and keratinocytes.\textsuperscript{58} More recently, allogenic cultured epidermis, obtained more quickly from donor skin mostly from neonatal foreskin, has been described. Cultured allografts act by providing a temporary wound covering while releasing multiple cytokines that act by stimulating quiescent host keratinocytes to multiply and migrate.\textsuperscript{53,55} All these variable wound covering modalities, nevertheless, are still extremely costly precluding their routine use except for extreme conditions such as extensive burns for which they may be life-saving.

A new concept in local wound management applicable to chronic ulcers is the negative-pressure dressing.\textsuperscript{59} It is primarily designed to prevent exudate collection while simultaneously preventing desiccation of the wound. It has been also claimed that these dressings increase oxygen tension in the wound, decrease bacterial count, increase granulation formation, and prevent shear force on the wound surface.\textsuperscript{50} Additional advantages include diminished need for daily dressing changes enhancing patient’s comfort, decreasing nursing work, and probably diminishing cost of wound care. Though the principle is basically simple, applying this type of dressing does require certain expertise and may not be applicable to extensive wounds.

It is obvious that the effective, practical, and affordable local wound care modality is not yet available. At any rate, the preferred modality should be one able to maintain moisture over the wound surface and preserve the cytokines and growth factors present in wound exudates. Further, it should provide an effective barrier against bacteria and injurious external physical factors, and must reduce pain. Moreover, it must facilitate debridement whenever needed. In addition, reduced cost and unlimited or prolonged shelf storage time are also factors to be considered.\textsuperscript{61} Practical considerations with regard to dressing application and maintenance in position should not be overlooked as well.

Not infrequently, dressings are applied for extended periods of time without ever achieving healing or even without any improvement in the wound condition. Obviously, some wounds are not expected to improve or heal, either because of their size or because of the uncorrected underlying medical or metabolic disease. In such cases, if surgery were not an option, the purpose of the local management protocol would be to maintain the wound surface in a healthy socially acceptable condition so that the patient can enjoy a relatively good quality of life. In such particular cases, whichever dressing is applied should not be over demanding by its complexity. The most appropriate dressing, mainly for non-hospitalized patients, would be one that the patient can simply apply by himself if able to do so or by a member of his family. Dressings that require special expertise for application such as occlusive or semi-occlusive dressings should definitely be avoided.

For wounds that are expected to heal, a 50% healing index increase over 2 weeks is an indication of good favorable progression and of the efficacy of the treatment modality that must be continued. Less than 50%, on the other hand, necessitates reevaluation of the techniques and implementation of surgical or more effective dressing modalities. The maximal effect of the moisture retentive ointment application under investigation can be expected at 4 weeks for most ulcers. If by then healing did not occur either because
of the original large ulcer size or because some other underlying medical or surgical condition, it is fair to assume that spontaneous secondary healing would be highly unlikely. Other measures become indicated such as surgical debridement with or without soft tissue coverage.

Though it is not a comparative study, this multicenter prospective study enabled us to establish the simplicity, safety and efficacy of the moisture retentive ointment in local management of cutaneous wounds and ulcers. The ointment may induce rapid reduction in ulcer size even after a prolonged stagnant state with other therapeutic modalities. Full effect of the ointment with maximal increase in healing index of any given ulcer is to be expected at 4 weeks following initiation of the treatment. As expected, healing potential of the ointment is limited by the mere size of the original defect and the underlying pathologies and associated diseases. When a healing plateau is reached, additional therapy mostly surgical debridement and coverage becomes indicated. If surgery is not an option, ointment application can be continued for prolonged periods of time without leading to the emergence of resistant bacterial strains while maintaining the wound in a relatively clean and socially acceptable condition. Thus patients may enjoy a relatively good quality of life. It is worth mentioning that non-neurotrophic ulcers showed a trend of better healing response to local ointment application than neurotrophic ulcers and that none of the complications described with the various occlusive moisture retentive dressings have been encountered during the study period. A more specific comparative study is definitely required in order to clearly demonstrate the advantages of this topical treatment modality of chronic ulcers over existing practices.

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