

MOIST EXPOSED BURN OINTMENT (MEBO) IN PARTIAL THICKNESS BURNS

A RANDOMIZED, COMPARATIVE OPEN MONO-CENTER STUDY ON THE EFFICACY OF DERMAHEAL (MEBO) OINTMENT ON THERMAL 2ND DEGREE BURNS COMPARED TO CONVENTIONAL THERAPY

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Abstract

Objective: Wound healing in burn wounds presents a challenge in healthcare, and there is still a lack of alternatives in topical burn wound treatments.

The purpose of this study was to evaluate the efficacy of a new therapeutic ointment (MEBO) in the treatment of partial thickness burns.

Methods: 40 patients received either topical treatment with Moist Exposed Burn Ointment (MEBO) or standard Flammazine treatment. All patients suffered from partial-thickness burn injuries (< 20% TBSA). Wounds were evaluated for 60 up to days regarding wound healing, water loss, inflammation, and pain alleviation.

Results: For transepidermal water loss, there was a difference of 2.3 gr/m²/h between MEBO, and Flammazine, favoring MEBO. However, this difference was not statistically significant (p=0.78). For all secondary efficacy parameter results were similar.

Conclusions: This study showed that MEBO ointment for topical treatment of burn injuries presents an attractive alternative for the topical treatment of limited partial thickness thermal burns.

Key words: MEBO, Flammazine, wound dressing, ointment, partial thickness burns, wound healing.

INTRODUCTION

Superficial, and partial-thickness burns usually heal within 2 weeks unless complications such as infection or chronic diseases occur [1]. Topical ointments such as Flammazine are commonly used for the treatment of superficial, and partial thickness burns to keep the wound environment in moist condition, decrease pain, and prevent bacterial infection [2, 3].

Moist exposed burn ointment (MEBO) is a Chinese burn ointment with a USA patented formulation since 1995 [4].

Unlike currently used topical products, the ointment produces the necessary moist environment for optimal healing, and re-epithelialization [5, 6]. It has been introduced two decades ago as a topical agent based on the methodology of moist exposed therapy

[7]. MEBO provides physiological moisture for optimized wound healing, and is also easy to apply irrespective of site, extent, and local condition of the wound. MEBO is pure herbal, natural in origin, containing β -sitosterol phellodendron amurense, scutellaria baicalensis, coptis chinensis, pheretima aspergillum, beeswax, and sesame oil. The pharmacological effects are attributable to: 1. β -sitosterol, isolated from Phellodendron amurense, 2. Flavonoids mainly baicalin, isolated from Scutellaria baicalensis, 3. Alkaloids, mainly berberine, isolated from Coptis chinensis, 4. Beeswax, and sesame oil.

Animal experiments proved a promotional effect of MEBO on wound healing. Oral administration of 5 g MEBO per kg body weight in rats produced no toxic effects. The primary skin irritation index of MEBO is 1.33, i.e. MEBO causes no dermal or ocular irritations. Side effects or medication interactions are not known for MEBO. MEBO reduces severe pain of burns, prevents shock, and reduces dermal infections. Wound healing is promoted by prevention of dermal water loss. Additionally, MEBO shows anti-inflammatory, anti-bacterial, and analgesics effects.

The goal of our study was to investigate, whether MEBO could serve as a potential alternative to common topical burn treatment in superficial, and partial-thickness burn injuries. Further hypotheses of the study were that a therapy with MEBO induces a fast wound healing accompanied by a low hazard of infection, and that the use of analgesics can be reduced or stopped.

MATERIAL AND METHODS

Methodology:

Randomized parallel group open mono-center pilot study. MEBO was compared to standard Flammazine treatment.

All clinical work conducted in the study was subject to Good Clinical Practice Rules, and all applicable local laws, and regulations.

The study was performed based on current ICH guidelines for Good Clinical Practice, Standard Operating Procedures (SOPs) of the Coordinating Center for

Clinical Trials Cologne (KKS), the Declaration of Helsinki 1964 (modified in Tokyo 1975, Venice 1983, and Hong Kong 1989, and Somerset West, Republic of South Africa, October 1996), and local regulations. The study was approved by the ethics committee of the University of Witten/Herdecke, Witten, Germany.

Informed consent was obtained prior to study participation in all patients, i.e. prior to randomization.

40 male, and female Patients with a mean age of 42.2 (20-65 years old) with no history of acute or chronic disease or current medications, suffering from limited partial-thickness burns less than 20% TBSA have been included into this study.

Inclusion criteria:

- Age at randomization visit ≥ 18 years, and ≤ 70 years
- 2nd degree thermal burns < 20 % TBSA ; start of therapy within 48 hours after day of burn.

Exclusion criteria:

- Non-conformance of an inclusion criterion, sepsis, severe vascular disease which affects micro circulation, expected limited life expectancy (e.g. advanced stage of cancer), severe injury which is in need of a special therapy,
- HIV positive patient, present renal insufficiency (creatinine > 2.0 mg/dl), present hepatic insufficiency (bilirubine > 0.2 mg/dl or AST > 200 U/l), pregnancy or lactation,
- primary immune deficiency, sustained systemic cytostatic or immune suppressing therapy or foreseeable need of such therapy, chemical burns, insulin dependent diabetes, known contraindication to ingredients of MEBO or Flammazine (e.g. sulfonamide contraindication), intake of β -sitosterol containing drugs within 1 week before inclusion, consumption of food containing high levels of phytosterole within 1 week before inclusion.

Patients were enrolled within 48 hours post- injury, and randomly divided into two groups: Study group received MEBO ointment topical wound treatment. The second group received standard Flammazine based therapy, and served as positive control.

Study treatments:

MEBO or Flammazine were administered to the patients until wound closure (about 2 – 3 weeks). The treatment was administered under supervision of an investigator: removal of the previous bandage, removal of necrotic tissue, and remainders of ointment, if necessary, using a wooden spatula, application of ointment (layer of at least 5 mm) using a wooden spatula, cover of wound with a sterile compress, synthetic cotton, and elastic bandage.

Dressing changes were performed once daily after removing superficial necrotic tissue with a sterile wooden spatula, and cleansing with Octenisept[®] (Schülke & Mayr GmbH, Norderstedt, Germany). Timepoints for analysis were set at day 2, 4, 6, 8, 10, 12, 30, and 60:

Wound Healing:

Wound healing was assessed by measuring the transepidermal water loss (TEWL) using a dermalab device

(Lawrenz GmbH, Bad Soden, Germany), and a wound closure index (calculated by clinical assessment, and photographic documentation of the epithelialization) was performed additionally.

Inflammatory response:

Evaluation of inflammatory response has been performed through clinical assessment, wound swabs, as well as blood parameters including white blood count, and C-reactive protein on day 0 and 8.

Pain assessment:

A pain assessment was performed using visual analogue scale 0 to 10 (0 = no pain; 1-2 = slight pain; 3-4 = mild pain; 5 = moderate pain; 6-9 = moderately severe pain; 10 = severe pain).

Statistical analysis:

The primary endpoint was defined as the change of epithelialization of the wound between baseline, and day 12. Epithelialization of the wound was measured as the difference of transepidermal water loss (TEWL) between intact skin, and the deepest part of the wound. The test planned for analysis of the primary endpoint was a two-sided Wilcoxon test at $\alpha = 5\%$.

Secondary endpoints were defined as the course of wound closure index (WCI), the patient's pain sensitivity, TEWL measured as area under the curve (AUC), expansion of wound, outcome of therapy, bacteriological evaluation, and used concomitant therapy/medication. The tests planned for analysis of the secondary endpoints were a two-sided Wilcoxon test at $\alpha = 5\%$, or a chi-square test, respectively. Concomitant medication/therapy was to be listed only.

Tertiary endpoints were defined as change of wound epithelialization and change of wound closure index (WCI). Only descriptive analyses were planned for those tertiary endpoints.

Since there was no information on the size of the expected effect before the start of the study, a sample size was chosen where at least information on a trend of the effects was to be expected. Additionally for ethical reasons the sample size was chosen low enough to minimize exposure of patients to possible risks.

To detect an effect size of $\delta / \sigma = 1$ with a power of $1 - \beta = 80\%$ using a two-sided significance level of $\alpha = 5\%$, 2 x 17 patients are needed. The sample size was fixed to 2 x 20 patients to compensate for possible dropouts.

All data were entered in a validated data management system (MACRO version 3.0, Infermed Ltd., London).

For statistical evaluation a two-sided Wilcoxon test at $\alpha = 5\%$, descriptive parametrical two-sided 95%-confidence interval was used.

RESULTS

Disposition of patients:

In total 40 patients were randomized in the study, with 20 patients in each treatment arm. The MEBO group included 6 female, and 14 male patients with an average of 5.3% (\pm) TBSA burn injury. The Flammazine group included 9 female, and 11 male patients with

two male patients undergoing skin graft treatment. The average TBSA in this group was 4.8%. 21 of all randomized patients completed the 60-days period of the study (MEBO: 12 patients, Flammazine: 9 patients). Throughout the 12-days period of the study, 12 patients withdraw from the study (MEBO: 4 patients, Flammazine: 8 patients). During the 60-days period of the study, 19 patients withdraw from the study (MEBO: 8 patients, Flammazine: 11 patients).

Data sets analysed:

Study medication was used at least once for all patients. That means the Evaluated-for-Safety (EFS) subset includes all randomized patients. For the primary efficacy parameter, defined as the difference between TEWL of the deepest part of the wound, and TEWL of intact skin in $\text{gr}/\text{m}^2/\text{h}$, baseline values at the day of randomization (day 0) were available for all patients. 3 patients had no post baseline assessment. The Intent-to-Treat (ITT) subset included all 40 randomized patients (MEBO: 20 patients, Flammazine: 20 patients). According to the study protocol, patients who changed the study treatment during the study should be excluded from the Treated-per-Protocol (TPP) subset. However, there were no treatment changes in study treatment during study conduct period, and therefore all randomized patients were valid for TPP subset, i.e. all 3 subsets (EFS, ITT, and TPP) were equal. In the following the title "All Randomized Patients" subset will be used for all other subsets like EFS, ITT, and TPP.

Demographic and other baseline characteristics:

The mean/median values of the demographic parameters gender, age at randomization, weight and height were similar between the treatment groups. About 65% of the patients were females. The mean/median age in the study was 39/40 years at randomization. Patient's weight was in mean/median about 75/78 kg, patient's height was 173/171 cm. In total 48% of patients were smoker, and 1 patient in the Flammazine group informed about drug intake. Alcohol use was specified as occasionally/moderate for 78% of the patients, and 22% of the patients informed about no alcohol use. Mean/median systolic blood pressure at baseline was 120/120 mmHg, the mean/median diastolic blood pressure at baseline was 79/80 mmHg, and the mean/median pulse was 76/75 bpm. 53% of the patients had light type of skin, 37% medium type of skin, and 10% dark type of skin.

Extent of burns was in mean/median 4.7/3.0 % TBSA (MEBO: 4.3/2.5 %, Flammazine: 5.0/3.0 %). Degree of burns 2A was in mean/median 3.6/2.0 % TBSA, degree of burns 2B was in mean/median 1.1/1.0 % TBSA, and degree of burns 3 in mean/ me-

dian was 0.2/0.0 % TBSA. Cause of injury was given as contact burns in 6 cases, as scald in 29 cases (MEBO: 14, Flammazine: 15), and as other in 5 cases.

Regarding all demographic and injury parameter, there were no conspicuous differences between treatment groups.

Trans epidermal water loss:

TEWL was assessed at day 0, day 2, day 4, day 6, day 8, day 10, and at day 12 as difference between TEWL of the deepest part of the wound, and TEWL of intact skin in $\text{gr}/\text{m}^2/\text{h}$. The difference between day 0, and last available post baseline value was defined as the primary time point for the confirmatory analysis in the ITT subset. Additionally, differences between day 0, and all other post baseline visits between MEBO, and Flammazine were examined. Transepidermal water loss in the MEBO group was 24.3 $\text{gr}/\text{m}^2/\text{h}$, whereas the Flammazine treated group showed 24.8 $\text{gr}/\text{m}^2/\text{h}$ on day 0. For the test of homogeneity at baseline, treatment groups were compared using Wilcoxon-Rank-Sum test, which resulted in a p-value of 0.95. That means that treatment groups were homogeneous regarding the TEWL at day 0. (Table 1 shows a difference of -0.5/10.4 $\text{gr}/\text{m}^2/\text{h}$ between the mean/median of MEBO, and Flammazine at day 0).

The Wilcoxon-Rank-Sum test for the difference between day 0, and the last post baseline value showed no difference between the treatment groups ($p = 0.78$). There was a mean/median difference of 2.3/2.9 $\text{gr}/\text{m}^2/\text{h}$ between MEBO, and Flammazine in advantage of MEBO. There was no statistically significant difference between MEBO, and Flammazine for the differences between day 0, and all other post baseline visits (Fig. 1).

TEWL was also analyzed as secondary efficacy parameter. The area under curve (AUC) between the x-axis, and the TEWL values from day 0 to day 12 per patient was calculated. The MEBO arm showed smaller mean/median AUC values compared to Flammazine (MEBO: 212/196; Flammazine: 240/207), but the difference between MEBO, and Flammazine was not statistically significant ($p = 0.84$).

Wound closure index (WCI):

The secondary efficacy parameter WCI was assessed at day 0, day 2, day 4, day 6, day 8, day 10, day 12, day 30, and at day 60 as percentage of the wound area relative from the wound area at day 0. For descriptive statistics at each visit, and at last post baseline visit, as well as for the difference between day 0, and last post baseline visit breakdown by treatment group

No clinical signs of infection or bacterial contamination occurred, and no positive wound swabs could be detected in the investigated wounds during this

Table 1. Descriptive results for TEWL in $\text{gr}/\text{m}^2/\text{h}$, all randomized patients (mean/median (standard deviation))

	MEBO N = 20	Flammazine N = 20
Day 0	24.3/28.7 (14.3)	24.8/18.3 (18.3)
Day 0 – last post baseline value	13.1/13.9 (16.9)	10.8/11.0 (19.5)

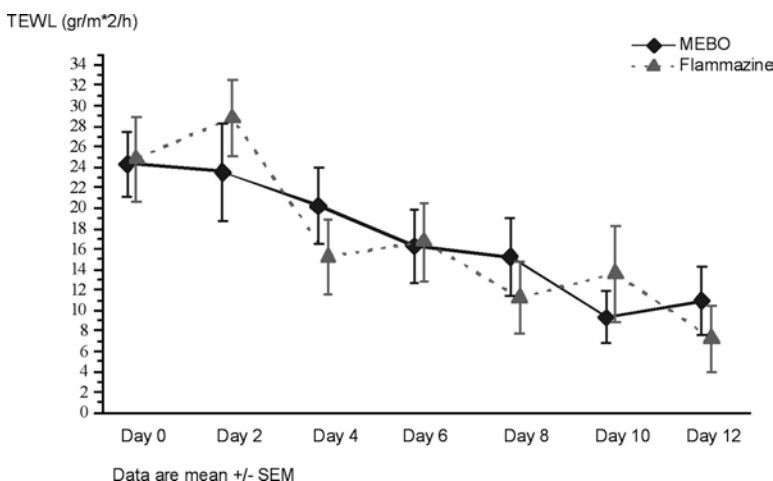


Fig. 1. Mean course of TEWL over the 12-days period of the study.

Table 2. Descriptive results for WCI in %, all randomized patients (mean/median (standard deviation))

	MEBO N = 20	Flammazine N = 20
Day 0	2/0 (7)	0/0 (0)
Day 0 – last post baseline value	83/100 (33)	70/100 (42)

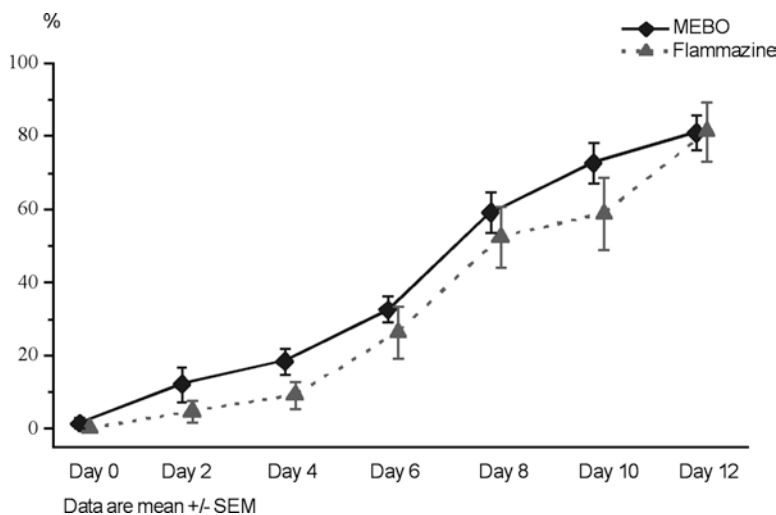


Fig. 2. Mean course of Wound Closure Index MEBO treated group versus Flammazine treated group over the 12-days period of the study. No significant differences could be detected between both groups.

study. For the test of homogeneity at baseline, treatment groups were compared using Wilcoxon-Rank-Sum test. The p-value was 0.34, and therefore treatment groups were homogeneous regarding WCI at day 0 (Table 2). The Wilcoxon-Rank-Sum test for the difference between day 0, and the last post baseline value showed no difference between the treatment groups ($p = 0.42$). There was a mean/median difference of 7/0 % between MEBO and Flammazine. No statistically significant difference between MEBO and Flammazine for the differences between day 0 and other post baseline visits with exception of the difference on day 4 was observed ($p < 0.05$, Fig. 2).

Patient's pain assessment:

The secondary efficacy parameter patient's pain sensitivity was assessed at day 0, day 2, day 4, day 6, day 8, day 10, and at day 12 as a score between 0 = no pain and 10 = maximum pain. The assessment of pain in

the patients according to the visual analogue scale showed a strong decrease in reported pain from an average of 5 (moderate pain) for both group to 3.8 for the MEBO study group and 3.5 for Flammazine respectively. The Wilcoxon-Rank-Sum test for the difference between day 0 and the last post baseline value showed no difference between the treatment groups ($p = 0.66$). There was a mean/median difference of 0.3/1.0 points between MEBO and Flammazine, favoring MEBO (Fig. 3).

Expansion of wound:

The secondary efficacy parameter expansion of wound was collected at day 0, day 2, day 4, day 6, day 8, day 10, day 12, day 30 and at day 60 in cm². Treatment groups were homogeneous at day 0 ($p = 0.28$). The Wilcoxon-Rank-Sum test for the difference between day 0 and the last post baseline value, showed no difference between the treatment groups ($p =$

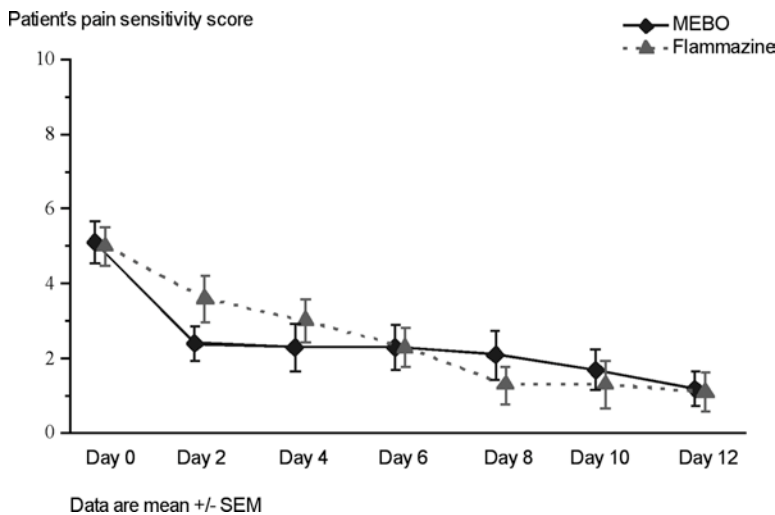


Fig. 3. Mean course of patient's pain sensitivity over the 12 days-period of the study, all randomized patients.

0.53). There was also no difference between MEBO and Flammazine group at any difference between day 0 and a post baseline visit.

Outcome of therapy:

The secondary efficacy parameter outcome of therapy was assessed at day 30 and at day 60 in two categories: wound area as normal/red/malfunction or wound area not cured and scar as no scar/atrophic/hypertrophic/keloid. Treatment groups were compared using the Chi-Square test. There was no statistically significant difference between both treatment groups regarding the absolute frequencies of outcome of therapy at both visits.

DISCUSSION

The local treatment of partial thickness burns currently uses different techniques and agents. Topical antimicrobial creams and ointments such as 1% Sulfadiazine cream, Bacitracin, Mafenide Acetate, Povidone Iodine cream, Polysporin ointment, Neomycin ointment, Vaseline impregnated gauze and others are used for dressing, and to prevent infections [1]. Biologic dressings such as xenogenic skin grafts, human allografts, and bismuth-impregnated petroleum gauze or bio-brane dressings are alternatives to these topical treatments. However, these dressings are cost intensive, difficult to apply and not easily available [7]. At present, Silver Sulfadiazine is known as the gold standard in local treatment of partial thickness burns. Therefore the assessment of Moist Exposed Burn Ointment (MEBO) as an alternative treatment for limited partial thickness thermal burns was compared to Silver Sulfadiazine in our study.

It is not exactly known how MEBO's ingredients act, but most probably its oil based ointment provides a moist environment, which may promote epithelial regeneration, anti-inflammatory effects and pain relief [7, 8].

MEBO's active component is β -sitosterol, based on beeswax, sesame oil and other components [9]. Clinical and experimental studies reported in the Chinese literature suggested, that the ointment reduces evaporation from the wound surface [10], Qu et al reported,

that it had a similar effect as Silver Sulfadiazine in controlling burn wound sepsis, and systemic infection with *Pseudomonas aeruginosa in vivo* [11, 12]. Finally, MEBO has been successfully used in treatment of local ulcers and chronic wounds 5.

This study was conducted to compare the efficacy of MEBO-ointment and Flammazine cream regarding the rate of wound healing, infection, and analgesia in partial thickness burns. 40 Patients between the ages of 20 and 65 were randomly assigned to receive either MEBO or Flammazine. These patients had partial-thickness thermal burns covering less or equal 20% of total burn surface area (TBSA). The mean age and total body surface area were very similar. This resulted in 20 patients in the MEBO group. The average age was 42.15 years (20- 54 years) and the average TBSA was 5.3%. The Flammazine group included also 20 patients, while two patients out of this group underwent surgery. The average age was 40.15 years (20-65) and the average TBSA was 4.8%.

In our study, MEBO shows matching results in partial-thickness burns covering equal or less than 20% TBSA with Flammazine or MEBO. Both of them show a similar course concerning wound healing. The analysis of the transepidermal water loss of the deepest spots of injury resulted in a balanced relation, while the superficial areas showed a better tendency towards the MEBO group up to day 10. In regards to pain relief, initially MEBO (day 0 to day 6) and later Flammazine (day 6 to day 12) showed a tendency to a better course. In addition, MEBO can be conventionally stored, does not need any additional dressing material and is less expensive than Flammazine.

We found no adverse events and drop-outs due to adverse events in our study.

Previous studies comparing MEBO with other conventional burn wound management, such as paraffin-impregnated gauze, transparent polyurethane adhesive film, silver sulfadiazine, 1% bacitracin ointment, sofratulle, and Tegaderm dressing, showed similar outcomes regarding wound healing rate, anti-inflammatory effect and pain relief [13-15]. In our clinical study the epithelial repair, scar quality, and cost effectiveness of MEBO - compared to Flammazine cream - seemed to be at least comparable with particular advantageous

characteristics [4, 6, 13, 16, 17]. In summary MEBO appears to be a valid and interesting alternative in the treatment of limited partial thickness thermal burns.

Acknowledgements: We sincerely thank Urs Harnischmacher and the Coordinating Center for Clinical Trials Cologne (KKSK) University Hospital Cologne, Germany, for expert statistical advice.

Conflict of interest statement: All authors disclose any financial or personal relationship that could influence the work for this study inappropriately.

REFERENCES

1. Kao, C. C. & Garner, W. L. Acute Burns. *Plast Reconstr Surg* 101, 2482-2493 (2000).
2. Stern, H. S. Silver sulphadiazine and the healing of partial thickness burns: a prospective clinical trial. *Br J Plast Surg* 42, 581-5 (1989).
3. Hauser, J. et al. [Local therapy of grade IIa burns: Efficacy and tolerability of a new hydrosome wound gel for the local treatment of grade IIa burns as compared with silver sulfadiazine ointment.]. *Unfallchirurg* 110, 988-994 (2007).
4. Atiyeh, B. S. et al. Benefit-cost analysis of moist exposed burn ointment. *Burns* 28, 659-63 (2002).
5. Atiyeh, B. S. et al. Efficacy of moist exposed burn ointment in the management of cutaneous wounds and ulcers: a multicenter pilot study. *Ann Plast Surg* 48, 226-7 (2002).
6. Ioannovich J, T. E., Tsoutsos D, Frangia K, Papalois A. Moist Exposed Burn Therapy: Evaluation of the Epithelial Repair Process. *Annals of Burns and Fire Disasters*, 13 (2000).
7. Schonfeld, N. Outpatient management of burns in children. *Pediatr Emerg Care* 6, 249-53 (1990).
8. Trung, L. Vietnamese Experience in the Treatment of Burns (The Gioi Publisher, Hanoi, 1996).
9. Yong, Y. in Report No. 99033191 (Institute of Science and Forensic Medicine, Department of Scientific Services, Health Science Division, Singapore).
10. Xu, R. The medicine of burns and ulcers, a general introduction. *Chinese J Burns Wounds Surf Ulcers* 1:68 (1989).
11. Qu, Y., Wang, YP, Qiu SC, Li BQ, Kang GY, Chen JR. Experimental study on the anti-infective effect of moist exposed Burn Ointment. *Chinese J Burns Wounds Surf Ulcers* 9, 4-9 (1997).
12. D, X. 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* 1, 76-7 (1989).
13. Ang, E. S. et al. Evaluating the role of alternative therapy in burn wound management: randomized trial comparing moist exposed burn ointment with conventional methods in the management of patients with second-degree burns. *MedGenMed* 3, 3 (2001).
14. Kogan L, L. A., Breiterman S, Eldad A. A Chinese Sesame-Oil-Based Ointment for Burns Compared with Bacitracin Ointment – An Animal Trial. *Annals of Burns and Fire Disasters* 1, 14 (2001).
15. Ang, E. et al. Pain control in a randomized, controlled, clinical trial comparing moist exposed burn ointment and conventional methods in patients with partial-thickness burns. *J Burn Care Rehabil* 24, 289-96 (2003).
16. Ang, E. S. et al. The role of alternative therapy in the management of partial thickness burns of the face--experience with the use of moist exposed burn ointment (MEBO) compared with silver sulphadiazine. *Ann Acad Med Singapore* 29, 7-10 (2000).
17. Atiyeh, B. S., El-Musa, K. A. & Dham, R. Scar quality and physiologic barrier function restoration after moist and moist-exposed dressings of partial-thickness wounds. *Dermatol Surg* 29, 14-20 (2003).

Received: August 28, 2008 / Accepted: September 10, 2008

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