Original Article

A Comparative Clinical Study of *Marham-e-raal* and Povidone-Iodine 5% Ointment in Nonhealing Ulcers

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Abstract

Introduction: Nonhealing ulcers are those that have not proceeded through timely and orderly reparation to produce anatomic and functional integrity. Povidone iodine is widely used ointment among physician and surgeons globally for wound dressings. In texts of Unani medicine literature, *Marham-e-raal* has been described as a potent ointment for gaining timely healing of wounds. The aim of this study is to compare the effects of povidone iodine and *Marham-e-raal* in nonhealing ulcers/chronic wounds. **Methods:** A randomized controlled study was carried out in the Department of Jarahat (Surgery) in National Institute of Unani Medicine, Bengaluru. A total of 45 subjects were included and randomized into *Marham-e-raal* and betadine dressing groups based on inclusion criteria. Dressing was done on daily basis and subjects were assessed on every 15 day from baseline to day 45 for primary outcomes (appearance of healthy granulation, epithelialization, and reduction in wound surface area) and secondary outcomes (decreases in tenderness score and depth of wound). **Results:** Nineteen out of 27 subjects in *Marham-e-raal* dressing group achieved complete healing as compared to one in povidone-iodine dressing group. There was significant reduction in wound surface area, median tenderness score and depth of wounds among subjects in *Marham-e-raal* dressing group at 0.05 level of significance. **Conclusion:** *Marham-e-raal* is an effective wound dressing and healing agent as compared to povidone-iodine ointment.

Keywords: *Marham-e-raal*, povidone iodine, unani medicine, wound dressing

Introduction

Nonhealing ulcers can be defined as those that do not show signs of healing with conservative therapy within 6 weeks.[1,2] A wound is a break in continuity of skin or mucus membrane due to molecular death.[3] Most wounds arise acutely and are trapped in one of the four healing stages and become nonhealing or chronic, owing to various causes.[4] Among them common causes are uncontrolled blood sugar, venous insufficiency, low hemoglobin level, low blood circulation, long-term contamination and unhygienic state, recurrent infection and bacterial load, and low oxygenation at wound site.[1,5,6]

The prevalence of chronic wounds in India was reported as 4.8/1000 population in 2004.[7] An increase in number of chronic wounds have been observed with increase in weight, diabetic morbidities, venous insufficiency, and advancing age.[8] Global wound care expenditure ranges from $13 billion to 15 billion annually.[9]

Marham-e-raal have been in use for years to treat acute and chronic wounds. It is a semi-liquid herbal and animal origin-drugs-based ointment prepared from *Kaat Hindi* (*Acacia catechu*), *Raal Hindi* (*Vateria Indica* Linn.), *Kafoor* (*Cinnamomum camphora*), *Mom zard* (Bees-wax) and *Roghan-e-gao* (Cow ghee/clarified butter).[10] As mentioned in Unani medicine texts, it helps gain healthy tissues and remove the dead ones from wound floor.[11] In India, most physicians and surgeons use povidone-iodine ointment and solutions for wound dressing.[12] Since there is no randomized controlled trial comparing the effects of *Marham-e-raal* with povidone-iodine ointment, we conducted this study to compare the effects of both.

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Methods

A comparative clinical study of *Marham-e-raal* and povidone iodine 5% ointment in nonhealing/chronic wounds was conducted in the inpatient Department of Jarahat (Surgery) section in our institute for 1½ year from June 2016. The institutional ethics committee of this institute approved this study. A total of 45 cases of chronic wounds were randomized using random number table into *Marham-e-raal* dressing group (Group-A, $n = 30$) and betadine 5% ointment dressing group (Group-B, $n = 15$). Cases were enrolled on the basis of inclusion criteria (both genders, wounds not healing for more than 6 weeks, age group 18–60 years) after their informed written consent. Cases diagnosed with gangrenous and malignant ulcers or having any severe systemic disease were excluded from the study. Figure 1 explains CONSORT flow diagram.

All cases underwent detailed clinical history, and physical examination including local clinical examination of wound to rule out possible cause (s) of wound. Following initial screening, routine investigations such as hemogram, blood sugar level, screening for human immune virus and hepatitis-B surface antigen, X-ray of affected site, and edge biopsy of ulcer (if required) were advised. Comorbidities such as diabetes mellitus, hypertension, cellulitis, and poor nutritional conditions were managed conservatively. *Marham-e-raal* was prepared in pharmacy of this institute using Hamdard Pharmacopoeae[10] following procurement of its contents from authorized crude drug market of Bengaluru. All raw drugs; *Kaat Hindi* (*Acacia catechu*), *Raal Hindi* (*Vateria indica* L.), *Kafoor* (*C. camphora*), and *Mom zard* (Beeswax) were identified and authenticated as original by center for repository of medicinal resources, Bengaluru. Povidone iodine was purchased as brand name betadine 5% ointment from an authorized retailer. The wound surface was cleaned by irrigation with normal saline. Unhealthy and necrosed tissue (if present) was debrided to create a fresh base for neo-granulations. Fibrosed and callous edges (if present) were removed for neo-epithelialization to occur early. Sterile gauze impregnated with ointment (*Marham-e-raal* for Group-A cases, and betadine for Group-B cases) was placed on wound, covered with sterile cotton pad, then dry gauze piece, and wrapped with roller bandage. The dressing was changed daily and the wound was assessed on every 15 day till day 45. The assessment was done for primary outcomes (complete healing of wound/or reduction in wound size >50%, appearance of granulations and epithelialization) and secondary outcomes (reduction in depth of wound and tenderness). Wound was defined as completely healed when its surface was fully epithelialized. To measure wound size, a tracing paper was used, placed on wound, and margins were marked with pencil, maximum length and breadth of outlined margins were measured on graph paper assuming one small square and large square equal to 1 mm and 1 cm, respectively. Length and breadth were multiplied to get surface area of wound in square centimeter. Red granulations were considered as a healthy one. Pale granulation was considered as slow growing and yellowish as unhealthy. Neo epithelialization was defined as reddish-blue epithelium growing from margins to the center of wound. Depth was marked on the strip of tracing paper after it was dropped into wound by its edge. The tenderness score was graded as 0; no tenderness, 1; mild, 2; moderate, and 3; severe.

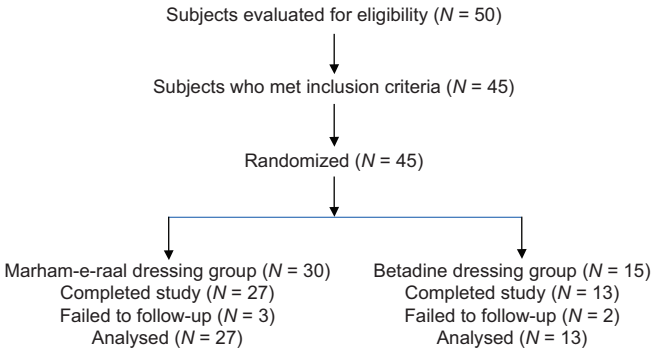

Figure 1: CONSORT flow diagram

Statistics

Descriptive and inferential statistics have been carried out. Continuous and categorical data have been presented as mean ± standard deviation and number (percentage), respectively. Paired *t*-test was applied for the significance of study on continuous data within group while unpaired *t*-test between the groups. The Chi-square test was used on categorical data between two groups. SPSS 18.0 software manufactured by IBM, New York, United States was used for statistics.

Results

Forty cases completed the follow-up period. Three cases in Group-A and two cases in Group-B failed to follow-up.

The mean age was 45.6 ± 10.8 years in Group-A and 51.8 ± 9.2 years in Group-B. A male predominance was recorded in both groups. 93.3% of cases were found to be lying in lower middle and upper lower class of socioeconomic status. 77.5% of cases in both groups were found to have chronic wounds for 6 months or less duration whereas, 22.5% cases had chronic wounds for more than 6 months' duration. Fifty percent of cases in both groups had chronic wounds located below ankle and another 50% of cases above ankle.

Majority of cases (42.5%) in both groups had chronic wounds of diabetic etiology followed by traumatic etiology (20%) and venous etiology (17.5%).

Two groups were comparable in terms of age, socioeconomic status, chronicity of wound, etiology, and site. Table 1 describes baseline characteristics. Two groups were comparable at baseline in terms of primary and secondary outcomes measures ($P > 0.05$).

Seventy percent of cases in Group-A and 7.7% of cases in Group-B achieved complete healing at day 45 ($P < 0.001$). The mean area of wounds in *Marham-e-raal* dressing group

was 32.53 ± 46.31 cm^2 at day 0, which reduced to 8.94 ± 24.98 cm^2 at day 45. In Group-B, the mean area at baseline was 38.68 ± 51.71 cm^2, which reduced to 21.28 ± 47.35 cm^2 at day 45. Figure 2 explains comparative reduction in surface area of wounds over the time in two groups. On intergroup analysis, a reduction of 72.51% in Group-A and 44.98% in Group-B in surface area of wounds was observed at endpoint ($P < 0.005$).

The mean percentage of granulations in Group-A was 32.71% ±38.61% at baseline, which increased to 99.74% ±1.34% at endpoint ($P < 0.001$). In Group-B, the mean percentage of granulations was 36.18% ±29.41% at baseline, which increased to 74.30% ±36.31% at endpoint ($P < 0.05$). The progression of granulations over the time in two groups is understood in Figure 3.

Mean epithelialization at baseline was 3.5% ±8.0% in *Marham-e-raal* dressing group, which increased to 85.20% ± 28.47% at day 45 ($P < 0.0001$). In povidone-iodine dressing group, mean epithelialization at day 0 was 3.0% ±7.97%, which increased to 59.49% ± 32.83% at day 45 ($P < 0.01$). A comparison between progression of epithelialization in two groups have been depicted in Figure 4.

The median tenderness score at baseline was 2.5 on 0–3 scale in *Marham-e-raal* dressing group, which reduced to 0 at day 45. Cases of povidone-iodine dressing group experienced no reduction in median tenderness score from 1 at baseline to 1 at day 45.

Mean depth of ulcers at day 0 was 0.523 ± 0.61 cm in Group-A, which reduced to 0.037 ± 0.11 cm at day 45. Cases of Group-B experienced a reduction in depth from 0.91±0.53 cm at day 0 to 0.30±0.45 cm on day 45. Intergroup analysis revealed a significant difference in the percentage of depth reduction in two groups (92.92% vs. 67.03%); $P < 0.05$. Table 2 explains primary and secondary outcomes of two groups studied.

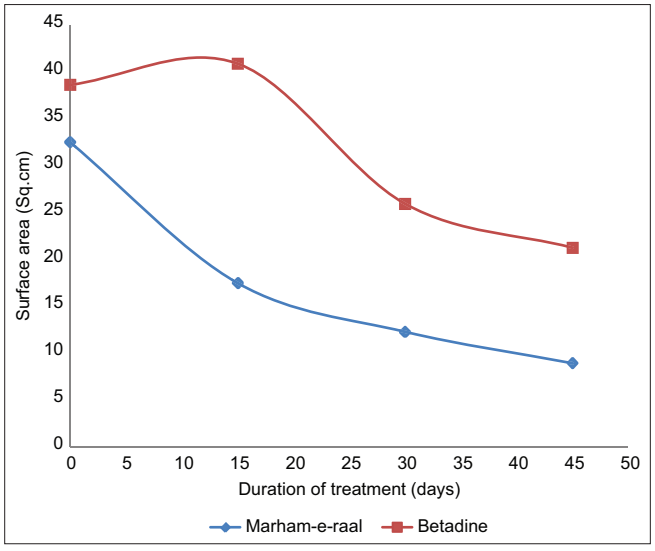

Figure 2: Relative reduction in mean surface area of wounds in two groups studied. The blue line indicates progressive reduction during the course of treatment in *Marham-e-raal* dressing group. Red line indicates cases of povidone-iodine group

Discussion

In the present study, there was a total of 69 wounds among 27 cases in Group-A at baseline and 61 wounds (88.40%) healed completely at day 45. Wainstein, *et al*. observed that 81% of wounds had achieved complete closure by ozone therapy.[13] Complete closure observed another study by

Table 1: Baseline characteristics of *Marham-e-raal* and betadine dressing groups

Variables	Marham-e-raal dressing group ($n=27$), n (%)	Betadine dressing group ($n=13$), n (%)
Age (years)	45.6±10.8	51.87±9.2
Gender		
Male	23 (85.18)	10 (76.92)
Female	4 (14.81)	3 (23.07)
Duration of wound (months)		
≤6	22 (81.48)	9 (69.23)
>6	5 (18.51)	4 (30.76)
Site		
Below ankle	15 (55.55)	5 (38.46)
Above ankle	12 (44.44)	8 (61.53)
Wound etiology		
Diabetic	11 (40.74)	6 (46.15)
Traumatic	5 (18.51)	3 (23.07)
Venous	3 (11.11)	4 (30.77)
Vasculitic	2 (7.4)	0
Arterial	2 (7.4)	0
Chemical burn	1 (3.7)	0
Pyoderma-gangrenosum	1 (3.7)	0
Callous ulcer	1 (3.7)	0
Lymphatic	1 (3.7)	0

Continuous data have been presented as mean±SD and categorical data as n (%). SD: Standard deviation

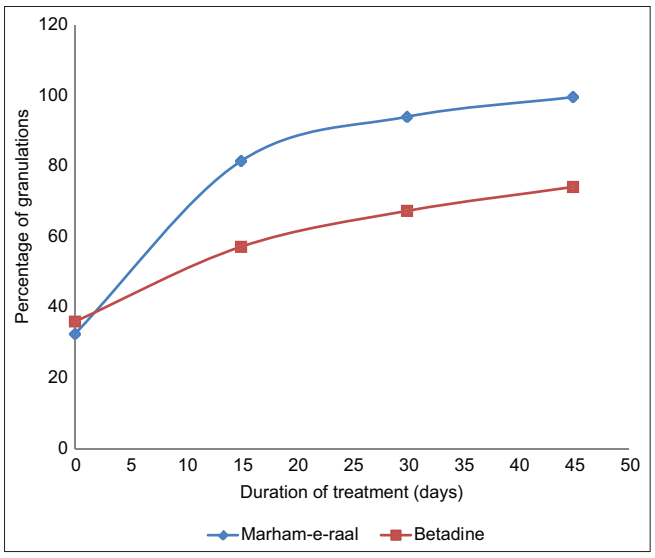

Figure 3: Relative progression of granulations in two groups studied. Blue line indicates mean progression during treatment in *Marham-e-raal* dressing group. Red line indicates povidone iodine dressing group

Table 2: Primary and secondary outcomes in two groups studied

Parameters	Group studied	Day-0	Day-45	*P*
Granulations (%)	*Marham-e-raal* dressing group	32.71±38.61	99.74±1.34	<0.001
	Povidone-iodine dressing group	36.18±29.42	74.30±36.31	<0.05
Epithelialization (%)	*Marham-e-raal* dressing group	3.5±8.0	85.20±28.47	<0.0001
	Povidone-iodine dressing group	3.0±7.97	59.49±32.83	<0.01
Surface area (cm^2)	*Marham-e-raal* dressing group	32.53±46.31	8.94±24.98	<0.0001
	Povidone-iodine dressing group	38.68±51.71	21.28±47.35	<0.05
Depth of ulcers (cm)	*Marham-e-raal* dressing group	0.52±0.61	0.037±0.11	<0.001
	Povidone-iodine dressing group	0.91±0.53	0.30±0.45	<0.005
Tenderness score (median)	*Marham-e-raal* dressing group	2.5	0	<0.001
	Povidone-iodine dressing group	1	1	>0.05

Continuous data have been presented as mean±SD. SD: Standard deviation

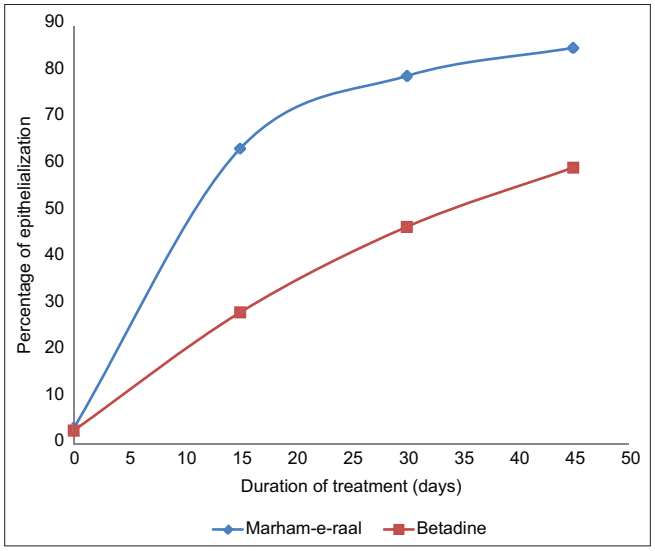

Figure 4: Relative progression in epithelialization over the time in two groups studied. Blue line indicates progressive increase in epithelialization in *Marham-e-raal* dressing group. Red line indicates povidone-iodine dressing group

hyperbaric oxygen therapy was in 52% and 66% wounds respectively.[14]

96.29% of cases in *Marham-e-raal* dressing group and 46.15% cases in betadine dressing group achieved healthy granulations by day-45. Nain *et al.*[15] and Blume *et al.*[16] observed healthy granulations by negative pressure wound therapy in 75% and 70.8% cases, respectively.

In the present study, 70.1% of cases (20 out of 27) in *Marham-e-raal* dressing group and 38.46% (5 out of 13) cases in betadine dressing group achieved 100% epithelialization on day 45. Oliveira *et al.* concluded in their study that 65% cases had achieved 100% epithelialization by HBOT within 16 weeks.[17] In an another study, 100% epithelialization in 68% cases of diabetic foot was observed by HBOT within 12 weeks.[18]

In a review of clinical trials conducted by Kramer in 1999, it was concluded that povidone-iodine did not promote good healing and did not reduce microbial wound infection.[19]

Results of *Marham-e-raal* found in this trial correlate with texts in Unani literature. The wound healing results of *Marham-e-raal* observed in our study maybe a combined effect of antibacterial, analgesic, antifungal, rubefacient, and putridity elimination and flesh regeneration properties contained in it. Crude beeswax has been found effective against both Gram-positive and negative bacteria.[20] Linalool and cineole, phytoconstituents of *Kafoor* (*C. camphora*), possess antifungal and antibacterial effects; linalool against *Candida albicans*, *Escherichia coli*, and *Staphylococcus aureus*[21] and cineole against Klebsiella spp., proteus spp., Pseudomonas spp., *E. coli*, and *S. aureus*.[22]

Camphor and phytol, major components of terpene, found in *Kaat Hindi* (*Acacia catechu*) are related with antimicrobial properties against bacillus subtilis, *S. aureus*, salmonella typhi, *E. coli*, *Pseudomonas aeruginosa,* and *C. albicans*.[23] As 70% of cases in *Marham-e-raal* dressing group experienced no pain at endpoint of the study, the result may reflect a combined effect of anti-inflammatory, antinociceptive, and local analgesic properties. Several authors have found in their review that camphor had reduced pain by activating some transient receptor potentials such as TRPV1, TRPV3, TRPM8, and inhibiting TRPA1.[24,25] Anand David *et al.* In their overviews concluded that quercetin inhibits inflammatory enzymes such as cyclooxygenase and lipooxygenase thereby decreasing inflammatory mediators such as prostaglandins and leukotrienes.[26] Quercetin is a flavonoid found in *Kaat hindi* (*Acacia catechu*). de Cássia da Silveira E Sá *et al.*, and Kozioł *et al.* in their overviews observed that monoterpene was a potent anti-inflammatory molecule.[27,28] Monoterpene is another biological active compound found in *Raal hindi* (*Vateria indica* Linn.). Catechin, a flavonoid in *Kaat hindi* (*Acacia catechu*) has an effect on endothelium-dependent vasodilatation which helps maintain good blood flow.[29,30] Xiong *et al.* observed in their study that borneol helps regenerate flesh and remove putridity thereby proving to be a healing agent.[31] Borneol is one of the phytoconstituents of *Kafoor* (*C. camphora*).

Conclusion

Cases of *Marham-e-raal* dressing group experienced better outcomes in terms of healthy granulations, reduction in surface

area, and median tenderness score. The Number of complete healings was more in *Marham-e-raal* dressing group than povidone-iodine dressing group.

Limitations of study

Sample size was short in the present study. There was no blinding, no multicentric trial, and not all cases in the two groups completed the follow-up period. No attempt was made to identify and quantify the microorganisms on the wound site.

Financial support and sponsorship

The national Institute of Unani Medicine (NIUM), the Ministry of AYUSH, supported this study. They provided dressing materials and funded expenditures for drugs identification and authentication. The present study has been carried out at NIUM.

Conflicts of interest

There are no conflicts of interest.

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