MEBO JOURNAL

Volume 1
Number 2
April 2022

MEBO JOURNAL

Striving for

Human Regenerative Life

MEBO JOURNAL

Latest Clinical Trial

Website
en.mebo.com

Facebook
@meboglobal

Twitter
@MEBOInternatio1

Instagram
@meboglobalcommunity

MEBO JOURNAL

Academic Express

Hindawi
International Journal of Dentistry
Volume 2021, Article ID 2548665, 10 pages
https://doi.org/10.1155/2021/2548665

Research Article

Clinical Comparison of MEBO and Hyaluronic Acid Gel in the Management of Pain after Free Gingival Graft Harvesting: A Randomized Clinical Trial

Ahmed Hassan,[1,2] Enji Ahmed,[1,2] Dalia Ghalwash,[2] and Azza Ezz Elarab[1]

[1]*Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University, Postal Code: 11553, Cairo, Egypt*
[2]*Oral Medicine and Periodontology Department, Faculty of Dentistry, The British University in Egypt, Postal Code: 11837, El- Sherouk, Egypt*

Correspondence should be addressed to Ahmed Hassan; ahmed.hasan@bue.edu.eg

Received 20 May 2021; Accepted 6 August 2021; Published 14 August 2021

Academic Editor: Vincenzo Iorio Siciliano

Copyright © 2021 Ahmed Hassan et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Aim. This study aimed to compare the effect of MEBO versus 0.2% hyaluronic acid gel (Gengigel®) applied to the palatal donor site on postoperative pain reduction and wound healing after free gingival graft harvesting. *Methodology*. Thirty-nine patients with different mucogingival defects were included in this study for harvesting a free gingival graft (FGG) for soft tissue augmentation. Patients were randomly assigned into three equal groups: group I (MEBO), group II (0.2% HA Gengigel®), and group III (control). Postoperative pain was recorded by using the Visual Analogue Scale (VAS). Analgesic consumption was recorded for 7 days postoperatively. Wound size was measured at baseline and on days 3, 7, 14, and 21. Postoperative healing of the palatal wound was assessed by the VAS score for color match on days 3, 7, 14, 21, and 42. *Results*. Results of this study showed significant postoperative pain reduction for the three groups; MEBO showed statistically significant less VAS score compared to the other two groups, while HA showed statistically significant less VAS score compared to the control group. Both MEBO and HA showed statistically significant less total analgesic consumption. No statistically significant difference was observed between groups for wound size. MEBO showed statistically significant higher VAS for color match. *Conclusions*. Both treatment modalities could reduce postoperative pain following harvesting of FGG and improve the palatal wound healing. However, MEBO showed better outcomes in terms of postoperative pain and color match.

1. Introduction

Surgical treatment of mucogingival defects aims at obtaining soft tissue coverage of exposed root surfaces and/or augmentation of gingival tissue dimensions. Autogenous gingival grafts are still considered the gold-standard procedure in both single and multiple root coverage with proven clinical success [1, 2], with the palate being the most frequent donor site for grafts [3].

A free gingival graft is considered to be the most reliable method for increasing the attached gingiva and is one of the most frequently used techniques [4]. This treatment modality is used to increase the keratinized gingiva, prevent and treat gingival recession, improve esthetics, reduce or eliminate root hypersensitivity, increase the vestibular depth, and ameliorate pigmented and pathologic oral mucosa [5].

A whole free gingival graft (FGG) may be used at the recipient site or the graft may be deepithelialized after being harvested from the palate to get a subepithelial connective tissue graft (SCTG) [6]. Both techniques can be used to increase tissue thickness, to cover gingival recession, and/or to prevent the development and progression of gingival recession [2].

The palate is the most common donor site for gingival grafts [7]. FGG is considered superior to synthetic or allogenic grafts owing to its autogenous nature, which yield them excellent clinical results [8]. However, harvesting a FGG leaves an open wound at the donor site, which takes two to four weeks to heal. Patients' postoperative pain and discomfort and the delayed wound-healing in the palate are of great concern [4].

Recently, patients' subjective assessment of medical procedures has gained importance in healthcare; thus patients' expectations might be crucial in the selection of treatment measures [7].

The Moist Exposed Burn Ointment (MEBO) is a Chinese burn ointment with a registered USA patented formulation since 1995. MEBO is a pure herbal extract, which is natural in origin, containing beta-sitosterol, *Phellodendron amurense*, *Scutellaria baicalensis*, *Coptis chinensis*, *Pheretima aspergillum*, Beeswax, and sesame oil [9]. MEBO was claimed to have analgesic and antibacterial effect, while its beta-sitosterol component possesses an anti-inflammatory effect [10]. Sesame oil extract has a beneficial role in wound-healing, and its wound-healing properties may be due to the free radical scavenging and its antioxidant capacity [11].

0.2% hyaluronic acid (HA) gel was known for hygroscopicity that allows it to maintain conformational stiffness and to retain water [12]. Another major feature is viscoelasticity that provides stability and elasticity to tissues and delays penetration of viruses and bacteria [13]. In periodontology, HA has been advocated as monotherapy [14] or as an adjunct to nonsurgical and/or surgical periodontal treatment to reduce inflammation and promote wound-healing [15].

Both MEBO [16] and HA [12] have shown promising results in promoting healing and postoperative pain reduction of intraoral wounds that heal by secondary intention. Therefore, the aim of this study was to compare the effect of MEBO versus 0.2% hyaluronic acid gel (Gengigel®) applied to palatal donor site on postoperative pain reduction and wound-healing after free gingival graft harvesting.

2. Subjects and Methods

This study was conducted in the Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University, Egypt. Thirty-nine subjects were selected from the outpatient clinic, Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University, between March 2019 and September 2020. This clinical trial was registered in U.S. National Institutes of Health Clinical Trials Registry (Clinicaltrials.gov ID: NCT03728244).

The study protocol was approved by the Ethics Committee of Scientific Research, Faculty of Dentistry, Cairo University, on 25 December 2018 (approval number: 18-12-17). Sample size calculation was achieved using PS program (Power and Sample Size program: biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize) and approved by medical biostatistics unit, Cairo University, in October 2018.

Inclusion criteria included the following: patients with mucogingival defects scheduled for free gingival graft, systemically healthy patients, and patients with good oral hygiene.

Exclusion criteria included the following: patients with any uncontrolled local or systemic disease where periodontal plastic surgery might be contraindicated, history of recent periodontal surgery at the donor site, smokers, pregnancy and lactation, patients allergic to the used agents, severe gagging reflex, and inability or unwillingness to provide informed consent.

Patients were randomly assigned with simple randomization using computer-generated random numbers done by the cosupervisor E. A. into three equal groups; in group I, MEBO was applied to the palatal donor site and covered with periodontal pack; in group II, 0.2% hyaluronic acid gel (Gengigel®) was applied to the palatal donor site and covered with periodontal pack; and, in group III (control group), palatal donor site was covered with periodontal pack only.

The palatal donor site in the three groups was prepared, and then the decision of which drug to be used to protect the denuded area was made according to the randomized numbers in a sequentially numbered, opaque sealed envelope. The number was picked by the cosupervisor D. G.

3. Treatment Protocol

3.1. Presurgical Phase. Full-mouth supragingival and subgingival debridement was performed using ultrasonic device and Gracey's curettes. Proper oral hygiene instructions were given to the patients including brushing teeth 2 times daily by soft toothbrush.

Chemical plaque control with 0.125% Chlorhexidine HCL mouthwash was prescribed to be used twice daily for 2 weeks.

3.2. Preparation of the Recipient Site. In the three groups, preparation of the recipient site was performed according to Zucchelli and Mounssif [17] as follows: Two horizontal incisions were performed, being traced 1 mm coronal to the cementoenamel junction (CEJ) and extending 3 mm mesiodistally. Two vertical incisions diverging slightly in a coronoapical direction and extending 4 to 5 mm beyond mucogingival junction were performed. The trapezoidal area thus outlined was dissected using split-thickness incision to expose 3 to 4 mm of the apical periosteum to bone dehiscence. The soft tissue consisting mainly of alveolar mucosa that covered the recipient bed was removed with surgical scissors.

4. Harvesting the Free Gingival Graft (FGG) from the Palate

In all of the three groups, FGG was harvested from the palate as described by Zucchelli et al. [3] as follows: Two horizontal incisions were performed, where the coronal incision was 2 mm apical to the gingival margin of the adjacent teeth and two vertical incisions were traced to delineate the area to be grafted. The blade was inserted along the coronal horizontal incision at one edge perpendicular to the bone and once the adequate thickness of the graft was obtained which was 1–1.5 mm, the direction of the blade was changed to be parallel to the hard palate and moved in mesiodistal direction elevating the graft at one side until the graft became completely detached from the palate. The thickness of the graft was maintained uniform while proceeding apically with the blade. Care was taken to avoid removing the palatal periosteum. Once the graft was harvested, it was placed on a sterile gauze with saline to avoid the shrinkage of the graft. The FGG was positioned and firmly adapted to the recipient area and stabilized with two simple interrupted periosteal sutures and a criss-cross sling suture using 5–0 Vicryl suture material (M-Nature sutures; International Sutures Manufacturing Co., Egypt.) and Castroviejo Needle Holder (Nordent Manufacturing Inc., USA) [17].

5. Management of the Palatal Wound

After harvesting the FGG, the bleeding was controlled by application of pressure using sterile gauze for 5 min until it stopped.

5.1. Group I (MEBO). MEBO (Julphar®, Ras Al Khaimah, United Arab Emirates) was applied using sterile plastic syringe, and the palatal wound was immediately covered by noneugenol periodontal pack (Pericem) (Pericem cement quengco, Non-Eugenol, Italy). Three days postoperatively, the patients were recalled, and the periodontal pack was removed for evaluating the healing of the palatal wound. Then MEBO was reapplied again, and the palatal donor site was repacked with periodontal pack.

5.2. Group II (0.2% HA). 0.2% hyaluronic acid gel (Gengigel®, Ricerfarma S.r.l., Milano, Italy) was applied using sterile plastic syringe and the palatal wound was immediately covered by noneugenol periodontal pack (Pericem). Three days postoperatively, the patients were recalled, and the periodontal pack was removed for evaluating the healing of the palatal wound. Then 0.2% HA gel was reapplied again, and the palatal donor site was repacked with periodontal pack.

5.3. Group III (Control Group). The palatal wound was immediately covered by noneugenol periodontal pack (Pericem). Three days postoperatively, the patients were recalled, and the periodontal pack was removed for evaluating the healing of the palatal wound and then repacked with periodontal pack.

5.4. Postsurgical Protocol. The periodontal pack was finally removed after 1 week [3]. Patients received 600 mg Ibuprofen (Abbott, Egypt) on surgery day for pain control, and they were instructed to take Ibuprofen 600 mg only if needed and to count the number of pills taken for the purpose of indirect pain measurement via mean consumption of analgesics (mg). Patients were advised to rinse with antiseptic mouth rinse (0.12% Chlorhexidine HCL) twice daily for 1 minute for a period of two weeks after the surgery. Patients were instructed to avoid any hard brushing and trauma to the surgical site for 3 weeks. Three weeks postsurgically, the patients were instructed to gently brush the operated area with a soft toothbrush using circular scrub technique. The sutures were removed fourteen days after the surgery from the recipient site that was augmented by the FGG. Clinical photographs were taken for the palatal wound on day 3, then after 1, 2, and 3 weeks, and finally on day 42 postsurgically for evaluation of the healing of the palatal wound at different time intervals; see Figures 1 and 2.

5.5. Primary Outcome

5.5.1. Postoperative Pain (Visual Analogue Scale). Pain score was reported by the patient directly through Visual Analogue Scale (VAS) score (between 0 and 10; 0: no pain, 1: minimal pain, 5: moderate pain, and 10: severe pain) [18]. VAS was recorded daily for 1 week [7].

5.5.2. Postoperative Pain (Mean Consumption of Analgesics). Postoperative pain was assessed indirectly by mean consumption of analgesics for 7 days postoperatively, recorded in milligrams [3].

5.6. Secondary Outcomes

5.6.1. Wound Size. Wound size was measured using (UNC-15) periodontal probe to the nearest measurement of 0.5 mm on surgery day [19]. Wound-tracing was done on days 3, 7, 14, and 21 via planimetric method, a transparent film was placed on top of the wound, and the margin of the wound was traced with a pen. The tracing was subsequently placed on a metric grid and wound area was determined by counting the number of squares in the grid covered by the traced area [20].

5.6.2. Color Match. On day 3, day 7, day 14, day 21, and day 42, the color of the palatal mucosa was assessed by comparing it with that of the adjacent and opposite side by using the objective VAS (VAS score 0–10) represented by a continuous line by the main supervisor who was blinded to the treatment group assignment. A score of 0 indicates no color match, and a score of 10 indicates excellent color match with the adjacent tissues [12].

6. Results

6.1. Demographic Data. The study population in this randomized, controlled, parallel-grouped clinical trial included 39 patients with different mucogingival defects that required harvesting a free gingival graft (FGG). Only 30 patients completed their follow-up period. The data of all subjects who were examined and completed their follow-ups in the present study were recorded, tabulated, and subjected to statistical analysis. This study was reported according to CONSORT guidelines [21]; see Figure 3.

Females constituted 80% and males 20% of patients in group I, while in group II and group III 90% of patients were females and 10% were males, with no statistically significant difference between groups ($p = 0.749$). Patient's age ranged from 24 to 49 years, and the mean ± SD age of group I was 40.60 ± 2.02, that of group II was 37.80 ± 2.65, and that of group III was 34.20 ± 2.19, with no statistically significant difference between groups ($p = 0.163$).

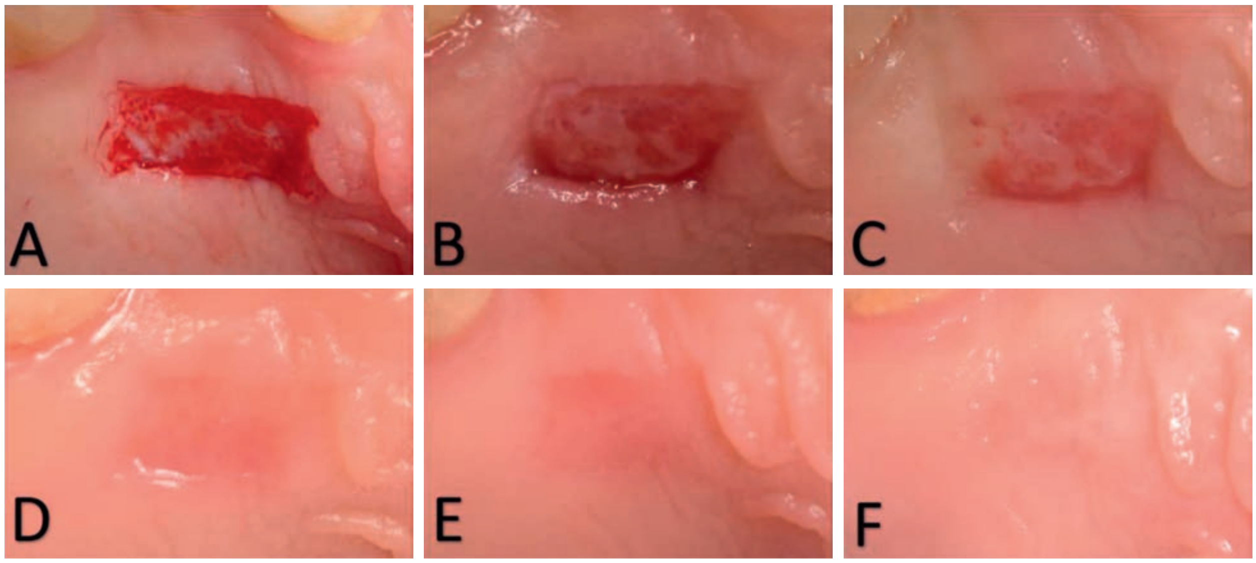

Figure 1: Clinical photographs showing palatal wound healing for the MEBO group: (a) day 0, (b) day 3, (c) day 7, (d) day 14, (e) day 21, and (f) day 42.

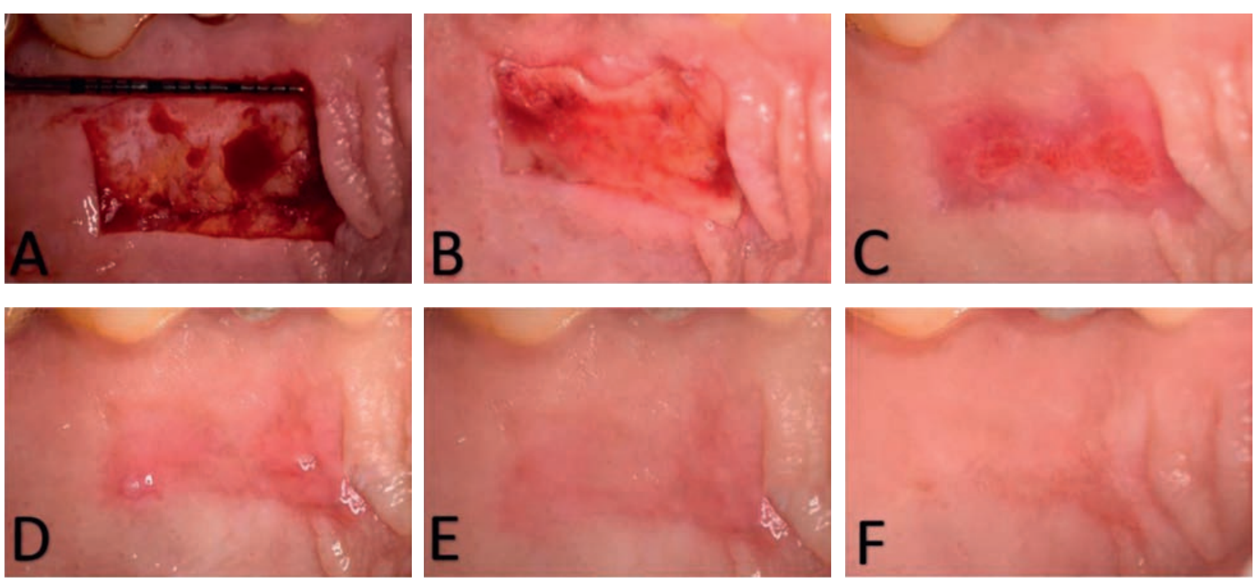

Figure 2: Clinical photographs showing palatal wound healing for the HA group: (a) day 0, (b) day 3, (c) day 7, (d) day 14, (e) day 21, and (f) day 42.

6.2. Primary Outcome

6.2.1. Postoperative Pain (Visual Analogue Scale (VAS)). Regarding median and range values for intragroup comparison in postoperative pain measured by VAS daily from day 1 to day 7 within each group, there was a statistically significant decrease in VAS by time in the three groups.

Median and range values of intergroup comparison in postoperative pain measured by VAS daily from day 1 to day 7 in the three groups are presented in Table 1. On days 1 and 2, there was no statistically significant difference between the three groups with the highest median and range for VAS pain score being recorded in group III. On day 3, there was a statistically significant difference between the three groups in pain score being statistically significantly lower in group I and statistically significantly higher in group III. From day 4 to day 6, there was no statistically significant difference between the three groups with the highest median and range for VAS pain score being recorded in group III. On day 7, all patients in the three groups reported no pain at all.

6.2.2. Postoperative Pain (Analgesic Consumption in mg). Median and range values for intragroup comparison in postoperative pain measured by analgesic consumption (mg) daily from day 1 to day 7 in the three groups showed that the three studied groups showed statistically significant decrease in analgesic consumption from day 1 to day 7.

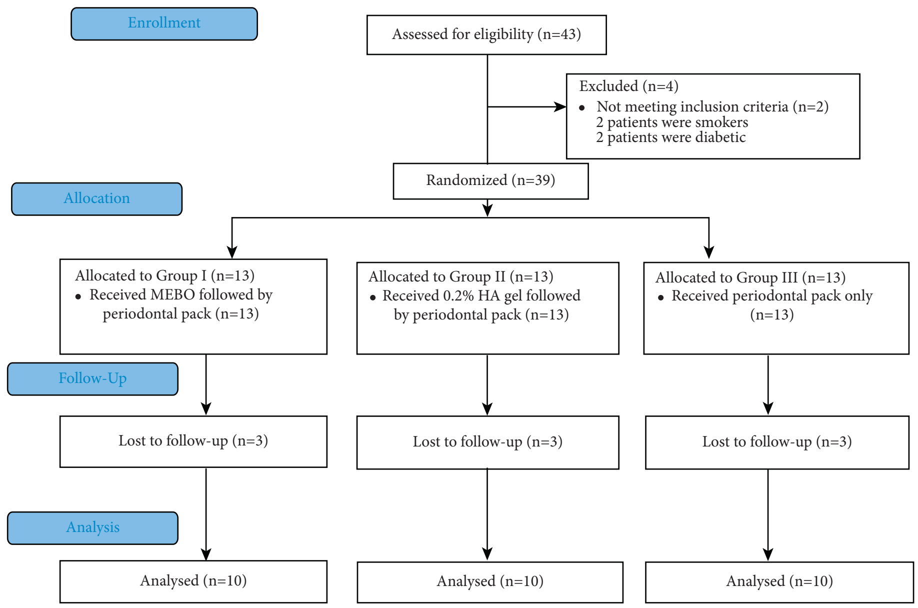

Figure 3: CONSORT flow diagram.

Table 1: Median and range values for intergroup comparison of postoperative pain measured by the VAS score daily from day 1 to day 7 in the three groups.

VAS pain score		Median	Min	Max	p value
	Group I	3	0.00	5.00	
Day 1	Group II	3	0.00	4.00	0.119 ns
	Group III	5	0.00	10.00	
	Group I	0^{b}	0.00	3.00	
Day 2	Group II	2.5^{a}	0.00	5.00	0.006*
	Group III	4.5^{a}	0.00	6.00	
	Group I	0^{c}	0.00	1.00	
Day 3	Group II	0.5^{b}	0.00	4.00	0.008*
	Group III	4.5^{a}	0.00	7.00	
	Group I	0	0.00	4.00	
Day 4	Group II	0	0.00	5.00	0.091 ns
	Group III	2	0.00	5.00	
	Group I	0	0.00	3.00	
Day 5	Group II	0	0.00	4.00	0.485 ns
	Group III	0	0.00	6.00	
	Group I	0	0.00	1.00	
Day 6	Group II	0	0.00	0.00	0.573 ns
	Group III	0	0.00	2.00	
	Group I	0	0.00	0.00	
Day 7	Group II	0	0.00	0.00	1 ns
	Group III	0	0.00	0.00	

Significance level: $p \leq 0.05$; *significant; ns = nonsignificant.

Table 2: Median and range values for intergroup comparison of postoperative pain measured by analgesic consumption (mg) daily from day 1 to day 7 in the three groups.

Total analgesic consumption		Median	Min	Max	p value
	Group I	600	0.00	1200.00	
Day 1	Group II	600	0.00	1800.00	0.068 ns
	Group III	1500	0.00	1800.00	
	Group I	00^{c}	0.00	0.00	
Day 2	Group II	300^{b}	0.00	1200.00	0.002*
	Group III	900^{a}	0.00	1800.00	
	Group I	00^{c}	0.00	0.00	
Day 3	Group II	300^{b}	0.00	1800.00	0.004*
	Group III	900^{a}	0.00	1800.00	
	Group I	0.00	0.00	1800.00	
Day 4	Group II	0.00	0.00	1200.00	0.415 ns
	Group III	0.00	0.00	1200.00	
	Group I	0.00	0.00	600.00	
Day 5	Group II	0.00	0.00	0.00	0.573 ns
	Group III	0.00	0.00	1200.00	
	Group I	0.00	0.00	0.00	
Day 6	Group II	0.00	0.00	0.00	1 ns
	Group III	0.00	0.00	0.00	
	Group I	0.00	0.00	0.00	
Day 7	Group II	0.00	0.00	0.00	1 ns
	Group III	0.00	0.00	0.00	
	Group I	600^{b}	0.00	3000.00	
Total	Group II	1200^{b}	0.00	4800.00	0.002*
	Group III	4200^{a}	600	6000.00	

Significance level: $p \leq 0.05$; *significant; ns = nonsignificant.

Results for median and range values for intergroup comparison of postoperative pain measured by analgesic consumption (mg) daily from day 1 to day 7 in the three groups are shown in Table 2. On day 1, the highest median and range values for total analgesic consumption were recorded in group III; however, this difference did not reach the level of statistical significance. On days 2 and 3, there was a statistically significant difference in analgesic consumption between the three groups, where the highest values were recorded in group III and the lowest values were recorded in group I. On day 4 and day 5, there was no statistically significant difference in analgesic consumption between the three groups. On day 6 and day 7, all patients in the three groups reported no analgesic consumption at all.

For total analgesic consumption (in the 7 days) per patient|, statistically significantly higher median and range values were recorded in group III in comparison to group II and group I. Meanwhile, statistical significance was not found between group I and group II.

6.3. Secondary Outcomes

6.3.1. Wound Size. Results for mean and SD values for intragroup comparison of wound size measured by UNC 15 probe and transparent paper (mm) on days 0, 3, 7, 14, and 21 within each group showed the following: In group I, there was no statistically significant difference between the time points; however, there was a statistically significant reduction from day 0 and day 3 to day 7. In group II, there was no significant difference between day 0, day 3, and day 7, while there was a significant reduction on day 14 and day 21 compared to day 0 and day 3. There was a statistically significant reduction in wound size from day 0 to day 21. In group III, there was a gradual statistically insignificant decrease in wound size by time with no significant reduction in wound size on day 21.

Results for mean and SD values for intergroup comparison of wound size (mm) measured by UNC 15 probe and transparent paper (mm) on days 0, 3, 7, 14, and 21 between the three studied groups are presented in Table 3.

On day 0 and day 3, the highest mean value was recorded in group II; however, the difference between groups did not reach the level of statistical significance. On day 7, the highest mean values were recorded in group I and group II, respectively; however, the difference between groups was not statistically significant. On day 14 and day 21, the highest mean value was recorded in group I; however, the difference between groups did not reach the level of statistical significance.

6.3.2. Color Match (Visual Analogue Scale). Results for median and range values for intragroup comparison of color match measured by Visual Analogue Scale score within each group at all time points showed the following: In group I, values recorded on day 3, day 7, and day 14 were significantly lower compared to the subsequent observations. On day 42, the median and range values of color match score showed a statistically significant increase by time compared to day 3 and values recorded on day 21 and day 42 were significantly higher compared to previous observations.

In group II, the median and range values of color match score showed a statistically significant increase by time with the lowest value being on day 3 and highest value being on day 42. In group III, the median and range values of color match score showed a statistically significant increase by time with the lowest value being on day 3 and the highest values being on days 21 and 42. There was a statistically significant increase in color match by time in all groups.

Results for median and range values for intergroup comparison of color match measured by Visual Analogue Scale score between the three studied groups at all time points are presented in Table 4.

On day 3, day 7, and day 14, the highest median and range values were recorded in groups I and II, respectively, compared to group III; however, there was no statistically significant difference between the three groups.

On day 21, higher median and range values were recorded in groups I and II, respectively, compared to group III. There was no statistically significant difference between group II and both group I and group III. However, there was a significant difference between group I and group III. On day 42, significantly higher median and range values were recorded in group I in comparison to groups II and III.

7. Discussion

Various clinical trials were carried out aiming to reduce postoperative patients' morbidity following soft tissue grafts harvesting; most of these trials achieved positive outcomes using different materials such as hyaluronic acid (HA) gel [12], ozone therapy [22], topical simvastatin gel [23], and advanced platelet-rich fibrin (A-PRF) [24].

The present clinical trial aims to compare the effect of MEBO versus 0.2% hyaluronic acid gel applied to palatal donor site on postoperative pain reduction and wound-healing after FGG harvesting. Two concentrations are available for HA gel, 0.2% and 0.8%; however, in this clinical trial, 0.2% HA gel was used, since it was found to be more superior than 0.8% regarding the acceleration of the palatal wound-healing as reported by [12]. In the present study, MEBO was applied topically at the palatal wound site because, unlike currently used topical products, MEBO produces the necessary moist environment for optimal healing. MEBO provides physiological moisture for optimized wound-healing and reepithelialization and is also easy to apply irrespective of site, extent, and local condition of the wound. MEBO is pure herbal extract, which is natural in origin; thus it is neither irritant nor toxic to the oral mucosa [9].

Hyaluronic acid (HA) was also the product of choice in the present study to cover the palatal wound, since it has unique physiochemical and biological properties, being anti-inflammatory, antiedematous, antioxidant, bacteriostatic, and capable of accelerating wound-healing, preventing scar formation, and enhancing tissue regeneration through its ability to retain a large amount of water. HA has been the focus of study in many clinical trials due to its feasibility in the form of either gel or spray; also it is a noninvasive method for the patient which is easy to use. Therefore, HA was regarded as a useful dressing for treatment of the palatal wound following the harvesting of FGG [12, 25].

Various clinical trials have been done to test the efficacy of HA gel application in periodontal surgery [12, 14, 15]. However, very limited trials are available to test the efficacy of MEBO in periodontal surgery and intraoral wound-healing [16]. The present study was conducted on thirty-nine patients with different mucogingival problems indicated for FGG harvesting. The study ended with thirty patients, as seven patients did not complete their follow-ups due to Covid-19 pandemic and two patients did not attend their follow-ups for unknown reasons.

Table 3: Mean and SD values for the intergroup comparison of wound size (mm) in the three studied groups at all time points.

Wound size		Mean	Std. dev.	Std. error	95% confidence interval for mean		Min	Max	p value
					Lower bound	Upper bound			
Day 0	Group I	128.00	30.84	9.75	105.94	150.06	70.00	150.00	0.787 ns
	Group II	132.90	27.32	8.64	113.36	152.44	75.00	160.00	
	Group III	122.50	40.71	12.87	93.38	151.62	50.00	180.00	
Day 3	Group I	120.90	31.24	9.88	98.56	143.24	67.00	150.00	0.639 ns
	Group II	131.20	26.53	8.39	112.22	150.18	75.00	160.00	
	Group III	117.00	43.18	13.65	86.11	147.89	47.00	180.00	
Day 7	Group I	109.90	31.49	9.96	87.38	132.42	60.00	147.00	0.928 ns
	Group II	109.50	33.12	10.47	85.81	133.19	52.00	148.00	
	Group III	104.50	39.11	12.37	76.52	132.48	45.00	159.00	
Day 14	Group I	97.80	33.12	10.47	74.11	121.49	52.00	146.00	0.859 ns
	Group II	90.20	26.71	8.45	71.09	109.31	48.00	130.00	
	Group III	91.30	38.75	12.25	63.58	119.02	36.00	140.00	
Day 21	Group I	81.40	33.50	10.59	57.44	105.36	35.00	130.00	0.778 ns
	Group II	72.30	20.19	6.39	57.85	86.75	44.00	100.00	
	Group III	79.40	34.26	10.83	54.89	103.91	28.00	130.00	

Significance level: $p \leq 0.05$; ns = nonsignificant.

Table 4: Median and range values for the intergroup comparison of color match measured by the Visual Analogue Scale score between the three studied groups at all time points.

Color match		Median	Min	Max	p value
Day 3	Group I	3	2.00	5.00	0.128 ns
	Group II	3	2.00	4.00	
	Group III	2	0.00	4.00	
Day 7	Group I	5	0.00	5.00	0.095 ns
	Group II	4.5	3.00	7.00	
	Group III	4	4.00	5.00	
Day 14	Group I	6.5	1.00	5.00	0.054 ns
	Group II	6	1.00	7.00	
	Group III	5	4.00	8.00	
Day 21	Group I	8^{a}	4.00	7.00	0.032^{*}
	Group II	$7^{a,b}$	4.00	7.00	
	Group III	6.5^{b}	4.00	8.00	
Day 42	Group I	10^{a}	6.00	9.00	0.006^{*}
	Group II	8^{b}	4.00	8.00	
	Group III	7.5^{b}	5.00	8.00	

Significance level: $p \leq 0.05$; *significant; ns = nonsignificant.

Postoperative pain is correlated more to wound depth rather than surface area [26]. Thus, in the present study, care was taken to obtain a uniform thickness of the graft to be ranged from 1 to 1.5 mm, as a thin graft was found to have a low resistance to functional forces and was more prone to secondary contraction. However, a more than 1.5 mm thick graft could provide more functional resistance to the forces but is more liable to the primary shrinkage [2], as well as to avoid exaggerated pain and necrosis encountered with graft thicker than 2 mm [26]. On the contrary, Wyrebek et al. [7] conducted a clinical trial on the effect of graft dimension on patients' morbidity and concluded that the correlation between postoperative morbidity and the graft size loses value when the palatal wound is covered by an individual stent.

Postoperative pain was measured in this study both directly via VAS and indirectly via consumption of analgesics; thus patients received Ibuprofen 600 mg on surgery day for pain control and were instructed to take Ibuprofen 600 mg only if needed to make sure that any reported pain scores are related to the intervention used [3]. No other systemic medications were prescribed including antibiotics. The prevalence of postoperative infections following periodontal surgery is less than 1% and this low risk does not justify the use of systemic antimicrobials just to prevent infections [27].

Reapplication of MEBO, HA, and periodontal pack was done on the third day. Although wound-healing can be traumatized during the removal and renewing of periodontal dressing, this was done on purpose for many reasons, on one side, to evaluate the wound at least at one measurement point as early as suggested by the relevant literature [26] and, on the other side, to use the periodontal dressing benefits on surgical wound care, wound protection, and pain reduction as well as HA and MEBO retention and renewal. Since periodontal dressings were reapplied to all groups, all patients encountered the same degree of trauma without jeopardizing the results of this study [12].

Postoperative pain was evaluated in this study daily till the seventh day as pain reaches its maximum level at the initial healing phase (0–3 days) and completely disappears on day 14 using 0.2% HA gel, even when compared to negative control [12]. Furthermore, Mahmoud et al. [16] evaluated postoperative pain using VAS for seven days only when comparing the effects of HA and MEBO to negative control on wound-healing in vestibular deepening procedures.

Wound size was measured in the present study via planimetric method of wound size assessment as using linear measurements only (length x width) does not provide accuracy due to irregular healing pattern of the palatal wound. This parameter was evaluated in the present study on day 0, day 3, day 7, day 14, and day 21 as complete epithelial healing occurs after 21 days [28].

Color match (CM) of the palatal wound was assessed by comparing it with that of the adjacent and opposite side by using the objective VAS. As healing of FGG takes place by secondary intention, color change is observed clearly and matching with adjacent normal tissue would reflect the degree of reepithelization and wound-healing. CM was evaluated in the present study on day 3, day 7, day 14, day 21, and day 42 [12, 29].

Results of the present study showed a statistically significant reduction by time in postoperative pain measured by VAS in group I (MEBO) since day 1 and showed significantly decreased postoperative pain to reach a VAS median of 0 (0–3) and median consumption of analgesics of 0 (0–0) on day 2 postsurgically with complete pain disappearance on day 6 for all subjects. These results are slightly superior to those of a study conducted by Mahmoud et al. [16] to evaluate the effect of MEBO on wound-healing in vestibular deepening procedures which reported a VAS median of 3 (2–3) on day 2 postsurgically. Vestibular deepening heals by secondary intention, which shows a similar pattern to palatal wound-healing. The previous study is the only study found in literature which uses MEBO to accelerate healing of postsurgical intraoral wounds that heal by secondary intention.

The results of the present study are in accordance with a previous study that used MEBO in treatment of upper gastrointestinal injuries which concluded that MEBO stimulates healing by improving microcirculation, promoting granulation tissue growth, and providing physiologic environment for wound repair by inhibiting bacterial overgrowth and providing a protective membrane preventing bacterial invasion [30].

For group II, results of the present study showed that 0.2% HA gel significantly reduced postoperative pain to reach a VAS median of 0 (0–5) and median consumption of analgesics on day 4 postsurgically with complete pain disappearance for all subjects on day 6, which could be explained by the anti-inflammatory, antiedematous, antioxidant, and antibacterial effects of HA [25]. The reduction of postoperative pain in the present study was more than that reported in another study in which VAS median was reported to be 2 (1–3) on day 4 [16]; this could be attributed to HA reapplication on day 3, while it was applied only once on surgery day in that study which could prolong the anti-inflammatory and antiedematous action of HA gel. On the other hand, our VAS median on day 3 was slightly higher but on day 7 the results of the present study were consistent with those of the study conducted by Yıldırım et al. [12].

For group III, results of the present study showed that the use of periodontal pack only could significantly reduce pain in terms of VAS and analgesic consumptions between day 1 and day 4 with complete disappearance of postoperative pain for all subjects on day 7, which is consistent with both related studies [12, 16].

Results of the present study showed a statistically significant reduction in postoperative pain measured by VAS in group I compared to group II and group III on day 2 and day 3. However, on day 3, group II also showed a statistically significant postoperative pain reduction when compared to group III. For intergroup comparison between MEBO and HA, no significant difference in terms of VAS score was present on day 2 and day 4, which is consistent with the results of the previous study [16], where no significant difference could be found on day 2 and day 4. However, in the present study, a significant difference in terms of pain reduction (VAS) in favor of group I was encountered when compared to group II on day 3. Because the pain perception is a subjective and personal feeling, VAS scale results may vary from a study to another [29].

Regarding indirect measurement of postoperative pain via analgesic consumption, the three studied groups showed a statistically significant decrease in their use from day 1 to day 7. However, in group I, median of analgesic consumption reached 0 on day 2, while group II and group III reached a median of 0 on day 4, reflecting the powerful analgesic and anti-inflammatory effect of MEBO.

All groups showed significant reduction in wound size from day 0 to day 42; however, no significant difference between groups was detected in wound size in each time point or in percent change in each time interval. These findings could be justified as the added effect of MEBO/HA is due to their anti-inflammatory properties of the active components rather than accelerating the epithelial creeping of palatal wound.

Concerning color match in the present study, all groups showed statistically significant increase by time. These results were consistent with the findings of Yıldırım et al. [12] for both 0.2% HA gel group and control group. A statistically significant difference between groups was observed on day 21 and day 42. Group I showed higher CM compared to group II on day 21 with no statistically significant difference but statistically significant higher CM compared to group III. A statistically significant higher value for CM was detected in group I on day 42 when compared to groups II and III.

Group II showed higher CM on day 21 when compared to group III but with no statistically significant difference, while the difference was statistically significant on day 42. This may be interpreted as a sign of better wound-healing which enables faster course of CM. Clinical studies have found that MEBO promotes debridement and epithelial repair and is associated with better scar quality [9, 30]. Furthermore, HA leads to tissue maturation and rapid epithelization, which ensures good CM [31].

To our knowledge, no study that reviewed the effect of MEBO on intraoral wound-healing used color match as an outcome. The pain reduction and rapid healing in intervention groups (group I and II) are possibly due to the anti-inflammatory and antioxidant effects of their main components as b-sitosterol for MEBO and sodium hyaluronate for HA gel rather than rapid epithelialization. This was reflected by our results, which showed improved outcomes for intervention groups in postoperative pain, analgesic consumption, and color match when compared to control group, while there was no statistically significant difference between groups in terms of wound size. However, MEBO showed superior outcomes in terms of postoperative pain control and color match compared to control and HA groups.

8. Conclusions

Topical application of MEBO or 0.2% HA gel (Gengigel®) on palatal wound following FGG harvesting could significantly reduce postoperative pain and promote palatal wound-healing. Nevertheless, MEBO application produced even more favorable effects on pain reduction and better color match which reflects the healing process. MEBO could be considered a practical alternative, since it is cheap, available, and easily applied.

Data Availability

The authors declare that all the data supporting the results of this study are readily available upon demand.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Acknowledgments

The authors report that this research was totally self-funded.

References

[1] V. Iorio-Siciliano, A. Blasi, A. Cuozzo, E. Vaia, G. Isola, and L. Ramaglia, "Treatment of gingival recessions using coronally advanced flap and connective tissue graft: a long-term retrospective analysis," *Quintessence International*, vol. 52, no. 8, pp. 686–693, 2021.

[2] E. T. Scheyer, M. Sanz, S. Dibart et al., "Periodontal soft tissue non-root coverage procedures: a consensus report from the AAP Regeneration Workshop," *Journal of Periodontology*, vol. 86, no. 2, pp. S73–S76, 2015.

[3] G. Zucchelli, M. Mele, M. Stefanini et al., "Patient morbidity and root coverage outcome after subepithelial connective tissue and de-epithelialized grafts: a comparative randomized-controlled clinical trial," *Journal of Clinical Periodontology*, vol. 37, no. 8, pp. 728–738, 2010.

[4] C. Popova, A. Mlachkova, and D. Emilov, "Effectiveness of nsaids aulin and ibu-profen on the postoperative pain at gingival graft procedures–a pre-liminary study," *Journal of IMAB*, vol. 2, pp. 12–15, 2008.

[5] C. O. Silva, É. D. P. Ribeiro, A. W. Sallum, and D. N. Tatakis, "Free gingival grafts: graft shrinkage and donor-site healing in smokers and non-smokers," *Journal of Periodontology*, vol. 81, no. 5, pp. 692–701, 2010.

[6] A. F. Bosco and J. M. Bosco, "An alternative technique to the harvesting of a connective tissue graft from a thin palate: enhanced wound healing," *The International Journal of Periodontics & Restorative Dentistry*, vol. 27, no. 2, pp. 133–139, 2007.

[7] B. Wyrebek, B. Górski, and R. Górska, "Patient morbidity at the palatal donor site depending on gingival graft dimension," *Dental and Medical Problems*, vol. 55, no. 2, pp. 153–159, 2018.

[8] M. R. Kulkarni, B. S. Thomas, J. M. Varghese, and G. S. Bhat, "Platelet-rich fibrin as an adjunct to palatal wound healing after harvesting a free gingival graft: a case series," *Journal of Indian Society of Periodontology*, vol. 18, no. 3, pp. 399–402, 2014.

[9] T. Hirsch, W. Ashkar, O. Schumacher, L. Steinstraesser, G. Ingianni, and C. C. Cedidi, "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," *European Journal of Medical Research*, vol. 13, no. 11, pp. 505–510, 2008.

[10] E. S. Ang, S. T. Lee, C. S. Gan 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," *Annals Academy of Medicine Singapore*, vol. 29, no. 1, pp. 7–10, 2000.

[11] M. R. Sharif, J. Alizarger, and A. Sharif, "Evaluation of the wound healing activity of sesame oil extract in rats," *Worled journal of medical science*, vol. 9, no. 2, pp. 74–78, 2013.

[12] S. Yıldırım, H. Ö Özener, B. Doğan, and B. Kuru, "Effect of topically applied hyaluronic acid on pain and palatal epithelial wound healing: an examiner-masked, randomized, controlled clinical trial," *Journal of Periodontology*, vol. 89, no. 1, pp. 36–45, 2018.

[13] M. D. Finn, S. R. Schow, and E. D. Schneiderman, "Osseous regeneration in the presence of four common hemostatic agents," *Journal of Oral and Maxillofacial Surgery*, vol. 50, no. 6, pp. 608–612, 1992.

[14] H. Hammad, M. Hammad, I. Abdelhadi, and M. Khalifeh, "Effects of topically applied agents on intra-oral wound healing in a rat model: a clinical and histomorphometric study," *International Journal of Dental Hygiene*, vol. 9, no. 1, pp. 9–16, 2011.

[15] K. M. Fawzy El-Sayed, M. A. Dahaba, S. Aboul-Ela, and M. S. Darhous, "Local application of hyaluronan gel in conjunction with periodontal surgery: a randomized controlled trial," *Clinical Oral Investigations*, vol. 16, no. 4, pp. 1229–1236, 2012.

[16] M. Mahmoud, M. Madi, and N. Mamdouh, "Topical surface modifiers to accelerate healing and Re-epithelization process in vestibular," *Gingival Extension Surgical Procedure Australian Journal of Basic and Applied Sciences*, vol. 9, no. 20, pp. 423–431, 2015.

[17] G. Zucchelli and I. Mounssif, "Periodontal plastic surgery," *Periodontology 2000*, vol. 68, no. 1, pp. 333–368, 2015.

[18] D. D. Price, P. A. McGrath, A. Rafii, and B. Buckingham, "The validation of visual analogue scales as ratio scale measures for chronic and experimental pain," *Pain*, vol. 17, no. 1, pp. 45–56, 1983.

[19] M. K. Samani, B. V. Saberi, S. M. Ali Tabatabaei, and M. G. Moghadam, "The clinical evaluation of platelet-rich plasma on free gingival graft's donor site wound healing," *European Journal of Dermatology*, vol. 11, no. 4, pp. 447–454, 2017.

[20] D. H. Keast, C. K. Bowering, A. W. Evans, G. L. Mackean, C. Burrows, and L. D'Souza, "MEASURE: a proposed assessment framework for developing best practice recommendations for wound assessment," *Wound Repair and Regeneration: Official Publication of the Wound Healing Society [and] the European Tissue Repair Society*, vol. 12, no. 3, pp. S1–S17, 2004.

[21] K. F. Schulz, D. G. Altman, D. Moher, and CONSORT Group, "CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials," *BMJ*, vol. 340, no. 1, p. c332, 2010.

[22] S. C. Isler, A. Uraz, B. Guler, Y. Ozdemir, S. Cula, and D. Cetiner, "Effects of laser photobiomodulation and Ozone therapy on palatal epithelial wound healing and patient morbidity," *Photomedicine and Laser Surgery*, vol. 36, no. 11, pp. 571–580, 2018.

[23] M. Madi and A. Kassem, "Topical simvastatin gel as a novel therapeutic modality for palatal donor site wound healing following free gingival graft procedure," *Acta Odontologica Scandinavica*, vol. 76, no. 3, pp. 212–219, 2018.

[24] F. Sousa, V. Machado, J. Botelho, L. Proença, J. J. Mendes, and R. Alves, "Effect of A-PRF application on palatal wound healing after free gingival graft harvesting: a prospective randomized study," *European Journal of Dermatology*, vol. 14, no. 1, pp. 63–69, 2020.

[25] P. Dahiya and R. Kamal, "Hyaluronic Acid: a boon in periodontal therapy," *North American Journal of Medical Sciences*, vol. 5, no. 5, pp. 309–315, 2013.

[26] R. Burkhardt, C. H. F. Hämmerle, and N. P. Lang, "Self-reported pain perception of patients after mucosal graft harvesting in the palatal area," *Journal of Clinical Periodontology*, vol. 42, no. 3, pp. 281–287, 2015.

[27] S. Oswal, S. Ravindra, A. Sinha, and S. Manjunath, "Antibiotics in periodontal surgeries: a prospective randomised cross over clinical trial," *Journal of Indian Society of Periodontology*, vol. 18, no. 5, pp. 570–574, 2014.

[28] P. V. Patel, V. Kumar, S. Kumar, V. Gd, and A. Patel, "Therapeutic effect of topical ozonated oil on the epithelial healing of palatal wound sites: a planimetrical and cytological study," *Journal of Investigative and Clinical Dentistry*, vol. 2, no. 4, pp. 248–258, 2011.

[29] A. Lektemur Alpan and G. Torumtay Cin, "PRF improves wound healing and postoperative discomfort after harvesting subepithelial connective tissue graft from palate: a randomized controlled trial," *Clinical Oral Investigations*, vol. 24, no. 1, pp. 425–436, 2020.

[30] C. Anthony, "Results of safety testing-MEBO product," *Case Consulting Laboratories*, pp. 00482–491, 1994.

[31] W. Y. J. Chen, "Functions of hyaluronan in wound repair," in *Hyaluronan*, pp. 147–156, Woodhead Publishing, Sawston, UK, 2002.

Efficacy of Treating Radiation-induced Oral Mucositis with Moist Exposed Burn Ointment

Min Zhenxing, Zhang Yong
Affiliation: Department of Surgery of Beijing Xuanwu TCM Hospital, 100050
Corresponding author: Min Zhenxing, Email: mzl19861107@sina.com

【Abstract】**Objective** To study the clinical efficacy of treating radiation-induced oral mucositis (RIOM) with Moist Exposed Burn Ointment (MEBO). **Methods** 30 patients with RIOM admitted to Beijing Xuanwu TCM Hospital from January 2019 to July 2020 were enrolled and randomized into study group (n=15) treated with MEBO, and control group (n=15) treated with compound mouthwash. Clinical efficacy and healing time between 2 groups were compared. **Results** For study group and control group, at week 2, healed patients 9 vs. 4, improved 6 vs. 8, ineffective 0 vs. 3; healing rate 60% vs. 26.7%, overall efficacy 100% vs. 80% ($z=-2.134$, $p=0.056$, $p > 0.05$). Healing time in study group (10.3 ± 2.1 days) was significantly shorter than control group (14.9 ± 2.4 days) ($t=5.587$, $p < 0.001$). **Conclusion** Treating RIOM with MEBO could effectively promote repair of oral mucosa and shorten healing time.

【Key words】Moist Exposed Burn Ointment; Compound Mouth Rinse; Radiation-induced Oral Mucositis; Oral Ulcer

Radiation-induced oral mucositis (RIOM) is an acute or chronic oral mucosa injury caused by poor blood supply due to swelling, stenosis or blockage of capillaries within the radiated area.[1] It is characterized by oral mucosa hyperaemia, red spot or white spot, erosion and fibrosis, complicated by pain, difficulty swallowing, dry mouth or taste disorder[2]; some patients may experience difficulty breathing, which could severely impact patients' life quality. To improve treatment effect, the author applied Moist Exposed Burn Ointment (MEBO) in treating RIOM and compared the result with compound mouth wash.

1. Clinical data

1.1 Baseline data

30 patients with RIOM admitted to Beijing Xuanwu TCM Hospital between January 2019 and July 2020 were enrolled and randomized into study group (n=15) and control group (n=15). Baseline data of 2 groups were not significantly different ($p > 0.05$). (Table 1) This study was approved by the ethics committee of Beijing Xuanwu TCM Hospital and all patients had signed informed consent forms.

Table 1 Baseline data

Group	Cases (n)	Sex (n)		Age (year, $\bar{x}\pm s$)	Course of disease (month, $\bar{x}\pm s$)
		Male	Female		
Study group	15	11	4	51.4±6.1	3.4±1.2
Control group	15	10	5	50.8±7.3	3.2±1.1
χ^2/t	0.159			0.244	0.476
p	0.690			0.809	0.638

Group	Primary disease (n)			Clinical staging (n)			
	Diabetes	Hypertension	Coronary heart disease	Stage I	Stage II	Stage III	Stage IV
Study group	4	6	5	2	5	7	1
Control group	3	5	4	2	6	6	1
χ^2/t	0.186	0.144	0.159	0.168			
p	0.666	0.705	0.690	0.983			

1.2 Inclusion and exclusion criteria

Inclusion criteria: 30-65 years old; diagnosed with RIOM[2]; informed of this study and signed informed consent forms. Exclusion criteria: severe malnutrition; allergic to ingredients of medicine used in this study; unable to cooperate with treatment due to mental illness; autoimmune diseases or receiving glucocorticoid treatment.

2. Methods

2.1 Treatment methods

Study group: besides systemic treatment, MEBO was used for the treatment of oral mucosa. After rinsing mouth with normal saline, keep 5-10g of MEBO in mouth. Wait until ointment melts into semifluid and tilt head backwards to make sure the fluid flows to throat and stay there for 1 min. Then blow cheek and allow MEBO fully contact with oral mucosa, use cotton swabs to apply when necessary. Remaining MEBO could be swallowed. Perform the above steps 4 times a day until oral mucositis fully healed.

Control group: besides systemic treatment, compound mouth wash (made with 500mL normal saline, 80mg Gentamicin, 5mg Lidocaine, 200mg Dexamethasone, 2mg Vitamin B_{12} and 200mg Vitamin C) was used for oral mucosa. Keep 10-15mL compound mouth wash in mouth, tilt head backwards to make sure the fluid flows to throat and stay there for 1 min. Then blow cheek and allow the mouth wash to stay in mouth for 30s before spitting it out. Perform the above steps 4 times a day until oral mucositis fully healed.

2.2 Clinical outcome and evaluation criteria

Clinical efficacy and healing time at week 2 between two groups were compared. Evaluation criteria for efficacy: complete recovery of oral mucosa is considered as "healed", size of injured oral mucosa reduced

≥ 50% as "improved" and size of injured oral mucosa reduced <50% or otherwise increased as "ineffective". Healing rate= number of "healed" / total cases × 100%. Overall efficacy=(number of "healed"+number of "improved")/total cases ×100%.

2.3 Statistical analysis

SPSS 17.0 was used for statistical analysis. Count data was represented as n (%), tested by *chi-square* test or *rank sum* test; measurement data was represented as mean ± standard deviation ($\bar{x} \pm s$), tested by *t test*.

3. Results

3.1 Clinical efficacy

At week 2, for study group and control group, the number of patients healed was 9 vs 4 and number of patients improved 6 vs 8. And in control group, the number of ineffective was 3. Study group has a healing rate of 60% and overall efficacy of 100%; while control group has a healing rate of 26.7% and overall efficacy of 80% ($z= - 2.134$, $p=0.056$, $p > 0.05$). Clinical efficacy between two groups was tested by *rank sum* test ($z=-2.134$, $p=0.056$, $p > 0.05$). Healing rate and overall efficacy were tested by *chi-square* test ($\chi^2=3.394, 3.333$, $p=0.065, 0.068$, $p > 0.05$).

3.2 Healing time

Healing time in study group 10.3 ± 2.1 days was significantly lower than control group 14.9±2.4 days ($t=5.587$, $p < 0.001$).

4. Discussion

RIOM, with a high incidence, is one of the common adverse reactions of radiation therapy for malignant cancer of head and neck.[3-4] Currently, there is no really effective treatment for RIOM in clinical practice. Although the use of recombinant human epidermal growth factor etc. could improve treatment efficacy, it is expensive and has been reported to cause adverse reactions such as flushing, fever, diarrhea or even acute allergic reaction.[5] Therefore, how to effectively improve treatment efficacy of RIOM has become a focus in clinical study.

Based on previous effective treatment results of various wounds with MEBO, it is chosen to treat RIOM in this study. Our study result demonstrated that MEBO could promote repair of injured mucosa of RIOM. This is possibly due to the fact that constituents in MEBO such as carbohydrate, fatty acid, amino acid and vitamin could provide sufficient nutrients for injured mucosa and improve immunity of local tissues.[6] MEBO could also activate potential regenerative cells into stem cells that proliferate and differentiate into various tissue cells. And these constituents could also promote angiogenesis in wound, accelerate growth of granulation tissue and mucosa, and repair wound in-situ.[7]

In summary, treating RIOM with MEBO could effectively promote repair of injured mucosa and shorten healing time.

References

1. Liu W, Li T-L, Yu J-Q. Progress on Treating Oral Mucositis Caused by Radiation Therapy for Nasopharyngeal Carcinoma [J/CD]. *Journal of Clinic Nursing's Practicability*, 2018, 3 (27):53.

2. Cheng B, Li C-Y, Xia J. Diagnosis and Treatment of Radiation-induced Oral Mucositis [J]. *Chinese Journal of Practical Stomatology*, 2008, 1 (9): 513-516.

3. Ferlay J, Soerjomataram Ⅰ, DikshitR, et al. Cancer Incidence and Mortality Worldwide: Source, Methods and Major Patterns in GLOBOCAN 2012 [J]. *Int J Cancer,* 2015, 136 (5): E359-E386.

4. Rao S, Hegde SK, Rao P, et al. Honey Mitigates Radiation-induced Oral Mucositis in Head and Neck Cancer Patients without Affecting the Tumor Response [J]. *Foods*, 2017, 6 (9): 77.

5. Zhao J, Dui A-X, Ma C-L et al. Treatment Progress of Radiation-induced Oral Mucositis [J]. *Medical Journal of Chinese People's Liberation Army*, 2017, 29 (3):113-116.

6. Lu Y-P. Wu X. Efficacy Observation on Treating Radiation-induced Skin and Mucosa Injury with Moist Exposed Burn Ointment and Kangfuxin Solution [J]. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2018, 30 (3): 197-204.

7. Min Z-X, Zhang Y, Zhang L. One Case Report of Treating Radiation-induced Oral Mucositis after Tongue Cancer Surgery [J]. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2020, 32 (3): 169-170.

Effect of Moist Exposed Burn Ointment on Indwelling Time of Indwelling Venous Catheters

Chen Yanbei, Yao Ping, Niu Huatao

Affiliation: Department of Neurosurgery of Yunnan Cancer Hospital and the Third Affiliated Hospital of Kunming Medical University, Kunming 650118, Yunnan

【**Abstract**】 **Objective** To study the effect of Moist Exposed Burn Ointment (MEBO) on the indwelling time of indwelling venous catheter (IVC). **Method** 200 patients in the Department of Neurosurgery of the Third Affiliated Hospital of Kunming Medical University were enrolled and randomly divided into study group (n = 100) and control group (n = 100), and study group was applied with MEBO on the insertion site, while control group only routine nursing care without topical medicine. **Results** For study group and control group: IVC maintained 72 hours (95% vs. 76%), incidence of complication (4% vs. 34%), and patient satisfaction (96% vs. 78%) (all $p <$ 0.05). **Conclusion** MEBO is effective in prolonging indwelling time and reducing complications in patients receiving infusion of high-concentration irritant drugs through IVC.

【**Key words**】MEBO; Valved indwelling venous catheter; Irritant / vesicant drugs; Indwelling time; Complication

Most cancer patients need to undergo radiotherapy and chemotherapy. Side effects related to these treatment such as vomiting could cause malnutrition etc., therefore these patients would need infusion therapy, and often the infusion solution are highly concentrated and irritating. In the case of drug leakage, serious damage could be done to local skin.

Due to various reasons, peripherally inserted central catheter (PICC) is contradicted for some patients, so IVC is chosen for infusion therapy instead. Drugs such as mannitol, potassium chloride, and fat emulsion are highly irritating and high in concentration, and tend to cause various complications,[1] seriously shortening the indwelling time of IVC. Moist Exposed Burn Ointment (MEBO) was used in IVC patients in our department - Department of Neurosurgery of Yunnan Cancer Hospital, to prolong indwelling time and reduce complications of IVC.

1. Materials and methods

1.1 Baseline data

From March 1, 2000 to September 1, 2020, 200 patients with IVC in our department were enrolled. Inclusion criteria: 1. IVC is inserted; transparent film (4 cm × 6 cm) is used to secure dressing; insertion site is at back of hand or forearm; 2. Before insertion, blood vessels and skin are intact without inflammation. 3. Age 18-80 years; 4. Total volume of daily infusion (mannitol, 10% potassium chloride, or 20% fat emulsion) is less than 1500 mL during study period. Patients were randomized into study group and control group. In study group, male (n = 43) and female (n = 57), age 18-72 years, mean age 50.5±6.4 years; in control group, male (n = 45) and female (n = 55), age 22-80 years, mean age 45.4±7.9 years. Both groups of patients were acknowledged of the research and signed informed consent document voluntarily. Difference on baseline data between two groups showed no statistical significance (all $p > 0.05$).

1.2 Method

Control group was given routine catheter care as follows. 1. Before infusion, examine insertion site to ensure no fluid leakage, phlebitis, swelling, thrombosis or other complications (pull out IVC once complication occurred); use 3-5 mL 0.9% sodium chloride solution to flush catheter. 2. After infusion, push 125 U/mL heparin 3-5 mL (heparin sodium 12500 U + 0.9% Sodium Chloride Injection 100 mL) into catheter to seal it. 3. According to guidelines for infusion therapy, indwelling time of IVC should not exceed 72 hours.

In addition to the above care, study group was treated with MEBO as follows, MEBO was applied around the insertion site at about 1-2 mm thickness, covering a size of about 4 cm×15 cm, and plastic wrap was used to cover. This MEBO dressing was removed 1 hour after application, and it was applied 2 times a day.

1.3 Clinical endpoint

Indwelling time and incidence of complications were compared in both groups.

1.4 Statistical analysis

SPSS was used for data analysis, and count data was represented as n (%). Difference between 2 groups was tested by χ^2 test.

2. Results

2.1 Indwelling time

Indwelling time of IVC ranged from 1 to 72 hours, and catheter was removed immediately once complications occurred. As administered drug was highly irritant at high concentration, indwelling time didn't exceed 72 hours for all patients. Number of patients with indwelling time of 72 hours and less than 72 hours were compared between 2 groups, showing statistical significance ($p < 0.05$) (Table 1).

Table 1 Indwelling time [n (%)]

Group	72 hours	< 72 hours	χ^2	p
Study Group (n = 100)	95 (95.0)	5 (5.0)		
Control Group (n = 100)	76 (76.0)	24 (24.0)	14.559	0.000*

$p < 0.05$*

2.2 Satisfaction rate

Satisfaction rate of patients in study group and control group were respectively 96% and 78%, showing statistical significance ($p < 0.05$) (Table 2).

Table 2 Satisfaction rate [n (%)]

Group	Much satisfied	Satisfied	Dissatisfied	Satisfaction rate	χ^2	p
Study group (n =100)	78 (78.0)	18 (18.0)	4 (4.0)	96 (96.0)		
Control group (n = 100)	50 (50.0)	28 (28.0)	22 (22.0)	78 (78.0)	14.252	0.000*

$p < 0.05$*

2.3 Incidence of complication

After infusion, complication such as fluid leakage, phlebitis, swelling, and thrombosis at insertion site were observed. Incidence in study group and control group were 4% and 34% ($p < 0.05$) (Table 3).

Table 3 Incidence of complication [n (%)]

Group	Fluid leakage	Phlebitis	Swelling	Thrombosis	Total Incidence
Study group (n =100)	1 (1.0)	1 (4.0)	2 (2.0)	0 (0.0)	4 (4.0)
Control group (n = 100)	11 (11.0)	6 (22.0)	15 (15.0)	2 (2.0)	34 (34.0)
χ^2					29.094
p					0.000*

$p < 0.05$*

3. Discussion

In clinical practice, deep IV catheter are contradiction for many tumor patients due to deep venous thrombosis,[2] superior vena cava syndrome, infection, or abnormal coagulation function, etc. So IVC was used for infusion of irritant drugs in our department. But complications related to IVC such as fluid leakage, phlebitis, swelling, and thrombosis could occur, which shortens indwelling time to less than 72 hours,[3] and rate of premature pulling out of IVC is high. Mild complications including pain and numbness in limbs, and necrosis of muscle and tissue, stiffness of tendon and joint dysfunction might occur. Multiple insertions could also cause much pain and even economic burden to patients.[4]

Complications and shortened indwelling time are common in infusion therapy of highly irritant, high-concentration drugs through IVC. It's of much importance and clinical value to search for a treatment method that not only prevents complication, but also prolongs indwelling time of IVC.

In 1962, Winter et al.[5-6] found that the activity of epithelial cells could be promoted in a moist environment, thereby accelerating wound healing. This important discovery laid foundation for the theory of moist wound healing for modern medicine.

According to some studies, MEBO could form a protective film on wound which prevents dehydration of cells.[7–8] Wound surface could be kept moist for wound healing, and be isolated from external stimulation. Moist environment is conducive to the differentiation and proliferation of epidermal stem cells in wound,[9] and could increase the expression levels of VEGF, bFGF, and EGF, etc. in wound tissue,[10] promote microcirculation of wound,[11] improve immunity,[12] and prevent bacterial invasion, which prevent infection.[13] In addition, MEBO could inhibit the excessive proliferation of fibroblasts, so as to reduce the incidence of scar formation.[14] According to some studies, MEBO could reduce the pigmentation of wounds.[15] MEBO has been widely used in the treatment of various chronic refractory wounds, such as pressure ulcer, burn wound, diabetic foot ulcer, and radiation induced skin injury, showing significant therapeutic effects.[16]

In this study, study group has a significantly higher number of patients with indwelling time reaching 72 hours ($p < 0.05$). Besides, incidence of complications was significantly lower, and satisfaction rate of the infusion therapy was significantly higher in study group (all $p < 0.05$).

In conclusion, MEBO could prevent common complications and prolong indwelling time of IVC.

Reference

1. Jiang Lin, Xu X-X, Yang Y-Y, et al. Clinical observation on the prevention of phlebitis by simultaneous infusion of normal saline and parenteral nutrition at a uniform rate. *Journal of Xinjiang Medical University*, 2015, 38(9): 1159-1161.

2. The National Health and Family Planning Commission of the People's Republic of China. Guidelines (WS/T433-2013) for Intravenous Treatment. *China Quality Inspection Press*, WST4332013.2013.

3. He S-X. Cause analysis and preventive care of extravasation following infusion therapy. *China Practical Medicine*, 2016, 11(22): 208-209.

4. Qiu J-Y, Zuo Huan, Yuan B-F, et al. Effect of Ji Desheng snake wine in the treatment of extravasation of fatty emulsion for infusion therapy. *Sichuan Medical Journal*, 2016, 36(2): 228-229.

5. Wei W, Liu Q-J, Tan Y, et al. Oxidative Stress, diabetes, and Diabetic Complications. *Hemoglobin*, 2009, 33(5): 370-377.

6. Tang Q-L, Han S-S, Feng J, et al. Moist exposed burn ointment promotes cutaneous excisional wound healing in rats involving VEGF and bFGF. *Mol Med Rep*, 2014, 9(4): 1277-1282.

7. Zhu D-L, Wang Xia, Jiang A-L, et al. Curative effect of 71 cases of diabetic foot ulcer treated with regenerative medical technology in situ. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2017, 29(3): 186-190.

8. Zhang L-Y, Yuan J-L. Clinical observation of MEBO in the treatment of refractory wounds. *Medical Journal of Liaoning*, 2019, 33(2): 53-55.

9. Li H-L, Deng Y-T, Zhang Z-R, et al. Evaluation of effectiveness in a novel wound healing ointment-crocodile oil burn ointment. *Afr J Tradit Complement Alterm Med*, 2016, 14(1): 62-72 .

10. Wang Shu, Ge Bin, Tang Q-L, et al. Effects of MEBT/MEBO on EGFR expression in chronic refractory wound. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2018, 30(1): 1-11.

11. Yan A-Z, Di D-K, Zeng X-F, et al. Effect of MEBO impregnated gauze in the treatment of wound caused by

pemphigus vulgaris. *Guangdong Medical Journal*, 2017, 38(16): 2580-2581.

12. Zhang X-L, Zhang Hong, Gao Xin, et al. Clinical application of MEBO in skin injury caused by radiotherapy patients. *Gansu Medical Journal*, 2015, 34(4): 284-286.

13. Li J-H, Huang Xin, Tang Q-L, et al. Clinical observation of MEBT/MEBO in the treatment of diabetic foot ulcers. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2016, 28(1): 22-25.

14. Liu J-S, Yu Y-M, Gao Z-H, et al. Efficacy of regenerative medical technology in the treatment of diabetic foot ulcers. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2017, 29(4): 262-266.

15. Zhu K-S. Clinical effect of MEBO in the treatment of wounds caused by laser freckle removal. *Journal of Dermatology and Venereology*, 2019, 4(2): 300-301.

16. Bi S-F. MEBO in the treatment of 67 cases of residual wounds in late stage of deep burn. *China Rural Health*, 2017, 9(19): 53-54.

Moist Exposed Burn Therapy in Treating Hypopigmentation of Vulva

Jiang Fulan, Zhang Jing, Wang Xiangning, Yuan Yuan, Zhang Yanli, Fu Zijun, Tu Yiyao

Fund project: Research Project of Rongxiang Xu Regenerative Life Non-Profit Fund, Chinese Red Cross Foundation (2019-296)

Affiliation: Department of Gynaecology and Obstetrics (Jiang Fulan, Yuan Yuan, Zhang Yanli, Xu Yiyao) and Department of Burn Wounds (Zhang Jing, Wang Xiangning, Fu Zijun) of the People's Hospital of Pidu, 611730, Chengdu, Sichuan Province

Corresponding authors: Jiang Fulan, Email: 3064563037@qq.com

【Abstract】 Objective To study the efficacy of treating hypopigmentation of vulva with Moist Exposed Burn Therapy (MEBT). **Methods** 28 patients with hypopigmentation of vulva admitted to the People's Hospital of Pidu from February 2019 to March 2020 were treated with surgery combined with MEBT or MEBT alone. **Results** 16 patients who received surgery were completely healed with a healing time of 20.0 ± 2.4 days. 3 months after treatment, 18 patients healed and 10 patients were effective; 6 months after treatment, 19 patients healed and 9 patients were effective, both of which have an efficacy of 100%. No adverse reactions were reported during and after treatment. **Conclusion** Treating hypopigmentation of vulva with MEBT could significantly relieve itching, restore skin elasticity and improve patients' life quality.

【Key words】 Hypopigmentation of vulva; Moist Exposed Burn Therapy; Moist Exposed Burn Ointment; Itching of vulva

Hypopigmentation of vulva is a chronic disease featuring degeneration of vulva skin and pigment change[1], which is also called white lesion of vulva or vulval leukoplakia. It is characterized by severe itching of vulva and local pain caused by skin damage due to repeated scratching, which could cause patients difficulty sitting or lying and unable to sleep throughout the night. Or even worse, it could cause contraction of vulva, vaginal stenosis or difficulty with sexual activities, which severely impact patients' life quality and their family stability. Research shows that hypopigmentation of vulva which fails to receive regular treatment or not healed in time has the possibility of canceration, with a rate of 2%-5%.[2] The causes for this disease are not yet clear and there is no effective treatment with low recurrence rate available. So seeking an effective treatment to relieve patients from pain currently is a focus in clinical research. In this study, the author used Moist Exposed Burn Therapy (MEBT) in treating hypopigmentation of vulva and achieved satisfying clinical results.

1. Clinical report

1.1 Clinical data

28 patients (53.0 ± 3.5 years old) who were admitted to the People's Hospital of Pidu from February 2019 to March 2020 were enrolled. Pathological examination showed that 5 patients had squamous intraepithelial lesion (3 with low-grade and 2 with high-grade), and 11 patients had lichen sclerosus. This study was approved the ethics committee of the People's Hospital of Pidu and all patients signed informed consent forms.

1.2 Inclusion criteria and exclusion criteria

Inclusion criteria: diagnosed with hypopigmentation of vulva; follow-up was over 6 months; informed of this study and signed informed consent forms. Exclusion criteria: unable to cooperate during treatment due to mental illness; complicated with functional disorder of major organs such as heart, liver or kidney; allergic to Moist Exposed Burn Ointment (MEBO); had contraindication for use of estrogen; participated in other clinical trials at the same time.

2. Methods

2.1 Treatment methods

Examinations for blood, leucorrhea, coagulation function, liver and kidney functions, electrolyte, infection marker and electrocardiogram were performed. Lesion excision was conducted in 16 patients: after local anaesthesia, full-thickness excision was conducted within the lesion area and 5.0 mm beyond the lesion edge. During the excision procedure, tissue from the excision edge was taken and examined to be negative, then make #-shaped incisions on wound before applying MEBO and packing with MEBO impregnated gauze, indwelling catheter was inserted. After surgery, change dressing twice a day and continue to apply MEBO after wound was healed for 1 month to further improve treatment effect. For the other 12 patients who didn't require surgery, MEBO was used alone with the same method as above for 2 months.

2.2 Clinical outcome and evaluation standard

Clinical efficacy evaluation standard is as follows. Follow-up at 3 months, "healed": no recurrence of hypopigmentation of vulva, itching disappears or significantly relieves, skin elasticity and color basically returns to normal, pathological examination shows histological structure of skin returns to normal; "effective": no recurrence, itching relieves, partial recovery of skin elasticity and color, partial skin resumes normal histological structure; "ineffective": itching slightly relieves, no change or worsens, and no improvement of skin elasticity and color. Follow-up at 6 months, "healed": no recurrence, itching completely disappears or significantly relieves, skin elasticity and color basically returns to normal; "effective": no recurrence, itching relieves, partial recovery of skin elasticity and color; "ineffective": itching slightly relieves, no change or worsens, no improvement of skin elasticity and color. Efficacy=(number of healed cases + number of effective cases) / total cases×100%.

3. Results

3.1 Treatment results

16 patients who received surgery were completely healed with a healing time of 20.0 ± 2.4 days. 3 months after treatment, 18 patients healed and 10 patients were effective; 6 months after treatment, 19 patients healed and 9 patients were effective, both of which have an efficacy of 100%. No adverse reactions were reported during and after treatment.

3.2 Cases

Case 1: a 54-year-old female was admitted to our hospital for itching of vulva which lasted for over 2 months. The patient suffered from itching of vulva with unknown reasons 2 months before admission. Constant scratching caused skin broken with severe pain, difficulty sitting or lying, and unable to sleep throughout the night. To seek treatment, she came to our hospital. Examination on admission: hypopigmentation in the skin of bilateral labium majus, clitoris and perineum, partial skin and mucosa showing chapping appearance, thickening of bilateral labium minus, and small amount of exudates could be seen from the left labium minus (Figure 1). Clinical diagnosis: hypopigmentation of vulva complicated by squamous intraepithelial lesion of vulva; HPV infection. After admission, surgery was performed combined with the application of MEBO (Figure 2). At day 20, wound completely healed. Follow-up of 2 months found itching relieved, skin elasticity and color improved (Figure 3); Follow-up of 5 months showed itching significantly relieved and hyperpigmentation could be seen on partial healed skin (Figure 4); and follow-up of 7 months found histological structure of partial skin became normal (Figure 5).

Case 2: a 61-year-old female was admitted to our hospital for unrelieved itching of vulva for over 1 year. The patient suffered from itching of vulva with unknown reasons 1 year before admission. The patient also experienced difficulty sitting, lying and sleeping. To seek treatment, she came to our hospital. Examination on admission: hypopigmentation in the skin of bilateral labium majus, clitoris, posterior labial commissure and perianal skin, partial skin and mucosa showing white chapping appearance, thickening of partial bilateral labium majus, and part of labium minus shrank in size (Figure 6). Clinical diagnosis: hypopigmentation. After admission, surgery was performed combined with the application of MEBO. Follow-up of 2 months found itching of vulva significantly relieved, skin color partially improved, and size of white lesion significantly reduced (Figure 7-8).

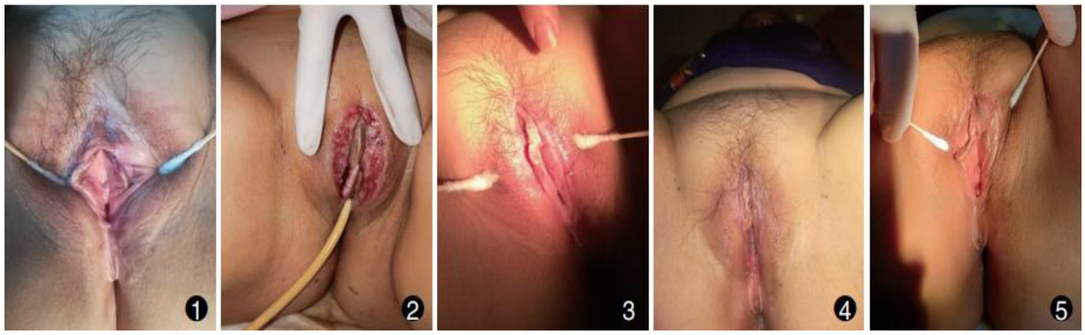

Figure 1. Before treatment; Figure 2. After surgery; Figure 3. 2 months after treatment; Figure 4. 5 months after treatment; Figure 5. 7 months after treatment

Figure 6. Before treatment; Figure 7-8. 2 months after treatment

4. Discussion

Currently, there is no effective treatment available for hypopigmentation of vulva due to its complicated causes and high recurrence rate. Therefore, how to effectively improve treatment effect remains a difficult problem in clinical research.[3-4]

Significant clinical effect has been achieved in treating multiple wounds including burns, diabetic foot ulcer and pressure ulcers as well as skin diseases with MEBT.[5-6] According to the treatment principle of MEBT, the author first conducted surgical debridement and then made #-shaped incisions on non-liquefied necrotic tissue within the epidermis layer. This allowed wound to be fully contacted with MEBO so as to activate local potential regenerative cells, promote growth of granulation tissues and epithelial cells, and restore normal elasticity, structure and color of skin.[7] In this study, itching of vulva was significantly relieved, and skin elasticity and color were significantly improved. The result demonstrated that MEBO could promote mirco-circulation, improve local blood supply and inhibit excessive proliferation and of fibroblasts. It could also prevent scar contracture caused by shrinkage of fibroblasts, which promotes recovery of the structure and functions of vulva tissues.[8-9]

In conclusion, treating hypopigmentation of vulva with MEBT could significantly relieve itching, restore skin elasticity and improve life quality of patients.

References

1. Xie X, Kong B-H, Duan T. Obstetrics and Gynecology [M]. 9th version. Beijing: People's Medical Publishing House, 2018: 234-236.

2. Buscema J, Stern JL, Woodruff JD. Early Invesive Carcinoma of the Vulva [J]. Am J Obstet Gynecol, 1981, 140 (5): 563-569.

3. Zhang Y, Tang Q-K. Clinical Observation in Treating 196 Patients with Cervical Intraepithelial Tumor-like Lesion with LEEP [J]. *Medical Journal of West China*, 2011, 23 (7): 1326-1327.

4. An Y-E, Zheng M-L, Zhang F-F. Clinical Diagnosis and Treatment of Intraepithelial Tumor-like Lesion of Vulva [J]. *The Chinese Journal of Human Sexuality*, 2019, 28 (8): 129-132.

5. Tang Q-L. Guidelines for Clinical Application of Moist Exposed Burn Therapy [M]. Beijing: China Press of Traditional Chinese Medicine, 2013: 91-100.

6. Xu R-X. Human Body Regeneration and Restoration Science [M]. Beijing: China Social Sciences Press, 2009:132.

7. Lv R-J, Liu X, Liu W, et al. Clinical Observation in Treating 55 Patients with Intraepithelial Non-Tumor-like Lesion of Vulva after Focuses Ultrasound Treatment with Moist Exposed Burn Ointment [J]. *China Practical Medicine*, 2014, 9 (10): 164-165.

8. Liu S, Zhang D-X, Li L. Clinical Observation in Treating 55 Patients with Vulva Ulcers with He-Ne Laser Radiation Combined with Moist Exposed Burn Ointment [J]. *Journal of Youjiang Medical University For Nationalities*, 2015, 37 (2): 270-271, 273.

9. Zhang H-Q. Clinical Observation in Treating Swelling of Greater Vestibular Gland of Vulva with Moist Exposed Burn Ointment Gauze Drainage [J]. Chinese Remedies & Clinics, 2016, 16 (2):254-255.

Efficacy of Moist Exposed Burn Therapy Combined with Adipose-derived Stem Cells in the Treatment of Chronic Refractory Wounds

Duan Qiong, Wang Jian, Liang Hongwei, Wang Tingjin

Affiliation: Plastic Surgery Department of Zhengzhou People's Hospital, Zhengzhou 450003, Henan Province

【**Abstract**】**Objective** To study the efficacy of Moist Exposed Burn Therapy (MEBT) combined with adipose-derived stem cell therapy in the treatment of chronic refractory wounds. **Method** 72 patients with chronic refractory wounds admitted to Zhengzhou People's Hospital from September 2017 to August 2019 were enrolled and randomly divided into study group (n = 36) and control group (n = 36) according to random number table. Patients in study group were treated with MEBT combined with adipose-derived stem cell therapy, and control group MEBT alone. Clinical efficacy at week 4 and week 8, and healing time were compared between 2 groups. **Results** At week 4, clinical efficacy of study group and control group: healed cases (5 vs. 1), significantly effective case (19 vs. 9), effective case (10 vs. 12), ineffective case (2 vs. 14) (z = -3.832, p < 0.001). At week 8, healed case (26 vs. 8), significantly effective case (7 vs. 11), effective case (3 vs. 17) (z = -4.463, p < 0.001). All wounds healed in both groups, and healing time of study group and control group were 39.85±22.48 days vs. 67.66±31.89 days (t = 4.277, p < 0.001). **Conclusion** MEBT combined with adipose-derived stem cell therapy could effectively promote the healing of chronic refractory wounds, and shorten healing time.

【**Keywords**】Regenerative medical technology; Adipose-derived stem cells; Moist Exposed Burn Ointment; Chronic refractory wound

As defined by World Union of Wound Healing Societies, chronic refractory wounds are wounds that fail to proceed through the normal phases of wound healing, or ones that fail to restore anatomic and functional results after treatment.[1] There are various causes for the formation of chronic refractory wounds, including old age, underlying disease, and recurring infection, which could lead to insufficiency of (or even no) potential regenerative cells (PRC).[2-3] At present, with the development of cell and molecular biology as well as regenerative medicine, adipose-derived stem cells therapy with regenerative effect, and Moist Exposed Burn Therapy have been used to treat chronic refractory wounds and become a focus in clinical research.[4-5] But combined use of adipose-derived stem cell therapy and MEBT has rarely been reported. In this study, efficacy of MEBT combined with adipose-derived stem cell therapy in treating chronic refractory wounds was studied.

1. Clinical data

1.1 Baseline data

72 patients with chronic refractory wounds admitted to Zhengzhou People's Hospital from September 2017 to August 2019 were enrolled and randomly divided into study group (n = 36) and control group (n = 36) according to random number table. Differences of baseline data between 2 groups showed no statistical significance (all p < 0.05) (Table 1). This study was approved by the ethics committee of Zhengzhou People's Hospital, and all patients signed informed consent document.

Table 1 Baseline data

Group	Cases (n)	Sex		Age	Wound size	Course of disease	Diabetic	
		Male	Female				Yes	No
Study group	36	21	15	48.6±25.1	23.8±11.5	49.9±28.7	11	25
Control group	36	18	18	52.4±29.5	25.7±15.8	45.5±32.2	9	27
χ^2/t		0.503		0.589	0.583	0.612	0.277	
p		0.478		0.558	0.562	0.543	0.599	

1.2 Inclusion and exclusion criteria

Inclusion criteria: 1. Patients is diagnosed with chronic refractory wounds; 2. For patients with diabetes, fasting blood glucose is stabilized within the normal range; for patients with vascular diseases, blood vessels are not completely occluded; for patients with radiation ulcers, radiotherapy is completed, or they no longer have exposure to radiation; and for patients with wound infection, infection is under control. 3. Patient is informed about the study and have signed informed consent forms voluntarily. Exclusion criteria: 1. Combined with heart, liver, kidney or other organ failure; 2. Combined with malignant tumor, Behcet's disease, severe anemia, Crohn's disease, or severe autoimmune disease; 3. Women in pregnancy or lactation. 4. Patient have received corticosteroids, immunosuppressants treatment within 3 months before enrollment.

2. Methods

2.1 Preparation of adipose-derived stem cells

10 minutes after local anesthesia (for drawing fat granules), a 3.0 mm-microcannula with perforations (diameter 1.0 mm) was connected to a 20 mL syringe. Fat granules were harvested radially. After drawing fat, syringe was placed vertically in ice-water mixture for 10 min. Supernatant was removed, and top layer of adipose tissue (1200 g) was centrifuged for 3 min. The supernatant was again removed, and adipose tissue was collected. Then adipose tissue was digested with 0.1% type I collagenase for 60 min. When adipose tissue became paste-like, phosphate buffer solution was added, and digestion was terminated. A 70 μm cell strainer was used for filtration, and the filtrate (2500 g) was centrifuged for 10 min, and supernatant was removed. 10% fetal bovine serum was added for culture.

Criteria for successful preparation is as follows. CD34 antibody is positive and CD45 antibody is negative on cell membrane as identified by flow cytometry. After osteogenic differentiation, the cells gradually changed from long spindle shape to polygon or irregular shape, and gradually proliferated and aggregated in clusters, and noticeable calcium deposits formed at week 4, and after histological staining, red calcium deposits could be seen under microscope. After adipogenic induction, cells proliferate slowly, and gradually changed from long spindle shape to polygon, circle, and ellipse shape. The volume of cells decreased, and fat droplets gradually emerged and aggregated in cytoplasm. At week 4, most of the cells were activated into adipose cells, showing obvious adipose formation.

2.2 Local treatment

Control group: After debridement, Moist Exposed Burn Ointment (MEBO) was evenly applied on wound, and MEBO impregnated gauze was placed on top or was packed in wound cavity (if any), and sterile dressing was used to secure. Dressing was changed once daily until wound healed completely.

Study group: After debridement, MEBO was evenly applied on wound, and MEBO impregnated gauze was placed on top or was packed in wound cavity (if any), and sterile dressing was used to secure. Dressing was changed once daily. When necrotic tissue was cleared and infection subsided on wound, adipose derived stem cells were injected subcutaneously (0.2 mL/cm^2) to wound base and peri-wound. MEBO was applied continuously until wound healed completely.

2.3 Clinical outcomes and evaluation criteria

Clinical efficacy at week 4 and week 8, and healing time were compared between 2 groups. Evaluation criteria was as follows. Healed: wound healed completely; significantly effective: wound healing rate ≥80% [wound healing rate = (wound size before treatment - wound size after treatment) / wound size before treatment × 100%]; effective: 50%≦wound healing rate<80%; ineffective: wound healing rate<50%. Total effective rate = (number of healed cases + number of significantly effective cases + number of effective cases) / number of total cases × 100%.

2.4 Statistical analysis

SPSS 22.0 was used for statistical analysis. Count data was represented as frequency or percentage, and tested by *chi-square* test or *rank sum* test. Measurement data that conforms to normal distribution was represented as mean ± standard deviation ($\bar{x} \pm s$), and independent-samples t-test was used for pairwise comparisons between groups. $p < 0.05$ is considered statistically significant.

3. Results

At week 4, clinical efficacy of study group and control group: healed case (5 vs. 1), significantly effective case (19 vs. 9), effective case (10 vs. 12), ineffective case (2 vs. 14); total effective rate (94.4% vs. 61.1%) ($z = -3.832$, $p < 0.001$).

At week 8, healed case (26 vs. 8), significantly effective case (7 vs. 11), effective case (3 vs. 17), total effective rate was 100% for both groups. ($z = -4.463$, $p < 0.001$).

All wounds healed completely in 2 groups, and healing time of study group was 39.85±22.48 days, which was significantly shorter than control group, 67.66±31.89 days ($t = 4.277$, $p < 0.001$).

4. Discussion

Wound healing is a complex biological process, including four stages: hemostasis, inflammation, proliferation and remodeling. Infection, ischemia, recurring damage, the presence of foreign bodies or necrotic tissue, combined immunodeficiencies, malnutrition or other diseases could affect wound healing at one of the wound healing stages and lead to prolonged wound healing.[6-7] Studies have shown that the molecular biological mechanism for prolonged wound healing could be division of cells and synthesis of bioactive factors that could effectively promote granulation tissue growth and angiogenesis are insufficient in chronic refractory wounds.[8]

Studies in recent years have shown that there is a large number of mesenchymal stem cells (MSCs) in fat tissue with the potential of in vitro proliferation and multilineage differentiation. And these MSCs could secrete vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), etc., which could promote wound healing.[9-10] While MSCs are derived from mesoderm, and they are conventionally believed to differentiate only into mesoderm derivatives. But some researchers have recently found that through gene reprogramming and use of inducer, they could differentiate into adipocytes, osteoblasts, cartilage cells, dopaminergic neurons, lymphatic endothelial cells, etc., and secrete some cytokines that promote wound healing in different stages.[15] Active constituents in MEBO could activate PRCs into stem cells which subsequently differentiated and proliferated into various tissue cells in situ for skin regeneration and wound healing.[11-13] These constituents in MEBO could react with necrotic tissue through a series of biochemical reactions such as hydrolysis, enzymolysis, rancidification, saponification, and esterification. As a result, necrotic tissue is liquefied and removed without damage. A physiological moist environment is also created, which facilitate skin regeneration and wound healing. However, chronic refractory wounds often lack stem cells or adipocytes that have potential of regeneration,[14] which prolongs wound healing.

In this study, MEBT and adipose-derived stem cell therapy were combined in the treatment of chronic refractory wounds. The result showed that compared with control group, study group had significantly higher efficacy and shorter healing time. Benefits of MEBT combined with ADSC therapy include: 1. injection of MSCs into wound tissue provides sufficient amount of PRCs, adipocytes, etc.; 2. MEBO provides a favorable physiological environment for the proliferation and differentiation of MSCs; 3. carbohydrates, fatty acids, amino acids, vitamins, etc. in MEBO provide sufficient nutrients for MSCs to ensure the normal differentiation and proliferation of MSCs.[16] Combined use of MEBT and adipose-derived stem cell therapy is more conducive to wound healing than MEBT alone.

In conclusion, the combined use of MEBT and adipose-derived stem cell therapy could significantly promote the healing of chronic refractory wounds. In addition, adipose tissue could be harvested from various sources, with minimal damage to donor site, and its use has few ethical issues. The use of autologous or closely matched ADSCs could prevent or reduce immune rejection, and could be applied widely in clinical practices.

Reference

1. Xiong J-C, Song J-X. Research progress of adipose-derived stem cells in the treatment of chronic refractory wounds. *Chinese Journal of Reparative and Reconstructive Surgery*, 2018, 32 (4): 457-461.

2. Zhuang Jing, Yang Yu, Ding Li, et al. Adipose-derived stem cells combined with collagen bioengineering scaffold transplantation to interfere the expression of VEGF in chronic refractory wounds of rats. *Chinese Journal of Tissue Engineering Research*, 2018, 22(33): 5274-5280.

3. Deng C-L, Feng J-W, Lu Feng. Research progress of adipose-derived stem cells in promoting the healing of refractory wounds. *Chinese Journal of Plastic Surgery*, 2017, 33 (6): 477-480.

4. Yin D-J, Sun J-Y, Zhao X-Z, et al. Research progress of combined traditional Chinese medicine and western medicine in situ skin regeneration therapy combined with adipose-derived stem cell therapy in the treatment of refractory wounds. *China Journal of Traditional Chinese Medicine and Pharmacy*, 2019, 34 (4): 1609 - 1613.

5. Chen M-H, Dang Y-N, Zhu X-D, et al. Feasibility of adipose-derived mesenchymal stem cell sheet transplantation to promote wound healing. *Chinese Journal of Tissue Engineering Research*, 2019, 23 (5): 790 - 796.

6. Yoshimura K, Asano Y, Aoi N, et al. Progenitor-enriched adipose tissue transplantation as rescue for breast implant complications. *Breast J*, 2010, 16 (2): 169-175

7. Wei C-Y, Gu J-Y. Research progress on the role of adipose-derived stem cells in chronic wound healing. *Chinese journal of Clinical Medicine*, 2017, 24 (4): 650-655.

8. Kim SS, Song CK, Shon SK, et al. Effects of human amniotic membrane grafts combined with marrow mesenchymal stem cells on healing of full-thickness skin defects in rabbits. *Cell Tissues*, 2009, 336 (1): 59-66.

9. Ding S-C, Zhang P-H. Research progress of autologous adipose stem cell transplantation in wound healing. *Hainan Medical Journal*, 2017, 28 (7): 1127 - 1129.

10. Jung KH, Song SU, Yi T, et al. Human bone marrow-derived clonal mesenchymal stem cells inhibit inflammation and reduce acute pancreatitis in rats. *Gastroenterology*, 2011, 140 (3): 998 - 1008.

11. Yin D-J, Zhao X-Z, Sun J-Y, et al. Application of Moist Exposed Burn Therapy combined with autologous nano-fat in chronic refractory wounds. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2019, 31 (1):

9-13.

12. Li Y-Z, Lei Yun, Chen Li, et al. Analysis of the effect of sequential application of Moist Exposed Burn Therapy and negative pressure wound therapy in the treatment of chronic refractory wounds. *The Chinese Journal of Burns Wounds & Surface Ulcers*, 2019, 31 (3): 153-156.

13. Tang Q-L, Zeng H-M, Wang Shu, et al. Effects of Moist Exposed Burn Therapy on the expression of PTEN in different periods of chronic refractory wounds in rats. *Chinese Archives of Traditional Chinese Medicine*. 2017, 35 (9): 2218-2221.

14. Zhang H-L, Liu J-H, Zheng Wei, et al. Clinical efficacy of local injection of adipose stem cells in the treatment of chronic diabetic ulcers. *Journal of Clinical and Pathological Research*, 2019, 39(9): 1940-1945.

15. Chen M-L. Related research topics of autologous fat transplantation. *Chinese Journal of Aesthetic Medicine*, 2019, 28 (2): 2-4.

16. Jiang Y-F. Epidemiological study of chronic refractory wounds on body in China. Beijing: PLA Medical College, 2011.

United Nations Academic Impact Global Regenerative Medicine Symposium was Held in China and Mongolia

On March 29, 2022, United Nations Academic Impact Global Regenerative Medicine Symposium, co-hosted by International Society of Regenerative Medicine and Wound Repair (ISRMWR), several hospitals in Mongolia, and People's Hospital in Pidu District of Chengdu, was held in a hybrid way and joined by more than 100 medical professionals from China, Mongolia, Thailand, South Korea, and the Philippines, etc.

Venue in China

Venue in Mongolia

In the kickoff session, Xu Weiwei, Director of Beijing Office of ISRMWR, introduced the mission and development of ISRMWR. Subsequently, Ms. Tuul, general manager of Lenus Medical Center updated the application of regenerative medical technology in Mongolia. In the end, Xu Fengcheng, President of People's Hospital in Pidu District of Chengdu, demonstrated the encouraging achievements from years of application of regenerative medical technology in the hospital.

As the symposium went on, 8 Mongolian doctors came up for a competition sharing their treatment experience using regenerative medical technology. Among them, Dr. Baljinnyam, Dr. Battulga and Dr. Baurjan stood out as winners, respectively sharing treatment of trauma on finger, DFU complicated with PVD, and boils and abscesses. Dr. Wang Xiangning, director of Department of Burn, Wound and Ulcer Surgery of People's Hospital in Pidu District of Chengdu, wrapped up the symposium by sharing a difficult case with extensive infection on lower extremity. Comprehensive thinking and rigorous treatment strategies were key to saving the patient's leg.

This was the second time that ISRMWR carried out international competition of clinical cases. This symposium not only served as a valuable platform for global medical staff communication, but also fueled up the development of regenerative medical technology.

The 54th Annual Meeting of the American Burn Association was held in Las Vegas

The 54th Annual Meeting of the American Burn Association (ABA) was held on schedule in Las Vegas from 5th to 8th April after 2 years' virtual meeting. Burn experts around the world were able to discuss face-to-face about how to better carry out academic researches and implement clinical treatments under the current circumstance during the 4-day meeting. It is believed that this meeting would greatly promote the exchanges and cooperation among global burn experts and push forward the future development of burn treatment.

The meeting covered various fields like burn prevention, wound reconstruction, surgery and critical care, rehabilitation, nutrition, psychology etc. In addition, the meeting again set up the ever-popular poster presentation, as well as various seminars and CME courses that could provide hands-on opportunities and stimulate in-depth discussion among attendees.

In addition to the academic sessions, well-designed booths also attracted the attendees. Attendees could learn about the latest research and development of drugs and medical devices as well as the most cutting-edge treatment methods.

MEBO International was once again invited by ABA as the gold-level sponsor this year to discuss the future development of burn treatment together with global experts. Mr. Luis Lu representing MEBO International had an in-depth discussion with the ABA Organizing Committee regarding how to further strengthen partnership between the two parties in the future.

Gold-level Sponsor

MEBO International has participated in the ABA for 6 years in a row since 2016, which not only fully demonstrated the achievements of regenerative life science on this world-class academic platform, but also established a close partnership with ABA. MEBO International and ABA will continue to work together closely in order to advance and innovate burn treatment worldwide.

Website
en.mebo.com

Facebook
@meboglobal

Twitter
@MEBOInternatio1

Instagram
@meboglobalcommunity