Topical Surface Modifiers to Accelerate Healing and Re-Epithelization Process in Vestibular/Gingival Extension Surgical Procedure

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Abstract

Background: Periodontal plastic surgeries with partial thickness flaps usually aim at increasing attached gingival length and management of recession. These procedures cause exposed connective tissue area which cause pain, discomfort to the patient and need long time for healing. Objective: The aim of the present study was to accelerate the healing process of vestibular/gingival extension surgical procedure by modulating the cellular metabolism, accelerating tissue re-epithelialization while subsequently decreasing patient experience of pain and discomfort through topical application of either hyaluronic acid gel (HA), or a moist exposed burn ointment MEBO post-surgically. Results: 21 subjects indicated for sulcus deepening procedure were selected and divided into three groups, following sulcus deepening procedure, surgical beds were managed with application of HA in group I, MEBO in group II or without applying any material in group III (control group). Evaluations were done by wound healing scores and VAS. Similar procedure was obtained experimentally for histological evaluation. Significant difference was found between both group I and group II in relation to the control group. While no significant difference was found between group I and group II. Histologically the incision area was completely covered by a thin layer of epithelium after 4 days in both groups I and II while in contrast to the control group. Conclusion: HA and MEBO can be used as topical surface modifiers to accelerate healing and re-epithelialization following sulcus deepening mucogingival surgeries.

Introduction

Periodontal plastic surgery is “surgical procedures performed to prevent or correct anatomic, developmental, traumatic or disease-induced defects of the gingiva, alveolar mucosa or bone.” (Proceedings of the World Workshop in Periodontics 1996).

Many soft and hard tissue procedures are designed to treat narrow zone of attached gingiva, shallow vestibules, and aberrant frena. (Friedman et al., 1957).

The vestibular extension procedure for increasing the width of gingiva using periosteal retention procedure (Staffileno, 1962, 1966) was introduced as a modification of denudation technique. (Ochsenbein, 1960) It involves removing the superficial portion of the oral mucosa within the wound area leaving the bone covered by periosteum.

The conventional procedure of deepening the vestibule and placing surgical pack for prevention of epithelial re-attachment is a successful procedure for gaining the width of attached gingival. However, patient experience post-operative pain along with potentially extended period of healing due to the large denuded subepithelial connective tissue area present common postoperative complication. (Viera, 2010)

Many inflammatory chemical mediators are released as a consequence of periodontal tissue injury caused by the surgical trauma. Together with stress, anxiety, nature, duration, and extent of surgery, also influence the pain intensity. Thus, postoperative pain and patient discomfort commonly occur following periodontal surgery. (Pillatti, 2006).

Tissue repair is a combination of dynamic interactive process that involves soluble mediators, blood components, the production of extra-cellular...
Hyaluronic acid (HA) is a linear polymer of glucuronic acid and N-acetylglucosamine disaccharide. The main function of HA includes tissue healing including activation and moderation of the inflammatory responses, promotion of cell proliferation, migration, angiogenesis and subsurface hydration (Bevilacqua, 2012, Koshal, 2007). Additionally, it also promotes re-epithelialization via proliferation of basal keratinocytes. HA is a hygroscopic macromolecule and its solutions are significantly effective with rapid hydration potential. In the oral mucosa, this property enables to maintain tissue hydration during periods of inflammatory process or response to tissue injury resulting in ulcer formation. (Lalenti, 1994, Kapoor, 2011)

Studies (Sutherland, 1998, Dahiva, 2013) have reported that Hyaluronan as a viscoelastic substance could assist in periodicontal regenerative procedures by maintaining spaces and protecting surfaces. It can influence the cell functions that modify the surrounding cellular and the extracellular micro and macro environments. The viscoelastic properties of the material may slow the penetration of viruses, and bacteria, a feature of particular interest in the treatment of periodontal diseases.

On the other hand, Moist exposed burn ointment (MEBO), is an oil-based ointment containing sesame oil, beta-sitosterol, berberine, and other small quantities of plant ingredients. (Rongxiang, 1994) It has been proposed as the ideal burn wound treatment. The main ingredient of MEBO is beta-sitosterol, which has been shown to have anti-inflammatory effects, (Gupta, 1980) and berberine, which has antimicrobial effects. (Trung, 1996)

Laboratory tests indicated that MEBO was not a mucocutaneous irritant nor orally toxic when used experimentally in rats. Additionally, repeated cutaneous patch tests in humans did not show any potential for dermal irritation or sensitization. (Anthony, 1994)

MEBO has been used also in the management of oral mucosa and upper gastrointestinal burn, and results showed favorable effectiveness with rapid wound healing without complications, the drug has also potent analgesic effect. (Hou, 2003)

The purpose of this study was to evaluate the effectiveness of hyaluronic acid shield, or MEBO as surface biological modifiers to accelerate wound healing, promote early re-epithelialization and controlling postoperative pain and discomfort following mucogingival surgeries.

MATERIALS AND METHODS

A. Clinical section:
21 participants lacking sufficient zone of attached gingiva with inadequate vestibular depth and indicated for sulcus deepening procedure were selected from Oral Medicine and Periodontology department, faculty of Dentistry, Alexandria University. All patients were systemically healthy and non-smokers, non-pregnant or lactating or taken drug therapy for the previous 3 months before surgery. Selected individuals were divided into three groups:

Group I: Consists of 7 subjects managed by vestibular extension surgery followed by application of Hyaluronic acid shield
Group II: Consists of 7 subjects managed by vestibular extension surgery followed by application of MEBO ointment
Group III: Consists of 7 subjects managed by vestibular extension surgery alone

Procedure:
History taking, clinical examination and periodontal evaluation were performed. Thorough scaling and root planing was applied for every participant.

For the vestibular deepening, a supraperiosteal incision was performed using Bard Parker blade no. 15, blunt dissection using periosteal elevator was performed displacing the muscle attachment in more apical direction until the desired new width is achieved. All surgical procedures were performed with the same clinician. After bleeding was controlled, surface managements were obtained as follow:

Group I: Mebo mixed with orabase (1:1) was applied on the denuded surgical bed, left for ten minutes then periodontal pack was applied.
Group II: hyaluronic acid shield gel was applied evenly on the wound and left for ten minutes then periodontal pack was applied.
Group III: control group, only periodontal pack was applied.

Oral hygiene instruction and medications which included antibiotics and analgesics (if needed) and patients were recalled after 7, 14, and 30 days postoperative. Fig 1, 2 and 3.

Clinical evaluation:
The type of wound bed was evaluated by clinical observation and the scores were determined as follows (AL-Mashhadane, 2012):

4 - Necrotic Tissue (Eschar): black, brown, or tan tissue that adheres firmly to the wound bed
3 - Slough: yellow or white tissue that adheres to the wound bed
2 - Granulation Tissue: pink or beefy red tissue with a shiny, moist, granular appearance.
1 - Epithelial Tissue: for superficial ulcers, new pink or shiny tissue that grows in from the edges or as islands on the wound surface.
0 - Closed/Resurfaced: the wound is completely covered with epithelium.

Evaluations were obtained at day 0.7 and 14.
Comparison of total scores measured over time and the duration of healing in days provide an indication of the improvement or deterioration in wound healing. The wounds were measured by two examiners also digital photograph was taken for each wound for all groups.

B: VAS scores (Huskinson, 1976)

Patients were given log diaries and instructed to record the intensity of pain, the period of healing. The recordings were made just immediately after treatment and following recovery from local anesthesia and every 2 days thereafter for the first week postoperatively.

Experimental section (Hashemipour, 2013)

15 male Dawley rats, weighing 200 g – 250 g and between 6–7 weeks of age, were purchased from the research Institute, Alexandria Egypt.

The animals were housed under standard conditions (23°C 25° C; 12 hours of lightdark cycles) and given laboratory food and water ad libitum throughout the study.

Adult male rats were used in 4 groups (n = 5 per group):

Group I: wound created plus hyaluronic acid shield application

Group II: wound created plus MEBO application

Group III: wound created without any topical material applied

A wound in form of mucosal defect measuring 2 mm in diameter and 0.2 mm in wall thickness was created into the hard palate of each rat.

All wounds were created by the same clinician.

For topical application, a swab was soaked in the appropriate study material and packed into the wound. For the control group no material was applied. Histological samples were harvested on post-surgery days 2, 4, 6, and 8. Each animal was weighed daily following the procedure.

Fig. 1: Clinical photographs showing the sulcus deepening surgical site (MEBO group) (a) healing after one week (b) and healing after two weeks (c).

Fig. 2: Clinical photographs showing the sulcus deepening surgical site (Hyaluronic acid group) (a) healing after one week (b) and healing after two weeks (c).
Fig. 3: Clinical photographs showing the sulcus deepening surgical site (control group) (a) healing after one week (b) and healing after two weeks (c).

Samples were cut at the mid-portion of the wound, were sent to the laboratory where each part was then embedded in paraffin. Cross sections of both portions were thinly sliced (5 μm) and stained with hematoxylineosin. Light microscopy was used to evaluate the pathological changes (e.g. granulation tissue formation and reepithelialization in wounds) and comparisons were carried out with the normal tissue. (Sainte-Marie, 1962)

Results:
Clinical results:

There was a statistically significant reduction in wound healing scores in relation to group I and group II, when compared to the control group III one week postoperatively. However, statistically insignificant change was found between group I when compared to group II. (table 1).

There was a statistically significant reduction in VAS scores in relation to group I and group II, when compared to the control group III at 2,4 days and 1 week postoperatively. While A statistically insignificant change was found between group I when compared to group II at the same periods. (table 2).

| Table 1: Comparison between HA, MEBO, and control groups according to wound healing score. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-------------|
| Healing score                                  | Control group   | Hyaluronic acid | MEBO            | P           |
| Day of the operation                           | (n = 7)         | (n = 7)         | (n = 7)         | p₁/p₂/p₃    |
| Median (Min. – Max.)                           | 4.0 (4.0 – 4.0) | 4.0 (4.0 – 4.0) | 4.0 (4.0 – 4.0) | 1.000       |
| Mean ± SD                                      | 4.0 ± 0.0       | 4.0 ± 0.0       | 4.0 ± 0.0       | 1.000/1.000/1.000 |
| 1 week                                         |                 |                 |                 |             |
| Median (Min. – Max.)                           | 2.0 (2.0 – 3.0) | 1.0 (1.0 – 2.0) | 2.0 (1.0 – 2.0) | 0.015       |
| Mean ± SD                                      | 2.33 ± 0.53     | 1.43 ± 0.53     | 1.71 ± 0.49     | 0.010/0.030/0.298 |
| 2 weeks                                        |                 |                 |                 |             |
| Median (Min. – Max.)                           | 1.0 (1.0 – 1.0) | 1.0 (0.0 – 1.0) | 1.0 (0.0 – 1.0) | 0.135       |
| Mean ± SD                                      | 1.0 ± 0.0       | 0.57 ± 0.53     | 0.57 ± 0.53     | 0.060/0.060/1.000 |

Abnormally quantitative data was expressed in median (Min. - Max.) using Kruskal Wallis test and Mann Whitney test between control with each other group

p₁: p value for comparing between control and Hyaluronic acid
p₂: p value for comparing between control and MEBO
p₃: p value for comparing between Hyaluronic acid and MEBO

*: Statistically significant at p ≤ 0.05

| Table 2: Comparison between HA, MEBO, and control groups according to visual analogue scale (VAS). |
|-------------------------------------------------|-----------------|-----------------|-------------|
| Visual analogue scale (VAS)                     | Control group   | Hyaluronic acid | MEBO         | P           |
| Day of the operation                           | (n = 7)         | (n = 7)         | (n = 7)      | p₁/p₂/p₃    |
| Median (Min. – Max.)                           | 9.0 (8.0 – 10.0)| 10.0 (8.0 – 10.0)| 10.0 (9.0–10.0) | 0.629       |
| Mean ± SD                                      | 9.29 ± 0.76     | 9.57 ± 0.79     | 9.57 ± 0.53  | 0.389/0.475/0.762 |
| 2 Days                                         |                 |                 |              |             |
| Median (Min. – Max.)                           | 4.0 (4.0 – 5.0) | 3.0 (2.0 – 3.0) | 3.0 (2.0 – 3.0) | 0.001*      |
| Mean ± SD                                      | 4.14 ± 0.38     | 2.57 ± 0.53     | 2.71 ± 0.49  | 0.001/0.001/0.591 |
| 4 days                                         |                 |                 |              |             |
| Median (Min. – Max.)                           | 4.0 (3.0 – 5.0) | 2.0 (1.0 – 3.0) | 2.0 (1.0 – 3.0) | 0.003*      |
| Mean ± SD                                      | 4.0 ± 0.82      | 2.0 ± 0.82      | 1.86 ± 0.90  | 0.003/0.003/0.735 |
| 1 week                                         |                 |                 |              |             |
Discussion:
Surgical periodontal procedures are considered an integral component of the recent approach to the treatment of periodontal diseases.

However, delayed wound healing and postsurgical patient perceptions of pain which occur as a consequence of surgical trauma and release of pain mediators following periodontal surgeries are common postoperative sequelae. (Hagenaars, 2004, Seymour, 1984, Dinarello, 1989, Shapero, 1992)

<table>
<thead>
<tr>
<th>Median (Min. – Max.)</th>
<th>3.0 (3.0 – 3.0)</th>
<th>1.0 (0.0 – 1.0)</th>
<th>1.0 (0.0 – 1.0)</th>
<th>&lt;0.001</th>
<th>0.001/0.01/0.591</th>
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<tr>
<td>Mean ± SD</td>
<td>3.0 ± 0.0</td>
<td>0.57 ± 0.53</td>
<td>0.71 ± 0.49</td>
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<td>2 weeks</td>
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<tr>
<td>Median (Min. – Max.)</td>
<td>0.0 (0.0 – 1.0)</td>
<td>0.0 (0.0 – 0.0)</td>
<td>0.0 (0.0 – 1.0)</td>
<td>0.329</td>
<td>0.141/0.53/0.317</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.29 ± 0.49</td>
<td>0.0 ± 0.0</td>
<td>0.14 ± 0.38</td>
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Abnormally quantitative data was expressed in median (Min. - Max.) using Kruskal Wallis test and Mann Whitney test between each group

\[ p_1: \text{p value for comparing between control and Hyaluronic acid} \]
\[ p_2: \text{p value for comparing between control and MEBO} \]
\[ p_3: \text{p value for comparing between Hyaluronic acid and MEBO} \]

*: Statistically significant at \( p \leq 0.05 \)

Histological results:
(Hyaluronic acid)

At 2 days postoperatively: The incision area in the palatal mucosa revealed local disruption of epithelial continuity. An interesting finding was the re-epithelization process by the presence of a few proliferative epithelial cells at both edges of the wound not completely bridging the incision. Disorganized, moderate density of ground substance were seen in the lamina propria adjacent to the wound area. (Fig 4 A)

At 4 days postoperatively: The incision area of the palatal mucosa was completely covered by a thin layer of epithelium. The lamina propria showed interlacing strands of collagen fibers and increased density of ground substance. The underlying connective tissue revealed proliferating fibroblasts with newly formed collagen fibers and well defined proliferating capillaries just beneath the incision area. (Fig 4 B)

At 8 days postoperatively: The full thickness of the keratinized epithelium was fully restored at the incision area of the palatal mucosa. There was a continued accumulation and fibroblastic proliferation in the underlying lamina propria beneath the incision area. Interlacing collagen fibers with considerable ground substance density and invading blood capillaries were also illustrated. The inflammatory reaction was substantially diminished in the lamina propria. (Fig 4 C)

(Mebo group)

At 2 days postoperatively: The incision area in the palatal mucosa reveals loss of epithelial thickness. The area at the base of the incision showed epithelial proliferation from both wound edges yielding a thin continuous epithelial layer gapping the incision and bridging the connective tissue. Moderate amount of collagen fibers and ground substance were detected. Recognized inflammatory cells infiltration and developing blood capillaries in the underlying lamina propria. Normal keratinized epithelium at both sides of the wound and lamina propria were seen. (Fig 4 D)

At 4 days postoperatively: The epithelial two edges of the wound in the palatal mucosa were completely incorporated together. An active fibrogenic mucosa process in the underlying connective tissue manifested by increased collagen fibers and ground substance density bridging the incision surface. Few inflammatory cell infiltration were observed in the healed lamina propria at the wound area. (Fig 4 E)

At 8 days postoperatively: Complete healing was observed at the incision area of the palatal mucosa. The epithelium covers its normal thickness. Differentiation of surface cells yields a mature keratinized epithelium architecture with normal re-epithelization and rete pegs. The underlying connective tissue revealed dense, well organized collagen fibers and its nearly devoid of inflammatory cell infiltration. (Fig 4 F)

(Control group)

At 2 days postoperatively: The incision area at the palatal mucosa reveals loss of epithelial thickness. The area at the base of the incision showed bar area of connective tissue. Few numbers of inflammatory cells were seen in the lamina propria. Irregular distribution of collagen fibers were observed in the underlying lamina propria. (Fig 4 G)

At 4 days postoperatively: The two epithelial edges of the wound area of the palatal mucosa were not completely incorporated together but re-epithelization started by a thin continuous layer of epithelium bridging the incision area was found. Mild inflammatory reaction could be seen in the lamina propria. (Fig 4 H)

At 8 days postoperatively: The two epithelial edges of the wound area of the palatal mucosa were now completely incorporated being covered by a thin epithelial layer persistence of a mild inflammatory reaction could be seen in the underlying connective tissue. (Fig 4 I)
Fig 4: A: (hayluronicacid ; 2 days postoperatively) Light micrograph showing disruption in the epithelial continuity of the palatal mucosa. Inflammatory cell infiltration and collagen fibers of moderate density are seen below the incision area. B: (hayluronicacid ; 4 days postoperatively) showing the incision area completely covered by a thin layer of epithelium. Inflammatory reaction with proliferating fibroblasts well seen in the lamina propria at the wound area. Newly formed capillaries are noted. C: (hayluronicacid ; 8 days postoperatively) showing normal thickness of keratinized epithelium regeneration covering the incisional surface with diminished inflammatory reaction in the lamina propria. Interlacing collagen fibers and a considerable amount of blood vessels are seen in the lamina propria. D: (Mebo ; 2 days postoperatively) showing normal keratinized mucosa at the sides of the incision. Inflammatory cell infiltration at the wound area.E: (Mebo ; 4 days postoperatively) showing complete corporation of the epithelial edges of the wound, few numbers of inflammatory cells were observed in the healed lamina propria. F: (Mebo ; 8 days postoperatively) showing the keratinized epithelium recovering its normal thickness and re-epithelization at the incision area. The underlying connective tissue revealed dense well organized proliferation and it is nearly devoid of inflammatory cells. G: (control ; 2 days postoperatively) showing discontinuity of the keratinized epithelium. Few inflammatory cell infiltration were observed in the incision area. Note: bare connective tissue at the base of the wound area. H: (control ; 4 days postoperatively) showing incomplete incorporation of the epithelial edges with a thin layer of epithelium bridging in the incision area. Mild inflammatory reaction are also seen in the lamina propria.I: (control ; 8 days postoperatively) showing thin epithelium covering the incision with mild inflammatory reaction is seen in the lamina propria (H&EX100).

It is well known that whenever wound edges following periodontal surgery are approximated, primary wound healing or healing with primary intention will occur, however, if wound edges are not approximated as in sulcus deepening process, healing will take place by secondary intention. (Del Pizzo, 2002) Complete wound healing by secondary intention is obtained between 2 to 4 weeks postoperatively, sometimes 5 weeks as in gingivectomy to re-establish normal gingival epithelialization. (Amorim, 2006)

Wound healing is a complex process involving a variety of cellular and matrix components acting in concert to reestablish the integrity of the injured tissue. The complexity of the healing response can be simplified into four broad categories that coincide with the temporal sequence of normal healing: hemostasis, inflammation, cell proliferation or granulation and tissue remodeling. After tissue injury, red blood cells and platelets aggregate and form an initial hemostatic plug to protect the wound. Within 24 hours, neutrophils enter the wound site and scavenge cellular debris, foreign bodies and bacteria. After 2-3 days, the inflammatory cell population begins to shift to macrophages and fibroblasts appear in the wound site. After 3-5 days,
the fibroblasts become activated and begin synthesizing collagen. As the collagenous matrix forms, densely packed fibers fill the wound site and during remodeling, the wound gradually becomes stronger with time. (Norton, 2003)

It has been reported that the oral mucosa heals faster than skin, and wound healing in the oral mucosa is clinically different from dermal wound healing in terms of both its rapidity and lack of scar formation. (Szpaderska, 2003) Several factors are believed to contribute to these differences such as gingival fibroblasts (Schor, 1996), saliva (Mandel, 1987) and many intrinsic factors (Zelles, 1995). However, the environment of the oral cavity with a relatively large commensal flora and the possibility of trauma from mastication can be deleterious to oral wound healing. (Nooh, 2003) Therefore, drugs that can protect the wound area and accelerate the wound healing process could be needed.

Studies (Cleland, 2001, Gjermo, 1989, Bae, 2001, Biswas, 2003, Davis, 1989) have shown that the topical application of antibiotics, amino acids, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), disinfectants such as chlorhexidine and vitamins have been used to help in oral wound healing (Gjermo, 1989) However, these drugs have many adverse effects such as gastrointestinal impairment, bacterial resistance, stimulation of the oral mucosa, discoloration and dysgeusia (Bae, 2001) Hence, Many researchers have examined the effects of medicinal plants, or naturally produced substances on wound healing and found that they could have more healing and fewer adverse effects than other chemicals (Biswas, 2003, Davis, 1989).

In the present study, the effect of medicines with plants extracts as and HA and MEBO on wound healing following mucogingival sulcus deepening procedure have been investigated.

The present study results revealed a statistically significant reduction in postoperative pain VAS and wound healing scores in relation to the studied test groups I and II, when compared to control group (group III).

The accelerated rate of healing with lowering in VAS scores observed in HA group (group I) could be explained by studies that found that HA has shown anti-inflammatory, anti oedematous, antioxidant and anti-bacterial effects of HA. (Dahiva, 2013)

This is in accordance to several studies Sutherland, 1989, Pirnazar, 1999, Laurent, 1995, Jentsch, 2003, Waddington, 2000) that demonstrated anti-inflammatory, antioxidant, antibacterial, and accelerated healing in management of oral mucositis, oral ulceration, recurrent aphthous stomatitis, and these effects have been attributed to the biocompatibility, viscoelasticity properties and bacteriostatic effects when HA was used over wound bed.

The anti-inflammatory effects of HA is suggested to be due to its action as a scavenger by draining prostaglandins, metalloproteinases and other bioactive molecules found in HA. (Sutherland, 1989) The anti-oedematous effect is suggested to be due its osmotic activity which helps accelerating wound healing. (Pirnazar, 1999) while the antioxidant effects is due to HA action in scavenging ROS thus help stabilizing the granulation tissue matrix. (Laurent, 1995) Additionally HA could reduce bacterial contamination by its bacteriostatic action on many oral bacterial species thereby, lessening the risk of postsurgical infection promoting more predictable regeneration. (Jentsch, 2003) lastly the violaceous nature of HA assistance in maintaining spaces and protecting wound surfaces that help influencing cell functions that modify the surrounding cellular and extracellular micro and macro environment of gingival and periodontal regeneration. (Waddington 2000)

In the present study MEBO has also a significant reduction in VAS and wound healing scores when compared with the negative control group. These effects of MEBO may be due to its action on the exposed nerve endings of the wound area. When MEBO smeared on the wound surface it’s found to function to continuously drain the exudates and protect the wound surface from the stimulation of nerve endings, so fulfill the analgesic effects. Moreover, ingredients contained in MEBO could function as activating blood and dissolving stasis thus improving microcirculation. MEBO with its sesame oil contents and herbal extracts also provides a physiological environment for wound repair. It also found to remove necrotic tissues and promote granulation tissue growth where the necrotic tissue plus the exudates will undergo estrification and hydrolysis and removed out of the wound leaving favourable environment for tissue growth and repair. (Gupta, 1980, Trung, 1996)

This is in accordance with previous study (Anthony, 1994) that use MEBO in treatment of upper gastrointestinal burn injuries where they found that MEBO stimulate healing by improving microcirculation, promote granulation tissue growth and provides physiologic environment for wound repair by inhibiting bacterial overgrowth and providing a protective membrane preventing bacterial invasion. Others indicated that meb0 cause continuous draining of exudates from the wound surface thus decrease stimulation of numerous distributed nerve endings on the wound surface which help the analgesic effects obtained from MEBO

Conclusions:

Topical application of either Hyaluronic acid or MEBO on wound bed following sulcus extension procedure can be used to decrease post -operative pain and to reduce re-epithelialization time through potentiation of healing.
Recommendations:
Further studies needed to clarify the healing effect of Hyaluronic acid and MEBO on other mucosal lesions and wound areas.

REFERENCES


