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Review Article

Evaluating the use of Erythropoietin Gel with Modified Apically Repositioned Flap in Augmentation of Keratinized Tissue: A Case Report

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Abstract

Background: The keratinized tissue aids in the protection and maintenance of periodontal health and contributes to stabilization of the gingival margin against frictional forces and against gingival recession. Modified Apically Repositioned Flap (MARF) is a technique used for increasing KTW by using a partial thickness flap. The exposed periosteal bed left after the surgery is an open wound that may cause patients to experience postoperative pain, bleeding and discomfort during the healing process. EPO is one of the various biological materials that was introduced to accelerate wound healing and to control post-operative pain and discomfort. This study was carried out to investigate the effect of topical application of erythropoietin when combined with MARF technique.

Method: A 35 years old female patient diagnosed with miller class I recession and deficient keratinized tissue apical to the recession, had MARF technique performed to increase KTW combined with application of chitosan based erythropoietin gel. Visual analogue scale was used to assess patient's postoperative pain and discomfort at day 1, day 5 and day 7 after the surgery. Healing index score was used at day 7 and day 14 to assess wound healing. The KTW was measured at baseline and 1 month after the surgery.

Results: Chitosan based erythropoietin gel controlled postoperative pain and improved wound healing at the surgical site. The KTW increased 2mm after the surgery.

Conclusion: The use of chitosan-based erythropoietin gel adjunct to modified apically repositioned flap (MARF) improved wound healing and decreased patient's postoperative pain and discomfort during healing.

Keywords: Erythropoietin Gel; Apically Repositioned Flap; Augmentation; Keratinized Tissue

Introduction

Periodontal tissues health and maintenance is thought to be related to the presence of an adequate width of keratinized tissue that helps to resist external injury and contribute to stabilization of the gingival margin against frictional forces. According to Friedman., *et al.* [1]. an insufficient zone of attached gingiva would facilitate the accumulation of subgingival plaque because of the movable marginal tissues and insufficient seal. So, an adequate zone of keratinized gingiva, at least 2 mm, according to Lang and Loe [2] is needed to stabilize the gingival margin, and aids in dissipating physiological forces.

Augmenting attached gingiva is one of the objectives of periodontal plastic surgery in order to protect the underlying periodontium and stop or delay the progression of gingival recession [3]. The modified apically positioned flap (MARF) approach uses a split-thickness flap lifted at the level of the mucogingival junction with a single incision, and it is secured apically to increase the width of attached gingiva. The periosteum is left exposed in the area where gingival augmentation is needed, leaving the marginal gingival tissues intact [4]. The surgical site is covered with a periodontal dressing for 3-14 days, and no soft tissue graft is utilized. Healing would probably be by 2ry intention [5].

The MARF technique gives the clinician the ability to control the width of the keratinized tissue to be created by suturing the flap at any desired apical position depending on the requirements of each case [6]. The gingival margin is left intact, so the risk of recession and attachment loss associated with the full thickness apically repositioned flap is reduced. There is no palatal donor tissue used in this surgical technique, so this split thickness flap has a low rate of morbidity and perfect tissue matching since the newly formed tissues mix in nicely with the adjacent gingiva [6].

Some post-surgical complications can arise that delay the healing process, cause persistent inflammation, induce necrotic or hyperplastic tissue responses, cause malformations and tumor like lesions, or cause post-operative bleeding or infection. These complications may result in retarded epithelialization and bone exposure [4].

EPO is one of the several biomaterials that have been developed to accelerate wound healing and to manage post-operative pain and discomfort. One of the mechanisms by which EPO promotes wound healing is by increasing angiogenesis. EPO stimulates the proliferation and differentiation of endothelial cells, leading to enhanced angiogenesis in the wound area. Because of the increased blood flow, the wound site receives more oxygen and nutrients, which speeds up the healing process. In addition, EPO has also been shown to increase the expression of VEGF, a potent angiogenic factor [8].

EPO also promotes wound healing by reducing inflammation during wound healing by reducing the expression of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta), IL-6, IL-12, and IL-23 in the wound area, leading to a reduction in inflammatory response Furthermore, EPO has also been demonstrated to promote fibroblast migration and proliferation, which are the cells responsible for producing extracellular matrix components, such as collagen and elastin [9].

Case Description

A 35 years old female patient presented to the Periodontology Department in Ain Shams University, with a chief complain of sensitivity and discomfort at lower right side, the patient was medically free. Upon clinical diagnosis the patient was diagnosed with Miller Class I recession in lower first premolar and deficient keratinized tissue beyond the recession (1mm). Initial examination was done including full mouth probing using UNC15[1] Periodontal probe. Full mouth supra and subgingival debridement was performed using ultrasonic device with supragingival scaling tips followed by universal and Gracey's curettes[2] for proper subgingival debridement.

Gel preparation

An alpha recombinant human erythropoietin liquid vial was used as source of EPO and was transformed to a gel form. 0.4 g of chitosan with low molecular weight was dissolved in 5 ml of 1% acetic acid in sterile water under stirring and was left until complete swelling. 1 ml of the provided EPO vial is stirred with chitosan for 10 min.1.6 g of glycerophosphate (GP) was dissolved in 2 mL of sterile water using water bath sonicator until completely dissolved.GP solution is added dropwise into the chitosan-EPO mixture under stirring. After all GP solution is added the gel left stirred for 30 min for being homogenous. The final gel with EPO was sterilized using UV and divided into 10 sterile syringes using sensitive balance. Each 1ml syringe has 50 mg low molecular weight chitosan, 0.2 g GP and 500-unit EPO [10]. The preparation of the gel was performed at Nawah Scientific Lab, Egypt.

Surgical procedure

Oral antiseptic mouthwash (Hexitol, The Arab Drug Company (ADCO), Cairo, Egypt.) was used before anaesthetizing the surgical area. Administration of local anesthesia was performed with articaine 4% and 1:200,000 epinephrine. Using a scalpel with blade number 15C (Trinon sterile scalpel blades, Germany), a partial thickness horizontal incision was made at the level of the mucogingival junction of the targeted area to be augmented. Coronally to the horizontal incision, the gingiva remained intact. No vertical incisions were performed. A split-thickness flap is elevated, and the dissection is extended 5- 6 mms in an apical direction. The flap is stabilized to the apical periosteal tissues with simple interrupted bio absorbable sutures (5-0 Suture Egysorb, Egypt). Release of any muscle fibers overlying the periosteum is performed [7].

Chitosan gel loaded with Erythropoietin (is applied to the surgical site using micro brush to cover the exposed periosteum and the patient is instructed to apply the gel two times daily for two weeks [10].

Postoperative instructions

Warm saline-soaked gauze was advised for the patient to use as part of her oral hygiene routine. and to avoid tooth brushing for the first 2 weeks. She was also instructed to stick to a soft diet and to avoid eating or drinking for two hours after applying the gel on the surgical site.

Results

Healing index was assessed according to Landry., *et al.* (1988) [11] on the 7th and 14th postoperative days following surgery. This index assesses wound healing using scores from 0 to 5: a wound with very poor healing receives a score of 0, whereas excellent healing receives a score of 5 The healing index score was 3 at day 7 and increased to 4 at day 14. The visual analogue scale showed a score of 4 on day 1, 2 at day 5 and decreased to 1 after one week. The width of the keratinized tissue increased from 1mm at baseline to 3 mm 1 month postoperatively.

[1]UNC15 Periodontal probe, Nordent Manufacturing Inc, USA

[2]HuFriedy universal and Gracey's curette; HuFriedy, Chicago, USA.

Discussion

EPO is one of the various biological materials that was introduced to accelerate wound healing and to control post-operative pain and discomfort. Studies on human dermal wounds have showed the presence of EPO receptors on several cell types such as endothelial cells, macrophages and fibroblasts and basal cell layer of the normal oral mucosa [12,13]. Consequently, it was expected to accelerate wound healing. Due to the possible positive effects of erythropoietin, the aim of the current study was to investigate its influences on wound healing and postoperative pain and discomfort following MARF technique as this is the first study to use EPO gel in conjunction to MARF technique.

A chitosan-based EPO gel was used to cover the surgical site. The patient was instructed to apply the gel to the surgical site twice a day. According to Lindhe., *et al*. [5] this is the expected time of epithelialization of the split-thickness flap. The main events of periodontal wound healing are usually completed within two to three weeks, followed by tissue maturation and remodeling.

Regarding pain perception using VAS, the patient experienced mild to moderate pain on 1st day of surgery and the pain decreased gradually to minimal throughout the first week. The decrease in pain perception is thought to be related to the anti-inflammatory properties of EPO. EPO blocks nuclear factor kappa B (NF)-kB activation, as well as inactivation of cyclooxygenase 2 (COX-2), suppression of pro-inflammatory mediators, such as TNF-α, IL-1β, IL-6 and stimulation of IL-10 production. Through these multiple mechanisms of action, EPO presents an important role in the reduction in inflammation, apoptosis, and oxidative stress, due to hypoxia, toxicity, or injury [12,13].

Rahimzadeh., *et al.* [14] concluded that intra-articular prescription of erythropoietin in the joint is more effective for pain management in knee osteoarthritis patients than dextrose or pulsed radiofrequency. Moreover, Hosseinjani., *et al.* [15] detected less pain and severity of oral mucositis in patients receiving EPO mouthwash (50 IU/ml, 15 ml four times a day) during chemotherapy compared to those who received placebo mouthwash.

The surgical site showed convenient healing throughout the first 2 weeks. Yaghobee., *et al.* [16] showed that EPO could accelerate the rate of healing and reduce the degree of inflammation by detecting that areas treated with 1ml EPO gel in comparison to distilled water generally healed faster and experienced less inflammation compared to the control sites.

The KTW increased 2 mm from baseline to 1 month postoperatively. Carnio., *et al*. [7] demonstrated that the apico-coronal dimension of the keratinized tissue increased significantly compared to baseline when using the MARF technique. Keratinized tissue increased from 0 mm to 3.6 mm (Figure a-g, table 1-3).

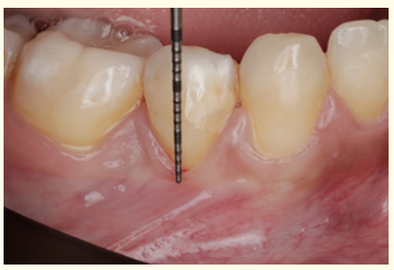

Figure a

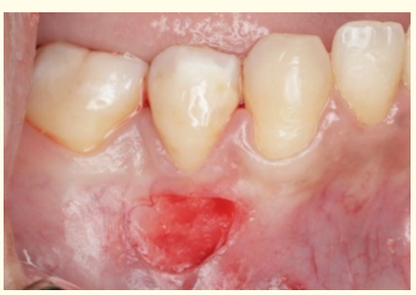

Figure b

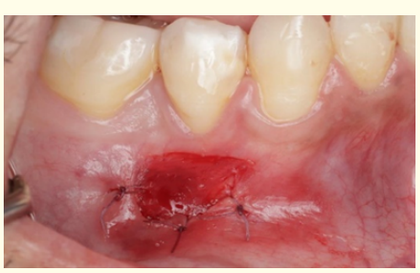

Figure c

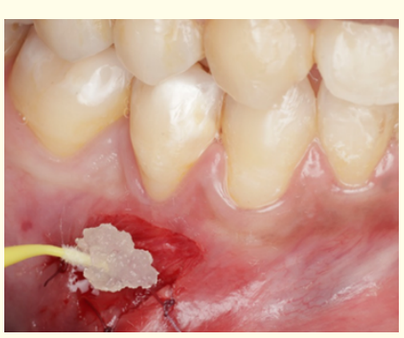

Figure d

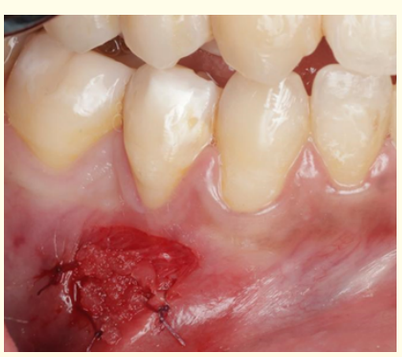

Figure e

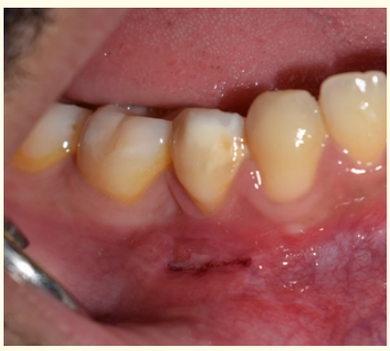

Figure f

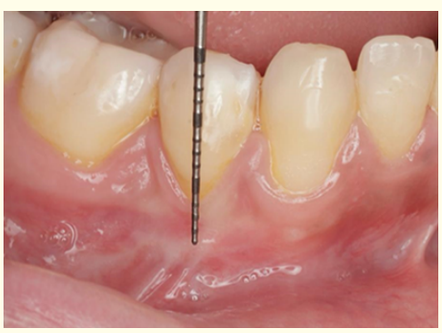

Figure g

Time	Clinical parameters	
	KTW	Attached Gingiva Width
Baseline	1	0
1 month	3	2

Table 1

Time	Healing index score
Day 7	3
Day 14	4

Table 2

Time	Visual Analogue Scale
Day 1	4
Day 5	2
Day 7	1

Table 3

Conclusion

It appears that chitosan-based erythropoietin gel may accelerate wound healing and reduce pain and inflammation in modified apically repositioned flap surgical site, which could be related to improved angiogenesis, epithelialization and decreased secretion of proinflammatory cytokines.

Conflicts of Interest

The authors declare no conflict of interest.

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