

Effect of aloe vera hydrogel on the scarring and healing of free gingival graft: Randomized controlled trial

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Abstract

OBJECTIVE: Several studies have used aloe vera hydrogel to enhance various tissues regeneration to reduce scar formation in wounds. This study aimed to prepare a hydrogel specified for the oral cavity and observe scar formation and healing of free gingival graft after its application compared with the natural healing and scarring of the graft without any material.

MATERIALS AND METHODS: This study is a randomized controlled clinical trial that included 22 patients with a width of attached gingiva less than 2 mm. after preparing the aloe vera hydrogel and completing the laboratory stage, the hydrogel was randomly applied for 11 patients after the free gingival graft procedure while the other 11 patients did not use any material after the same surgery. Landry's scale was used to assess the healing index, scarring was evaluated using Mucosal Scarring Index.

RESULTS: The healing index was higher in the intervention group with a statistical difference $P < 0.05$ than the control group after three weeks. Moreover, Scar formation in the intervention group was less in the intervention group with a significant difference $P < 0.05$ after 1,2,3,6 months.

CONCLUSION: Within the limitations of our study, the aloe vera hydrogel can be considered as a good topical treatment after oral surgery due to its ability to reduce scar formation and speeding up the healing in the receiving area in free gingival graft procedures.

KEYWORDS: free gingival graft; aloe vera; hydrogel; scarring

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Introduction

Several procedures were proposed to increase the width of the attached gingiva such as apically repositioned flap and subepithelial connective tissue graft. However, the free gingival graft is the gold standard for obtaining an adequate amount of it around teeth and implants,¹ but Free

gingival graft is associated with several complications in the receiving area, such as graft shrinkage after several months and lack of color matching between the graft and the surrounded area, where the graft appears as a patch giving a result that is not satisfying for patients.²

The traditional gingival dressings were initially used as a mechanical barrier only, which helped to prevent external factors from the wound area, but these dressings don't affect cell activity or have any role in the biological events that occur during wound healing (Review, n.d.). furthermore, these dressings do not

reduce pain after surgery or affect the speed of healing, as some studies had shown that healing without applying a dressing was better than applying it.⁴

Therefore, studies have tended to find substances that enhance healing and reduce following complications.

In addition, the indiscriminate use of drugs and the development of many antibiotic-resistant strains of germs directed scientists to look for alternative natural treatments and developed the ability to apply them topically.⁵

The number of orally topically applied drugs is very small, and they have been formulated similarly to those applied in dermatological treatments, without paying attention to the structural, environmental, and functional characteristics of the oral cavity.

In addition to the presence of saliva and its role in the instinctive cleaning in the oral cavity, which leads to decreasing the drug dosage which has been applied.

Therefore, it is necessary to obtain medicinal materials capable of adapting to the specificity of the oral cavity.⁶

Hydrogel is a three-dimensional hydrophilic mesh that absorbs a large amount of water and vital fluids.⁷

Aloe vera has been used for centuries because it has many advantages and

medicinal properties, because it is composed of a mixture rich in materials that accelerate healing, such as (vitamins, minerals, enzymes, sugars) but the therapeutic properties of each of its seventy-five components alone have not been determined yet.⁸

Topical application of aloe vera gel stimulates the activity of fibroblasts and collagen proliferation,⁹ because they contain glucomannan (a polysaccharide-rich in mannose) and gibberellin (a growth hormone) that interact with the growth factor receptors on the fibroblasts and increase their ability to reproduce.¹⁰

Hydrogels are commonly used in the biomedical fields and due to their ability to absorb different amounts of water, their properties have been modified in laboratory studies to be compatible with various biological systems.¹¹

The importance of this research comes from the hydrogel was used in it. Because it was specially formulated to comply with the oral cavity particularity, and it could stick to the mucosa so the desired effect of aloe vera increased without disturbed the patient or confused the treating doctor while dealing with traditional dressings.

This research aimed to study the effectiveness of aloe vera hydrogel on free gingival graft healing and reducing scarring in the receiving area.

Material and Methods

The laboratory stage

Hydrogel components

Aloe vera, Vitamin E, Glycerin, Water of injection, Carpobol 940, Hydroxypropyl Methylcellulose (HPMC), Acacia, Sodium benzoate, sorbate potassium, NaOH.

Aloe vera hydrogel preparing

Two laboratory forms of aloe vera hydrogel were prepared, the excipients made from [Glycerin (0.38%), Water of injection(14.3%), Carpobol 940 (0.97%), Hydroxypropyl Methylcellulose (Hpmc) (0.24%), Acacia (0.24%), Sodium benzoate(0.38%), sorbate potassium(0.2%)], these components were weighed by an electronic scale (Precisa company/ UK) according to specific quantities for each one then NaOH was added, two equal quantities were prepared and sterilized in Autoclave (JSR company, India) in 121C for 15 minutes, then the aloe vera and vitamin E mix were added to the excipients to made 100 ml from hydrogel, vitamin E percentage was (0.52%). The excipients and aloe vera were mixed in a planting tent (Class II, JSR company, India) to maintain the sterility of the material in two ways: the first quantity of excipients was mixed with the filtered aloe vera gel using sterile filters (Isolab®) and mix the second amount of excipient with aloe vera gel without filtering. the

hydrogel pH was measured by (PH 211, HANNA, Italy) and it was 6.35, the viscosity measured by (MYR rotary viscometer VR 3000, Spain) and it was 3333 centi Poise, the aloe vera percentage in the hydrogel was 82.52%.

A sterility test was performed for the resulting forms, and the two forms did not initiate any bacterial growth.

The hydrogel was filled with listed syringes and kept in a cool dry place to preserve its properties.

The hydrogel stuck to the work area for about half an hour, and the tissues absorbed it during this period.

The hydrogel was approved without filtration to facilitate the pre-clinical preparation.

The laboratory stage was carried out at the faculty of pharmacy, Damascus University.

Clinical stage

The study was registered in isrctn.com (registration number ISRCTN58370471) and conducted following the Helsinki Declaration of 1975 and was approved by the internal Ethical Committee of Damascus University No. 3679. Written informed consent was obtained from all patients who participated in this project. The sample size was determined based on the null hypothesis, which states that the aloe vera hydrogel has no effect

on free gingival graft healing and reducing scar formation in the receiving area. The confidence level was determined by 95%, the desired sample power was 95%, then G power (version 3.1.9) was used, and the required sample size was 22 patients. The CONSORT statement has been used, and the CONSORT flow diagram illustrates the research process (Figure 1).

Statistical Analysis

In this study, the level of significance (p-value) and power of the study was set at 0.05% and 95%, respectively. Mann-Whitney U test was done to evaluate mucosal scarring index and wound healing index.

All statistical analyses were conducted using SPSS 25.0 for Windows (SPSS Inc. Chicago, IL, USA).

2.3 Clinical Study design:

This study is a randomized clinical trial (RCT) which was conducted on patients from the department of periodontics, faculty of dentistry, Damascus University, Syria. With a total number of 22 patients. The procedure was explained to patients, written and verbal consent was obtained for the surgery and follow-ups.

Inclusion and exclusion criteria

The recruitment process began in (1/11/2020) and follow-ups were done for six months respectively after the placement of test materials. 22

participants were selected from patients attending the Periodontal Department at the Faculty of Dentistry, Damascus University that matched the following Inclusion criteria a) attached gingiva width is less than 2mm b) age is over 18 years old d) good oral hygiene.

Subjects were excluded if they had a) teeth mobility at graft place b) periodontitis patient c) patients with systemic diseases d) smokers e) pregnancy/lactation.

Clinical study phases

Pre-surgical phase

All patients received a full intra-oral examination, periodontal tissues were examined, and the following clinical index was recorded: plaque index, gingivitis, bleeding on probing, and attached gingiva width. As all this information was recorded on a special sheet for each patient, which also contains his personal information. Scaling and root planning were done for each patient and oral hygiene instructions were given; this session took place three weeks before the surgical procedure.

Surgical procedure

Local anesthesia was done using lidocaine 2% containing 1: 80,000 adrenaline. The flap design started with a horizontal incision following

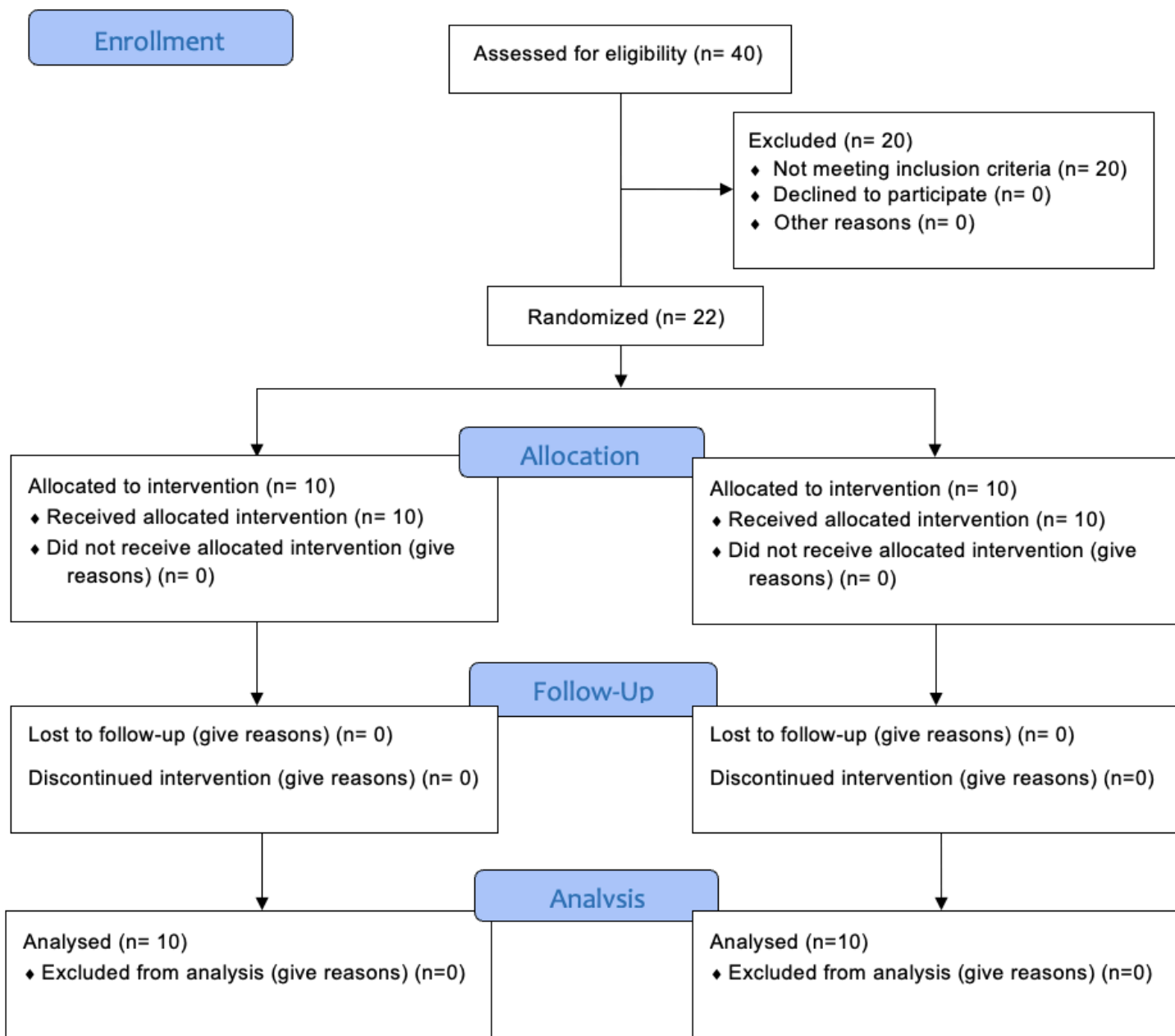


Figure 1. CONSORT 2010 Flow Diagram

the mucogingival junction (MGJ) and measuring approximately 12 mm. mesiodistally, 8 mm apico-coronally. a periosteal bed was prepared. Gauze moistened with saline was placed over the recipient bed until graft placement.

Obtain the graft from the donor site: The epithelial gingival graft is harvested from the palate with dimensions (12 x 8) using a #15 surgical blade from the side of the canine to the first molar at a distance

of 3 mm from the free gingival margin.

Graft placement: The graft was positioned and firmly adapted to the recipient area and stabilized with suspensory periosteal sutures (4-0 nylon monofilament), the sutures

were made with two sutures on both ends of the graft and an x-shaped suture minimizing any suturing-related trauma to the graft (Figure 2).



Figure 2. Hydrogel syringe with special heads

Post-surgical care

Each patient was given post-surgery instructions orally and written. And to avoid hard food in the first week, cold and hot food and drinks within 3 days, avoid lip, cheek, or lip lifting.

Each patient was given prescription:

1- Amoxicillin mg three times daily for five days

2- Panadol 500 mg three times daily for five days

Each patient in the test group was given the following instructions for using aloe vera hydrogel: Patients were recommended to apply 1/2 ml of hydrogel two times daily for ten days, and to store the syringe in a cool and dark place (Figure 3,4).

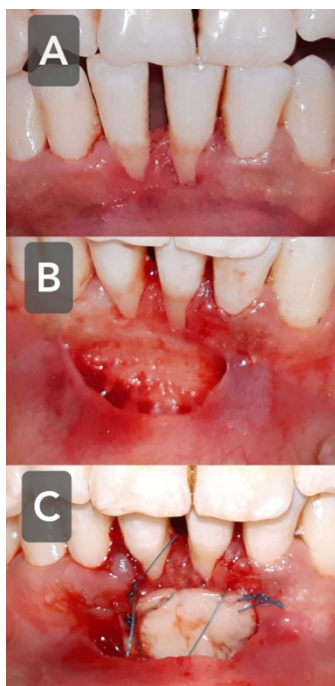


Figure 3. Free gingival graft surgical procedure
A: Before the surgery
B: periosteal bed
C: Graft placement

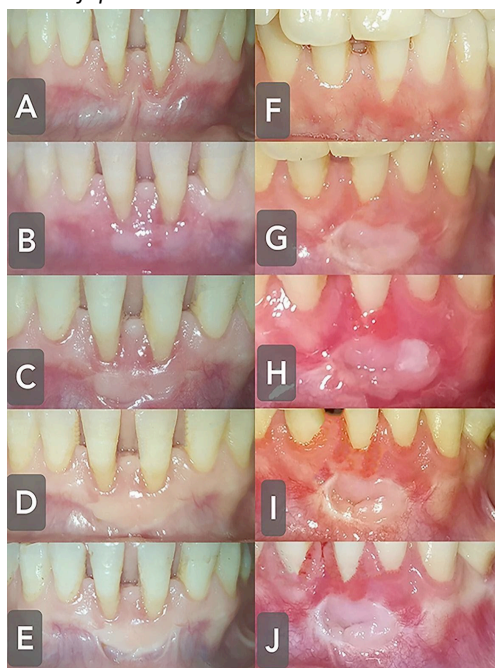


Figure 4. Free gingival graft (FGG) healing and scarring
{A, B, C, D, E: test group}
A: before (FGG), B: after three weeks, C: after one month, D: after three months, E: after six months
{F, G, H, I, J: control group}
F: before (FGG), G: after three weeks, H: after one month, I: after three months, J: after six months

Recalls took place after 1, 2, 3, 4 weeks and after 2, 3, 6 months.

Mucosal Scarring Index (MSI) is based on five parameters: width, height/contour, color, suture marks, and overall appearance. Each parameter was assessed with a 0–1–2 score, yielding an MSI score ranging from 0 (no scar) to 10 (most extreme scar).¹²

The scar was evaluated at all follow-up periods, and it was mild if the total score was less than 3, moderate if the score was between 3 and 7, and severe if it was more than 7

The wound Healing index was evaluated using Landry's et al index 1985.¹³

Results

22 patients participated in this study, randomly divided into two groups using a coin. control group to observe natural healing (11 patients) while in the intervention group aloe vera hydrogel was applied (11 patients). All patients continued all the follow-ups and there was no dropout.

The mean of patient's ages was 35 years, while the percentage of males was 27.3% and females were 72.3%. The plaque index was less than 1, attached gingiva width was less than 2 mm at baseline.

Statistical Package for the Social Sciences (SPSS 25.0 for Windows) was used to analyze data, statistical

difference was considered in value less than 0.05. Table 1 contains the results of mucosal scarring index (MSI) after 1, 2, 3, 4 weeks and after 2, 3, 6 months.

Table 1 contains the results of mucosal scarring index (MSI) after 1, 2, 3, 4 weeks and after 2, 3, 6 months. A positive significant difference was observed between the two groups after one month ($p=0.008$, effect size

$r=0.6$), after two months ($p=0.001$, effect size $r=0.8$), and after 3 months ($p=0.001$, effect size $r=0.8$), and after 6 months ($p=0.001$, effect size $r=0.6$) where the intervention group surpass the control group with less scar formation (Table 1).

Table 2 contains the results for the healing Index after 1, 2, 3, 4 weeks and after 2, 3, 6 months.

A positive significant difference was observed after 3 weeks ($p=0.031$ effect size $r=0.4$), the intervention group surpassed the control group. While no statistical difference was observed between the groups at 1, 2, 4 weeks, and at 2, 3, 6 months.

Discussion

The growing interest in maintaining healthy gingiva is due to its great

Table 1: Scarring index in the receiving area

	Study groups	number	Ranks Average	Total Ranks	P value	z	Effect Size r
Scar after one week	Test	11	11.50	126.50	1.000	0	0
	control	11	11.50	126.50			
Scar after two weeks	Test	11	10.18	112.00	0.298	-1.04	0.2
	control	11	12.82	141.00			
Scar after 3 weeks	Test	11	9.95	109.50	0.213	-1.244	0.3
	control	11	13.05	143.50			
Scar after a month	Test	11	8.23	90.50	0.008	-2.635	0.6
	control	11	14.77	162.50			
Scar after 2 months	Test	11	6.36	70.00	0.001	-4.056	0.8
	control	11	16.64	183.00			
Scar after 3 months	Test	11	6.36	70.00	0.001	-4.056	0.8
	control	11	16.64	183.00			
Scar after 6 months	Test	11	6.36	70.00	0.001	-4.056	0.8
	control	11	16.64	183.00			

Table 2: Healing index in the receiving area

	Study groups	number	Ranks Average	Total Ranks	P value	z	Effect size r
Healing after one week	Test	11	10.59	116.50	0.328	-0.978	0.2
	control	11	12.41	136.50			
Healing after two weeks	Test	11	12.36	136.00	0.505	-0.667	0.14
	control	11	10.64	117.00			
Healing after three weeks	Test	11	13.50	148.50	0.031	-2.160	0.4
	control	11	9.50	104.50			
Healing after a month	Test	11	12.50	137.50	0.147	-1.449	0.3
	control	11	10.50	115.50			
Healing after two months	Test	11	11.50	126.50	1.000	0	0
	control	11	11.50	126.50			
Healing after 3 months	Test	11	11.50	126.50	1.000	0	0
	control	11	11.50	126.50			
Healing after 6 months	Test	11	11.50	126.50	1.000	0	0
	control	11	11.50	126.50			

effect on increasing the ability of patients to control dental plaque,

which contributes to improving the oral health of individuals, so the best

treatment technique must be chosen to achieve the best results and obtain

the patient's satisfaction with attention to surgical complications and consider them while making a treatment plan.¹⁴ This hydrogel was formulated to avoid the drawbacks of topical application of drugs, especially in the oral cavity, which considers as a part of the mucous adhesive that secures adhesion to the oral mucosa, and leads to enhance the bioavailability of the drug in the treated area¹⁵, increases the drug contact with the tissues and reduces the frequency of drug administration and facilitates Dose control and drug termination.¹⁶ Several recent attempts have been made to investigate the benefits of applying hydrogels containing aloe vera for tissue regeneration.^{17 18} And this was the first study that applied hydrogel after free gingival graft to promote healing and reduce scarring in the area.

The scar formation was severe after a week (90.9%) in the test group, and it became mild (90.9%) after two months. While it was severe by (90.9%) in the control group by one week, and after 3 months it remained severe by (27.3%), and moderate by (72.7%). The absence of statistically significant differences in the first weeks is due to the irregularity of collagen fibers in the area, where the collagen fibers are at the beginning of the third stage of healing stages and the amount of glucosaminoglycans is large and the fibroblast cells turn into fibrous cells and the small-diameter blood vessels disappear, which forms

a scar in the area. During the healing process and after applying aloe vera to the area, the glucosaminoglycan content in the area decreases, the weakly structured collagen type III is replaced with collagen type I, the fibers regularity increases, the type of cross-linking improves, and the distance between them is reduced, which lead to reducing scarring in the treated area.^{19 20}

Aloe vera improved the ulcer's appearance. dimension and redness reduced and its color was similar to the adjacent mucosa color after healing in the study.²¹

(AR Pradeep et al, 2015) study results showed that the usage of aloe vera hydrogel improved clinical indices of patients with periodontitis in clinical attachment level, as well as decreasing probing depth and bleeding on probing, due to the healing properties of aloe vera.²²

It is noticed that the healing was weak in (81.8%) after one week in the test group, and recovery was completed in all samples (100%) after 3 weeks in the test group. Whereas healing was weak after a week (81.8%) in the control group, and healing was not completed at 100% after two months of surgery in the control group, which showed the superiority of the test group with statistically significant differences P-value < 0.005.

This is attributed to the mechanism of aloe vera in improving wound healing

by maintaining wound hydration, increasing epithelial cell migration, accelerating collagen maturation, enhancing collagen cross-linking, as well as increasing blood flow to the area.²³

The precise mechanism of the effect of aloe vera in wound healing is also attributed to the acceleration of the healing stages compared with natural healing, as it speeds up the end of the inflammatory phase by increasing the blood flow by accelerating the formation of new blood vessels in the area and reducing the amount of edema. The number of phagocytes increases in the area, which speeds up the process of phagocytosis and damaged tissues removal and reduces the lifespan of fibrin clot,²⁴ the polysaccharides present in aloe vera such as acemannan and mannose play a major role in increasing the number of phagocytes and cytokines.²⁵

Glucosaminoglycan and Hyaluronic acid also interact with growth factor receptors on the fibroblasts and stimulate their activity and proliferation, which increases collagen formation.⁹

Our study results were similar to (Ghada Mansour et al, 2014) study where the use of an aloe vera mucoadhesive gel accelerated the healing of aphthous ulcers and the location of the ulcers after healing was similar to the color of the adjacent mucosa.²¹

Conclusion

In this study limits, the aloe vera hydrogel can be considered as a good topical treatment after oral surgery due to its ability to reduce scar formation and speeding up the healing in the receiving area in free gingival graft procedures.

Ethics statement/confirmation of patients' permission

Ethics permission was taken from Damascus University board under number 3679. The patients gave permission for the procedure.

References

- Zuhr O, Bäumer D, Hürzeler M. The addition of soft tissue replacement grafts in plastic periodontal and implant surgery: Critical elements in design and execution. *Journal of clinical periodontology*. 2014;41 Suppl s:S123–S142. doi:10.1111/jcpe.12185
- Bertl K, Melchard M, Pandis N, Müller-kern M, Stavropoulos A. Soft tissue substitutes in non-root coverage procedures : a systematic review and meta-analysis. *Clinical Oral Investigations*. 2017. doi:10.1007/s00784-016-2044-4
- Review A. of Early Healing Events Periodontal Repair : A Review Significance. :158–165.
- Murthykumar K, Rajasekar A, Kaarthikeyan G. Assessment of healing after periodontal flap surgery with and without periodontal pack. *International Journal of Pharmaceutical Research*. 2020;12(August):125–130. doi:10.31838/ijpr/2020.SP1.020
- Buggapati L. Herbs in Dentistry. 2016;5(6):7–12.
- Paderni C, Compilato D, Giannola LI, Campisi G. Oral local drug delivery and new perspectives in oral drug formulation. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2012;114(3):e25–e34. doi:10.1016/j.oooo.2012.02.016
- Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. 2000;50.
- Mehta I. 'History OF Aloe Vera'-(A Magical Plant). *IOSR Journal Of Humanities And Social Science (IOSR-JHSS)*. 2017;22(8):21–24. doi:10.9790/0837-2208162124
- Hamman JH. Composition and applications of Aloe vera leaf gel. *Molecules*. 2008;13(8):1599–1616. doi:10.3390/molecules13081599
- Eshun K, He Q. Aloe Vera: A Valuable Ingredient for the Food, Pharmaceutical and Cosmetic Industries - A Review. *Critical Reviews in Food Science and Nutrition*. 2004;44(2):91–96. doi:10.1080/10408690490424694
- Mateescu A, Wang Y, Dostalek J, Jonas U. Thin hydrogel films for optical biosensor applications. *Membranes*. 2012;2(1):49–69. doi:10.3390/membranes2010040
- Wessels R, De Roose S, De Bruyckere T, Eghbali A, Jacquet W, De Rouck T, Cosyn J. The Mucosal Scarring Index: reliability of a new composite index for assessing scarring following oral surgery. *Clinical Oral Investigations*. 2019;23(3):1209–1215. doi:10.1007/s00784-018-2535-6
- Landry RG. Effectiveness of benzydamine HC1 in the treatment of periodontal post-surgical patients. 1985.
- Professor SA, Tanwar Post Graduate Student E, Graduate Student P, Tanwar E, Bhat D. Post-operative complications after periodontal surgery. ~ 152 ~ *International Journal of Applied Dental Sciences*. 2018;4(4):152–156.
- Mathew AK. Oral local drug delivery: An overview. *Pharmacy and Pharmacology Research*. 2015;3(1):1–6.
- Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Advanced Drug Delivery Reviews*. 2005;57(11):1595–1639. doi:10.1016/j.addr.2005.07.005
- Pereira R, Mendes A, Bártolo P. Alginate/Aloe vera hydrogel films for biomedical applications. *Procedia CIRP*. 2013;5:210–215. doi:10.1016/j.procir.2013.01.042
- Pereira R, Carvalho A, Vaz DC, Gil MH, Mendes A, Bártolo P. Development of novel alginate based hydrogel films for wound healing applications. *International Journal of Biological Macromolecules*. 2013;52(1):221–230. doi:10.1016/j.ijbiomac.2012.09.031
- Chithra P, Sajithlal GB, Chandrakasan G. Influence of Aloe vera on the glycosaminoglycans in the matrix of healing dermal wounds in rats. *Journal of Ethnopharmacology*. 1998;59(3):179–186. doi:10.1016/S0378-8741(97)00112-8
- Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: A systematic review.

- Burns. 2007;33(6):713–718.
doi:10.1016/j.burns.2006.10.384
21. Mansour G, Ouda S, Shaker A, Abdallah HM. Clinical efficacy of new aloe vera- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: A randomized, double-blind, vehicle-controlled study. *Journal of Oral Pathology and Medicine*. 2014;43(6):405–409.
doi:10.1111/jop.12130
 22. Pradeep AR, Garg V, Raju A, Singh P. Adjunctive Local Delivery of Aloe Vera Gel in Patients With Type 2 Diabetes and Chronic Periodontitis: A Randomized, Controlled Clinical Trial. *Journal of Periodontology*. 2016;87(3):268–274.
doi:10.1902/jop.2015.150161
 23. Gupta V, Malhotra S. Pharmacological attribute of Aloe vera: Revalidation through experimental and clinical studies. *AYU (An International Quarterly Journal of Research in Ayurveda)*. 2012;33(2):193.
doi:10.4103/0974-8520.105237
 24. Vázquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. *Journal of Ethnopharmacology*. 1996;55(1):69–75.
doi:10.1016/S0378-8741(96)01476-6
 25. Kim J, Lee I seok, Park S, Choue R. Effects of *Scutellariae radix* and Aloe vera gel extracts on immunoglobulin E and cytokine levels in atopic dermatitis NC/Nga mice. *Journal of Ethnopharmacology*. 2010;132(2):529–532.
doi:10.1016/j.jep.2010.08.049