

Collagen matrix membrane as a biological dressing in defects of the oral mucosa

ABSTRACT

Objectives: The objectives of this study were to evaluate the usefulness of the extracellular collagen matrix membrane as a biological wound dressing material for defects of the oral mucosa.

Materials and Methods: One hundred two patients were included in the study. A bovine-based extracellular matrix collagen membrane was used. The study was confined to those defects of oral mucosa which were large enough to close primarily.

Results: The results were evaluated under various parameters such as hemostasis, pain relief, granulation, epithelialization, and contracture of the wound. Secondary infection and allergenicity to the membrane were also considered, and finally, the usefulness of the collagen membrane was tested by the use of the Chi-square test and $P < 0.001$ was found.

Conclusion: We concluded that the extracellular collagen membrane could be used as a biological dressing in oral defects. Although it does not replace, it is proved as a good substitute of autologous graft.

Keywords: Biological dressing, collagen membrane, mucosal graft, oral defects

INTRODUCTION

Wound healing is an extremely complex and choreographed sequence of cellular and extracellular responses directed toward restoring the tissue intactness and functionality following injury. Understanding wound healing at various levels, molecular, cellular, biochemical, and physiologic, provides the surgeon with a framework for clinical decisions regarding the healing response of different wounds.^[1]

Wounds covered with dressing materials heal faster, show less contracture than those which are left open. All dressings materials, whether biological or nonbiological usually act by forming a barrier between wound and the environment; therefore, they prevent bacterial infection and wound desiccation. However, biological dressings show better adherence to the wound that not only helps to reduce pain but also lower the chance of infections, and consequently, increase the rate of healing.^[2]

The intra-oral surgical wounds due to trauma or excision of pathology need to be closed by the primary method or can be

left open.^[2] Ideally, open wounds should be covered by a graft to prevent microbial infection, excessive fluid loss, foreign material contamination, wound contracture, and to assist in the promotion of wound healing. Currently, oral mucosal grafts or skin grafts are used for this purpose; however, both of these grafts require a second surgical procedure and have other disadvantages as well. Oral mucosa is an excellent intraoral graft material, but its availability is limited.^[3,4] Split-thickness skin grafts are available in ample amount but

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having adnexal structures such as hair and sebaceous gland, and they express a different pattern of surface keratinization that can lead to the development of abnormal tissue texture in the oral cavity which could interfere with function.^[5]

Due to limitations in these autologous products, biological dressings have been introduced. These dressings, used for temporary coverage of open wounds, exert both mechanical and physiologic effects by protecting the wound, limit microbial contamination, and increase the rate of wound maturation.^[6] Thus, the search is on for an ideal dressing material to cover these defects. One of such biologic product is bovine-derived xenogenous collagen, a biologic plastic, which can be manipulated like wax into desired forms. Since its ample availability and low antigenicity, it has been used in many clinical conditions as temporary dressing materials.^[7-13]

Successful use of porcine and bovine based collagen in the management of burn and donor-site encouraged this clinical study of using bovine based extracellular collagen matrix membrane in intraoral defects.^[3,8,11,14-17] Our study was based on the clinical parameters in which patients were treated under local anesthesia, and various properties of dressing material were evaluated postoperatively.

MATERIALS AND METHODS

The present study was carried out as a single-center, prospective clinical trial evaluating the usefulness of extracellular collagen membrane as a bio-resorbable dressing material in defects of the oral mucosa. This study was done in 102 healthy patients with no history of any systemic disease in the age group of 20–70 years irrespective of sex, caste, religion, and socioeconomic status who were randomly selected from those reporting in the Department of Oral and Maxillofacial surgery. Medically compromised patients such as diabetic, immuno-compromised and patients on steroid therapy or with any active/acute infection were excluded from the study. The institutional ethical committee and hospital approved the clinical trial. Informed consent of all the subjects were obtained. The study was confined to secondary defects of the oral mucosa, which occur after excision of benign lesions and other conditions such as premalignant lesions, reactive proliferation, incisional biopsy wounds, and trauma as well. Only those lesions that were large enough and could not be closed primarily were included in the study.

The collagen used in this study was a bovine based cross-linked extracellular matrix native collagen membrane, available in the varying dimension of 5 cm × 5 cm, 10 cm

× 10 cm, 10 cm × 20 cm and 10 cm × 25 cm. The thickness of this collagen membrane was 100–150 μ, which was sterilized by gamma irradiation, and was marketed in aluminum pouch packing containing a mixture of isopropyl alcohol and water. There is no threat of HIV or hepatitis infections in bovine material, and it is obtained from countries free from Bovine Spongiform Encephalopathy (BSE). Also, it possesses a long shelf-life under normal storage conditions.^[18]

The surgical procedure was planned under local anesthesia. Following strict aseptic protocol, excision of benign lesions, and other conditions such as premalignant lesions, reactive proliferation, freshening of the traumatic wound, and incisional biopsies were performed.[Figure 1] Collagen membrane was removed from the aluminum pouch and washed twice in sterile saline to remove Isopropyl alcohol, a preserving media.[Figure 2] Then, the membrane was placed over the defect, stabilized by using 3–0 black silk suture.[Figure 3] After stabilization, excess membrane was trimmed by scissor. No pressure dressing was used. Patients were kept on a cold and liquid diet for 24 h followed by a soft diet for 3 days.

Most of the lesions treated in this study were excised in-toto, and surgical defect size was determined after excising the lesion by taking the longest dimension in the horizontal and vertical plane. The area of the wound was calculated in cm². The size of the wound produced after excision of the lesion ranged from 2.5 cm to 5.0 cm in the longest dimension, and the area of the surgical defect ranged from 5.12 cm² to 24.70 cm².

Results were evaluated using the following parameters:

- a. On the day of surgery-the following parameters were considered:
 - i. Hemostasis of the wound by the membrane was assessed 1 h and 1 day postoperatively. It was graded as:
 - Good-when the bleeding stopped within 5 min
 - Fair-when it was achieved after a more prolonged period
 - Poor-when interventions were required to stop bleeding.
- b. In the postoperative period, the following parameters were considered:
 - i. Pain, a subjective character, was recorded, on the basis of patient's own words on 3rd day postoperatively when the patient was taking no analgesic medications, as:
 - Good (none to mild)
 - Fair (moderate)
 - Poor (severe).

ii. Adherence was assessed by irrigation of the area with 10 ml sterile saline solution. It was recorded on the 5th postoperative day when sutures were removed and marked as to be present or absent [Figure 4]

iii. Granulation tissue: The presence of granulation tissue was noted at the end of the second week and rated as:

- Good (entire wound)
- Fair (nearly the entire wound)
- Poor (inadequate).

Granulation tissue formation was evaluated clinically that was bright red/pink in color, bumpy in appearance and did not bleed on touch.

iv. Biodegradability: The mean day on which collagen resorption occurred was recorded.

To evaluate membrane resorption, wound was gently irrigated with 5 ml of normal saline and visually inspected

for any remnants of translucent membrane over the wound surface after the 8th day.

v. Contracture of the wound site at the end of the month was noted and graded as:

- Good (<25%)
- Fair (25%–50%)
- Poor (severe i.e., 50% or more).

vi. Epithelization was evaluated at 4 weeks (1 month), 5 weeks and 6 weeks (1.5 months) [Figure 5] and rated as

- Good (entire wound)
- Fair (nearly the entire wound)
- Poor (inadequate).

Epithelization was monitored clinically in the initial stages that showed light pink appearance, while Cheraskin's method was used in the final stage to record it in which each wound was painted with toluidine blue (1%) for a minute followed by rinsed with 1% Acetic acid for 20 s. Since this dye adheres to non-epithelized tissue, wound area, which was completely healed, showed no staining clinically.^[19]

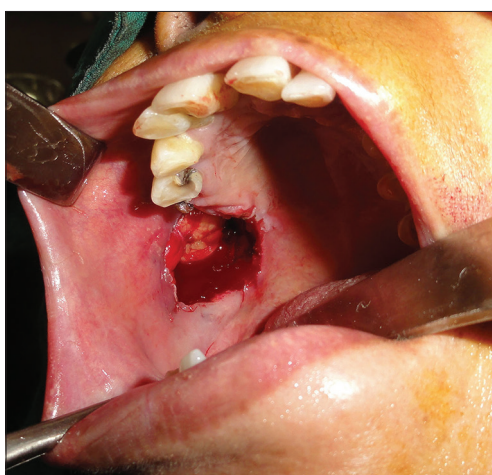


Figure 1: Defect of oral mucosa large enough to close primarily

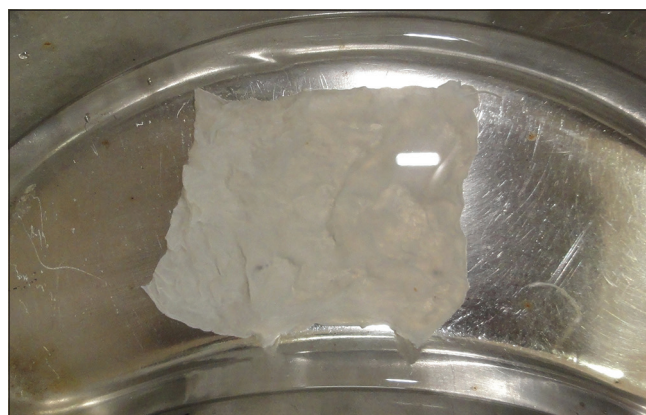


Figure 2: Showing Extracellular collagen matrix membrane



Figure 3: Collagen membrane placed over defect and stabilized with 3-0 black silk suture



Figure 4: Defect after suture removal showing adherence of membrane at 5th postoperative day



Figure 5: Postoperative photograph at 1.5 months

- vii. Reactivity/Allergenicity of the material was assessed depending on the reactions elicited and was graded as:
- None-when no reactions were seen,
 - Moderate- when few reactions were noted but resolved without any intervention,
 - Severe-when intervention and treatment was required.
- viii. Infection was assessed as any secondary infection was present or absent
- ix. Mouth opening was assessed preoperatively and postoperatively to evaluate the amount of contraction occurring, in case the lesion was present on the buccal mucosa, lip, or combined lesion including the lip and commissure or in case the lesion was present both in buccal mucosa and alveolus. Scoring was done on the basis of decreased mouth opening.

The criteria for judgment of collagen dressing membrane is based on the scoring pattern, which was used by Bessho *et al.*^[20] Using this scoring pattern, effectiveness, reactivity, and usefulness of membrane were evaluated in this study.

- The criteria for judgment were: hemostatic effects, pain relief, granulation, epithelization, and contracture of the wound and it was judged as good, fair or poor and was given the scores of 2, 1, and 0, respectively [Table 1].
- i. Effectiveness of this dressing material (E) was assessed by adding up the scores of hemostasis, pain relief, granulation tissue formation, epithelization, and contracture (decrease in mouth opening). It was graded as follows:
- Score 8–10-very effective
 - Score 5–7- effective
 - Score 0–4-ineffective.
- ii. Usefulness (U) of the material was assessed based on the scores of effectiveness and reactivity noted as being:

Table 1: Criteria for judgement of membrane (good=2, fair=1, poor=0)

Score	Definition
Hemostatic effect	
Good	No bleeding
Fair	Slight bleeding, no hemostasis required
Poor	Bleeding that required hemostasis
Pain relief (3rd day after operation)	
Good	None
Fair	Slight
Poor	Required analgesics
Granulation tissue formation	
Good	Entire wound
Fair	Nearly entire wound
Poor	Inadequate
Epithelization	
Good	Entire wound
Fair	Nearly entire wound
Poor	Inadequate
Contracture (%)	
Good	< 25
Fair	25–50
Poor	50 or > 50
Effectiveness	
Very effective	Score 8–10
Effective	Score 5–7
In effective	Score 0–4
Reactivity	
None	None
Moderate	Few, did not require treatment
Severe	Required treatment
Usefulness=effectiveness+reactivity	
Very useful	8–10 points+no side effects
Useful	5–7 points+no side effects

- Very useful (8–10 points + no side effects)
- Useful (5–7 points + no side effects) or
- Useless (0–4 points + side effects).

RESULTS

In this study, 102 patients (male-55, female-47) were selected in the age ranged from 20 to 70 years with the mean age of 42.90 ± 5.11 years (individual age groups of younger and older patients were not taken into account). The most common site in this study where the collagen sheet placed was buccal mucosa accounting for 35.29%, followed by lips with 25.49%. However, the most common lesion after excision of which dressing placed was found to be benign lesion (30.39%), followed by a traumatic wound (26.47%).

Collagen membrane showed good conformability in 94.12% cases while it was fair in 5.88% cases. Hemostasis was achieved within 5 min in 87.23% cases, while in 11.76% it was

achieved, but on the wide opening of mouth slight bleeding occurred, which did not require any active intervention, and bleeding stopped spontaneously. Pain relief was observed as good in 59.80% cases, fair in 31.37% cases, whereas it was poor in 8.82%. Similarly, in most of the cases (83.33%) healthy granulation tissue was formed over the entire healing wound. Epithelization was completed in 81.37% at the end of the month, but 18.62% took 7–10 more days for complete epithelization. In 59.80% cases, wound contracture occurred less than 25%, while 35.29% of cases showed contraction in the range 25%–50%; however, in 4.90% of cases, it was >50%. Dressing showed well adherence in 84 cases and the average time taken in its resorption was about 11.4 days.

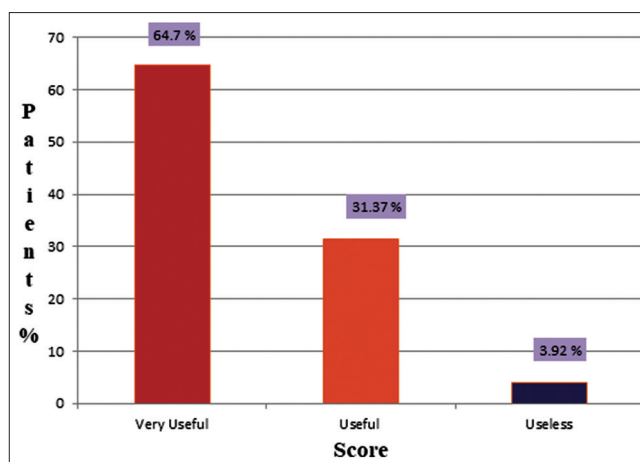
Moreover, the collagen membrane was proved very effective and very useful in 64.70% of patients. On the other hand, this dressing was found ineffective and useless in 3.92% of cases [Graph 1]. In addition, no patient reported with infection or any reactivity/allergenicity. Furthermore, the Chi-square test was applied, and *P* value was found <0.001, which is a statistically and clinically significant value.

DISCUSSION

Wound healing involves a complex series of events, including chemotaxis, cell division, neovascularization, synthesis of new extracellular matrix, and the synthesis and remodeling of the scar tissue. These events are regulated by several mediators, including platelets, inflammatory cells, cytokines, growth factors, matrix metalloproteinases, and their inhibitors. An avascular scar is the final stage of the wound healing process.^[21-23]

Wound healing in the oral cavity has to face some specific problems, namely moist environment with the constant fear of contamination from food ingestion and salivary secretion. Status of oral hygiene, oral habits, regular tongue, cheek, and masticatory movements also affect healing and graft acceptance.

Although various dressing materials are documented in the literature, which can be used to cover raw wounds of the oral cavity, each material has its own pros and cons. First, mucosal grafts are the best as they fulfil all the requirements of ideal graft material. However, its limited availability, technically difficult surgeries and donor site morbidity limit its usage. Second, skin grafts can also be used as a biological dressing, but they fail to attain the texture of the oral mucosa and retain the skin coloration. Third, dermal grafts can also be used to cover these defects, but they are not available in elder patients due to the loss of dermal layer.



Graph 1: Showing usefulness of collagen membrane

Apart from that, recently, *in vitro* culturing of human skin and oral keratinocytes provides autologous graft to cover these defects. Although these keratinocyte grafts provide good postoperative results, their use are limited up to elective surgeries and costly as well. In the race of biological dressings porcine or bovine based collagen membranes and human amniotic membrane come to next.^[5]

A fair amount of literature suggests that collagen affects all stages of wound healing and serves as the key extracellular component for repairing and remodeling of skin tissue. It acts as a scaffold that facilitates the infiltration of fibroblasts, macrophages lymphocytes, etc. In addition, it attracts monocytes to the wound area; thus, enhancing the metabolic debris removed and increased angiogenesis. Furthermore, collagen dressing inhibits the action of matrix metalloproteinases and encourages healing by enhancing the deposition of fibers by fibroblast and formation of granulation tissue in the wound bed. As healing progresses, collagen is deposited by the fibroblasts replacing the collagen portion of the membrane.^[1]

The present study of 102 patients revealed male predominance, in contrast to the study conducted by Bessho *et al.*^[20] where female predominance was found, and it was mainly due to precancerous and malignant lesions, which are more common in males. Furthermore, road traffic accidents and assaults affect mainly the male population in India.

The benign lesion in this study included large fibromas, pleomorphic adenomas, mucoceles, etc. Only those traumatic wounds were included in this study, which were large enough to close primarily. Reactive proliferations were accounted for 15.68%, which include large peripheral giant cell granulomas, pyogenic granulomas, and epulis fissuratum. Cases of premalignant lesions and conditions include leukoplakia

and lichen-planus were accounted for 13.72%. Malignant lesions accounted for 13.72%, comprised mucoepidermoid, verrucous, and myoepithelial carcinomas. These lesions were comparable to the study of Mitchell.^[23]

In this study, no allergic response was seen in any patient which was same like the study conducted by Wang *et al.*, who concluded that collagen did not elicit any antibody response.^[24] Although clinical reactions to collagen are rare, two cases of allergic reactions to bovine collagen were reported in the literature.^[25]

Collagen applied at the time of hemostasis acts as an auxiliary mechanism to augment clotting, which actually increases platelet adherence to the endothelial vessel wall, thus forming a plug and seals it off.^[26] Saroff *et al.* showed that microfibrillar collagen produced rapid and effective hemostasis.^[19] Similarly, in this study, hemostasis was achieved within 5 min in 87.23% of cases after application of the dressing.

The pain mainly occurs as a result of exposure of nociceptive receptors, which are free nerve endings present in the skin and deeper tissue, and its severity usually correlates with the level of tissue damage.^[27] In this study, 60% of cases were graded as good, having none to mild pain, but we observed that deeper and large-size wounds were more painful on the 1st day. Nevertheless, emotional, functional, and psychological factors were not taken into consideration.

Epithelization was evaluated in the same manner as described by Cheraskin.^[19] This study showed that in 83 cases, epithelization occurred over the entire wound at the end of the month. In the rest of the patients, it occurred nearly over the entire wound within 30 days, which was completed entirely in further 7–10 days. It is observed that by the use of collagen, primary hemostasis and granulation tissue formation and stabilization were enhanced that subsequently provided viable tissue for faster epithelization of wound. Moreover, it has many other properties such as nutritional and structural support on the wound healing process, which may have contributed for its earlier healing.^[28]

It was found that mouth opening decreased in some patients in which collagen was applied in buccal mucosa or in the commissural region or combined alveolus, buccal mucosa, or lip region. Contraction of the wound was found to be consistent and mostly occurred after 10 days. It was similar to autogenous mucosa or free-skin grafts. It is mediated to a great extent by the myofibroblasts, and its specialized connections with the surrounding extracellular matrix.^[29] Fujioka *et al.*, in their study, also concluded that the degree

of scar contracture was less in the collagen implanted sites.^[30] This was possibly due to the early healing of the wound and the formation of repaired dermis, whose scar structure was similar to normal.

Collagen applied on the surgical defect in this study showed no infection in all the 102 patients. Similarly, Mannai *et al.* also evaluated that collagen is a nontoxic material. Furthermore, collagen is a poor culture medium and does not support or enhance bacterial growth. In this study, collagen membrane over the wound got resorbed in 9–13 days with an average period of 11.4 days.

This study showed good resiliency and tensile strength of the extracellular collagen matrix membrane. However, the handling and manipulation of the membrane were a bit tedious as the sheet get rolled on the wound, but once it gets adapted to the wound surface, can be easily sutured. Small sample size, limited follow-up, and lack of histopathological studies in the assessment of membrane resorption and epithelization of wound can be considered as a limiting factor of the present study. Out of 102 cases in the present study, 13 cases which were present on the tongue, palate, and floor of the mouth where wound contracture could not be assessed directly due to the lack of fixed anatomical points. Hence, future studies need to be carried out at a larger scale comparing collagen and skin graft or collagen with wound without any dressing over it, including histopathological assessment to overcome the pitfalls of the present study.

CONCLUSION

It is evident that collagen serves as an important element in all stages of wound healing and plays a key role in regulating the arrival and activity of multiple types of cells involved in tissue repair and regeneration. Although the handling of collagen membrane is a little difficult, better postoperative results, ample availability, easy sterilization, and cost-effectiveness are the advantages over other biological dressings. Therefore, we advocate the use of collagen membranes as biological dressing in the defects of oral mucosa, where it simply acts as a good substitute of autologous graft.

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Conflicts of interest

There are no conflicts of interest.

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