Bioengineering in the oral cavity: our experience

ORI G I N A L  R E S E A R C H

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Background: To date, there are no studies reported in the literature on the possible use of bovine collagen, oxidized regenerated cellulose, or synthetic hyaluronic acid medications in the oral cavity. The aim of this paper is to report the use of bovine collagen, oxidized regenerated cellulose, and synthetic hyaluronic acid medications to improve wound healing in the oral cavity by stimulating granulomatous tissue.

Methods: From 2007 to 2011, 80 patients (median age 67 years) suffering from oral mucosal lesions participated in this double-blind study. The patients were divided into two groups, each consisting of 40 patients. One group received conventional medications, while the other group of patients were treated with the advanced medications.

Results: Advanced medications allowed re-epithelialization of the wound margin in 2–20 days, whereas patients receiving conventional medication showed a median healing duration of 45 days.

Conclusion: The results of this study demonstrate that treating oral mucosal wounds with advanced medication has an advantage with regard to wound healing time, allowing patients to have a rapid, functional, and esthetic recovery.

Keywords: bioengineering, oral cavity, mucosal recovery

Introduction

Wound healing is a physiologic process based on the homeostasis of reparative mechanisms which allow for formation of new tissue and destruction essential for removing damaged tissue.¹ ³ The oral mucosa is frequently exposed to a number of sources of stress, including mastication, speech, breathing, and bacterial invasion of the oropharynx. These factors delay oral wound healing and increase the risk of infection. Impaired saliva turnover and chronic mechanical and bacterial insults make the management of oral wounds particularly complex.

Application of bovine collagen, oxidized regenerated cellulose, and synthetic hyaluronic acid medications accelerate wound healing in the oral cavity in patients with traumatic, oncologic, and inflammatory pathologies, such as bisphosphonate-related osteonecrosis of the jaw. Promogran™ (Johnson & Johnson, New Brunswick, NJ, USA) consists of a sterile, freeze-dried matrix composed of collagen and oxidized regenerated cellulose pressed into a sheet approximately 3 mm thick and cut into hexagonal pieces.

In the presence of wound exudate, the matrix absorbs the liquid and forms a soft, conformable, and biodegradable gel. This gel physically binds and inactivates matrix metalloproteases, and has a detrimental effect on wound healing when present in exces-
sive quantities. Additionally, the gel binds naturally occurring
growth factors within the wound and protects them from
degradation by proteases, releasing them back into the wound
in an active form as the matrix is slowly broken down.

Promogran is indicated for the management of all types
of chronic wounds that are free of necrotic tissue and visible
signs of infection. These include leg ulcers, both venous
and arterial in origin, pressure sores, and ulcers occurring
on the feet of diabetic patients. The matrix, which also has
hemostatic properties, can be used in conjunction with com-
pression therapy. Promogran is delivered in a transparent
waterproof peel pouch, sealed with a laminated cover and
sterilized by gamma irradiation. It is available in two sizes,
ie, 28 cm² and 123 cm².

Hyalomatrix™ (Fidia Advanced Biopolymers, Abano
Terme, Italy) is a bilayered, sterile, flexible, and conform-
able wound dressing that acts as an advanced wound care
device. It is comprised of a nonwoven pad made entirely
of HYAFF, a benzyl ester of hyaluronic acid, and a semi-
permeable silicone membrane which controls water vapor
loss, providing a flexible covering for the wound surface and
adding increased tear strength to the device. As Hyalomatrix
is applied to the wound bed, the HYAFF wound-contact layer
provides a three-dimensional scaffold for cellular invasion
and capillary growth. When integration of the HYAFF-based
material into the newly formed dermal matrix has progressed,
well vascularized granulation tissue forms. This provides for
wound closure via spontaneous re-epithelialization and acts
as a suitable dermal layer for skin grafting.

The effects of these medications are well documented,
with several studies in chronic diabetic ulcers, corneal
transplantation, tympanic membrane perforation, and joint
surgery, as well as in burns patients having been reported.4–7
The major effects appear to be related to improved wound
healing of injured tissue.6 To our knowledge, no studies
concerning possible use of these medications in the oral cav-
ity have been reported in the literature. The purpose of this
paper is to report the use of the aforementioned materials to
improve wound healing in the oral cavity.

Materials and methods
Eighty patients (median age 67 years) were enrolled in this
study from 2007 to 2011 (Table 1). All patients suffered from
oral mucosal lesions of traumatic, oncologic, or inflammatory
etiology. The patients were divided into two groups, each
consisting of 40 patients. Each group consisted of 26 females
and 14 males. Twenty-two patients had undergone surgery
for oral cancer (six superior maxillary cancers, six mucosal
cancers, and ten mandibular cancers), with eight affected by
bisphosphonate-related osteonecrosis of the jaw and ten by
post-traumatic injury. The two patient groups had wounds
of the same size and type. The average wound size was
approximately 2 cm.

The first group of patients was treated with conven-
tional medications (iodoform gauze, hydrogen peroxide,
and iodopovidone). The second group of patients was
treated with advanced medications, ie, Promogran (con-
taining oxidized regenerated collagen) and Hyalomatrix
(containing hyaluronic acid). The collagen medication
was changed twice a day in the second group of patients,
while hyaluronic acid was changed after 2 weeks. Medica-
tions were applied depending of the type and position of
the wound using stitches when required. We did not use
specific criteria for assessing wound re-epithelialization and
instead based this on direct observation of wound heal-
ing. Patients were followed daily for the first 20 days and
weekly thereafter.

Results
Both conventional and advanced medications showed ben-
efits, but the main difference between the two related to
healing time. Advanced medications allowed wound heal-
ing within 2–20 days, whereas patients in the conventional
medication group took at least 45 days to reach complete
re-epithelialization of the oral mucosa. Only patients from the
second group presenting with sloping or declivities lesions
had a healing time close to the control group. All patients
had good post-treatment results without any complications.
The difference in healing time between the groups was sta-
tistically significant.

Discussion
The healing process includes three phases, ie, an initial
inflammatory phase required to eliminate damaged tis-
sue, the reconstructive phase, characterized by formation
of granulation tissue, and tissue modeling.8 Proteases
participate in each phase, and have been shown to be the
principal protagonists in the balance between synthesis and
degradation.9,10 Excessive protease activity can be caused

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<td><strong>Patients</strong></td>
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by positive feedback in the expression of protease genes, increased activation of extracellular latent protease, or by reduction of the activity of protease endogen inhibitors; this manifests as an increase in extracellular proteolysis, with greater imbalance in tissue destruction.\textsuperscript{11–13} Collagen and oxidized regenerated cellulose, components of advanced medications, are an optimum substrate for proteases, which are bonded and cannot interact further with the tissue.\textsuperscript{1}

Additionally, this bovine extract can act as a mechanical support and stimulate migration of fibroblasts and the metabolic activity of granulomatous tissue.\textsuperscript{12–14} The oral mucosa is hard to cleanse because of continuous mechanical, bacterial, and viral stimuli. Such factors predispose these patients to mucosal alterations, with loss of integrity and possible bone or osteosynthesis material exposure.

Within the field of dermal replacement products, derivatives of hyaluronic acid have a place of particular importance.\textsuperscript{15} Hyaluronic acid is a linear polymer of glucuronic acid N-acetylglucosamine disaccharide, a main glycosaminoglycan ubiquitously distributed in the extracellular space and involved in the process of wound repair, modulating the release of cytokines and other mediators.\textsuperscript{6,7,16} First isolated in 1934 from bovine vitreous humor, it was subsequently collected from other sources, such as soft connective tissues, synovial fluid, umbilical cords, and rooster combs. Hyaluronic acid is recognized by specific cell receptors such as CD44, and regulates the adhesion, growth, differentiation, locomotion, and activation of specific cell types, thereby modulating inflammation, angiogenesis, and healing processes.\textsuperscript{6,17} Both wound size and vascularization showed good improvement in response to treatment with hyaluronic acid.\textsuperscript{6} This may be partly explained by the effect of the degradation products of hyaluronic acid on endothelial cell proliferation, angiogenesis, and collagen deposition and organization.\textsuperscript{6,15,17} Its structural role is attributable to its hygroscopic properties which allow for hydration and modulation of the cellular microenvironment. For these reasons, it is easy to understand the important role of hyaluronic acid in tissue repair processes, and how it contributes to the orientation of the fibrous component of the extracellular matrix.

Hyaluronic acid benefits epithelial regeneration and has free radical scavenging properties.\textsuperscript{15} Hyaluronic acid medications are physically coupled with a transparent and flexible film of medical-grade synthetic elastomer which acts as a semipermeable barrier against external contaminants.\textsuperscript{15} When the product is applied to the wound bed, the hyaluronic acid wound-contact layer provides a three-dimensional scaffold which enables the product to be colonized by fibroblasts and onto which extracellular matrix components are laid down,

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**Figure 1** Post-traumatic palatal defect. (A) Outcome of massive trauma with a large residual palatal defect. (B) Reconstruction with palatal flap. Note a mucosal growth after advanced medication on follow-up at 7 days. (C) Total obliteration of the defect.

**Figure 2** Right oral mucosal cancer. (A) Tumoral lesion involving the hard palate and right oral mucous. (B) Surgical resection and reconstruction with Bichat’s fat pad. (C) Post-surgical defect outcomes. (D) Follow-up at 7 days. Total mucosal growth.

**Figure 3** Bisphosphonate-related osteonecrosis of the jaw. (A) Right mandibular osteonecrosis with bone exposure. (B) Curettage and application of advanced medication. (C) Follow-up at 7 days.

**Figure 4** Iatrogenic soft palate lesion. (A) Iatrogenic soft palate defect. (B) Reconstruction with local mucosal flap and application of advanced medication. (C) Total recovery of the palatal defect.
resulting in an ordered reconstruction of the dermal tissue. Advanced medications improve patient management by decreasing wound healing time, resulting in a prompt functional and esthetic recovery.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


