in vivo *36*: xxx-xxx (2022)
doi:10.21873/invivo.11xxx

No: 6235-K
Please mark the appropriate section for this paper
☐ Experimental
☐ Clinical

Effects of a Topically Applied Oral Wound Dressing Film on Intra-oral Wound Healing in Rabbits

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Abstract. *Background/Aim: Oral lesions are a common clinical symptom that can impair the quality of life of patients. Several treatments have been developed; however, therapies for wounds on the oral mucosa are symptomatic and unsatisfactory. This study aimed to evaluate the efficacy of an oral wound dressing (OWD) film in healing excision and chemical burns using a rabbit oral wound model and to demonstrate the effect of physical barriers during wound healing. Materials and Methods: Excision and chemical burn wounds were induced on the oral hard palate of animals. Four experimental groups were established. The OWD film was applied immediately after surgery and replaced every 24 h over the following 3 days. The animals were sacrificed at 3, 7, and 14 days after surgery. The hard palate tissues were analyzed by histological and immunohistochemical evaluation. The degree of epithelialization, number of proliferating cells, and collagen deposition were evaluated. Statistical significance was analyzed using the Student's t-test. Results: Following application of the OWD film to the excision and chemical burn wounds, the OWD treatment group's epithelial gap and proliferation showed a significant difference compared to those of the untreated group during the proliferative stage of wound healing. However, there was no difference in the epithelial gap in the chemical burn wound model, whereas the OWD treatment group showed a significantly reduced ulcerated area. Collagen deposition in the OWD treatment group was significantly increased during the remodeling stage of wound healing. Conclusion: The OWD film treatment promoted wound healing in the oral mucosa by accelerating wound closure and reconstruction.*

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Key Words: Animal study, chemical burn wound, excision wound, oral wound dressing, oral wound healing.

The skin and oral mucosa are crucial barriers against exogenous substances, pathogens, and mechanical stresses (1). Compared to the healing of cutaneous wounds, wound healing of the oral mucosa proceeds quickly and leaves less scar formation (2, 3). The causes of mucosal wounds are classified as physical, chemical, and thermal. Physical and mechanical traumas of the oral mucosa include linea alba, chronic biting, epulis fissuratum, and inflammatory papillary hyperplasia. Chemical injuries of the oral mucosa include chemical burns, post-anesthetic ulceration of the hard palate, and contact allergic stomatitis (4).

Topical treatment is more effective than systemic treatment for healing physical traumas and chemical injuries in the oral mucosa (5). Various topical treatments, such as adhesive tablets, gels, and films, have been developed for oral wound healing (6). Among these treatment types, films possess properties such as adhesiveness and flexibility and protect the wound surfaces, reducing pain and increasing treatment effectiveness (7, 8).

An oral wound dressing (OWD) film, commercial name Curatick® or Ora-Aid® (TBM Co., Gwangju, Republic of Korea) comprises laminates consisting of a hydrophilic bioadhesive and a backing layer. The inner layer can absorb

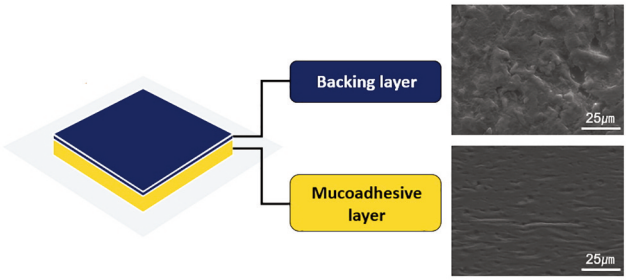

Figure 1. *Oral wound dressing film (OWD film), prepared by TBM Corporation (Gwangju, Republic of Korea). The OWD film consists of a backing layer that protects against external factors and a mucoadhesive layer in contact with the wound. Scanning electron microscope images of each layer of the OWD film.*

Table I. *Experimental groups and treatments.*

Group	Treatment	Site of wound
EXCISION	Excision wound only	Right rostral surface of the hard palate
EXCISION+OWD[a]	Excision wound with OWD film	Left rostral surface of the hard palate
BURN	Chemical burn wound only	Right caudal surface of the hard palate
BURN+OWDa	Chemical burn wound with OWD film	Left caudal surface of the hard palate

[a]OWD film replacement every 24 h over the following 3 days. OWD: Oral wound dressing.

the wound exudate and maintain a moist oral environment. These properties promote wound healing. In a previous clinical study, a patient treated with Curatick® reported lower post-operative pain, bleeding, and dietary discomfort after oral surgery (9). In the present study, we histopathologically evaluated the effect of the OWD film on healing physical traumas and chemical injuries using a rabbit oral wound model.

Materials and Methods

Oral wound dressing film. OWD film, commercial name Curatick® or Ora-Aid®, was provided by the manufacturer (TBM Corporation, Republic of Korea). According to the manufacturer's specifications (10), the OWD film comprises two layers (Figure 1): an outer layer, the backing layer, which is composed of a lipophilic polymer complex allowing for the slow dissolution of the inner layer; the inner layer, a mucoadhesive layer, which is composed of a hydrophilic polymer complex; and the mucoadhesive layer, which reacts with the moisture of the oral mucosa to change into a gel state and partially swells, helping to maintain the wound moisture state *via* absorbing wound exudate and micro bleeding. The OWD film is highly flexible, attaching well to the oral wound surface, and has a more minor foreign body sensation. Mucoadhesion is maintained until the hydrophilic polymer dissolves; the outer layer is automatically eliminated from the mucosa approximately 6-8 h later.

Experimental animals. New Zealand white rabbits (18 males, bodyweight 2.6-3.0 kg) were purchased from Samtaco Bio Korea (Osan, Republic of Korea). The animal study protocol was approved by the Institutional Animal Care and Use Committee of Chonnam National University (CNU IACUC-YB-2019-99), and the animals were cared for as per the guidelines for the Care and Use of Laboratory Animals. Rabbits were maintained at a temperature of 20±3˚C and relative humidity of 50±10%. Each rabbit was provided with standard rabbit feed and experimental animal drinking water.

Construction of a wound model. The test groups were established as follows: EXCISION, EXCISION+OWD, BURN, and BURN+OWD (EXCISION: Excision wound only, EXCISION+OWD: Excision wound with OWD film, BURN: Chemical burn wound only, BURN+OWD: Chemical burn wound with OWD film). The excision wounds were formed on the rostral surface, and the chemical burn wounds were formed on the caudal surface of the hard palate of the rabbit. The OWD film was applied to the left side of the hard palate of the rabbit (Table I).

Before surgery, the rabbit received ketoprofen (3 mg/kg; Eagle Ketoprofen 10% INJ 100 mg/ml; Eaglevet, Republic of Korea) and tramadol hydrochloride (10 mg/kg; Tramadol HCl 50 mg/ml; Huons Co., Seongnam, Republic of Korea) *via* subcutaneous injection. Next, the rabbit was premedicated with xylazine (5 mg/kg; Rumpun 23.32 mg/ml; Bayer Korea Ltd., Seoul, Republic of Korea) using intramuscular injection. Anesthesia was induced by intramuscular administration of ketamine (35 mg/kg; Yuhan ketamine 50 INJ 50 mg/ml; Yuhan Corp., Seoul, Republic of Korea). The excision wounds were formed using a 4 mm round biopsy punch on the rostral of the hard palate symmetrically (11). The chemical burn wounds were induced as follows. A round filter paper (Whatman, UK), 4 mm in diameter, was soaked in 50% acetic acid and pressed to the caudal surface of the hard palate of the rabbit for 60 s (12). The distance between wounds was at least 3 mm to prevent chemical disturbance from other wounds. The OWD film was applied on the left-hand side wound site and fixed with suturing to prevent any detachment caused by the mechanical irritation of tongue movement. After the operation, the rabbits were anesthetized and a new OWD film was replaced every 24 h over the following 3 days. The wounding day was considered day 0 (Figure 2).

Sampling was conducted after euthanasia based on the experimental schedule. Rabbits were sacrificed at 3, 7, and 14 days after the operation *via* potassium chloride intravenous injection. Next, the wound tissues were harvested and fixed in 10% formalin for histological analysis. A schematic of the experimental schedule is presented in Figure 3.

Histopathological study. On days 3, 7, and 14 post-wounding, hard palatal mucosa tissues at the wound site were excised, embedded in paraffin wax, and cut into serial sections (4 μm thickness). These sections were stained with hematoxylin and eosin and examined using an Axio Scan.Z1 (Zeiss, Jena, Germany).

Masson's trichrome staining. Paraffin sections (4 μm in thickness) were cut, deparaffinized, and rehydrated. The tissue sections were placed in Bouin's solution for 1 h at 56˚C. Next, they were rinsed under running tap water for 10 min to remove the yellow color,

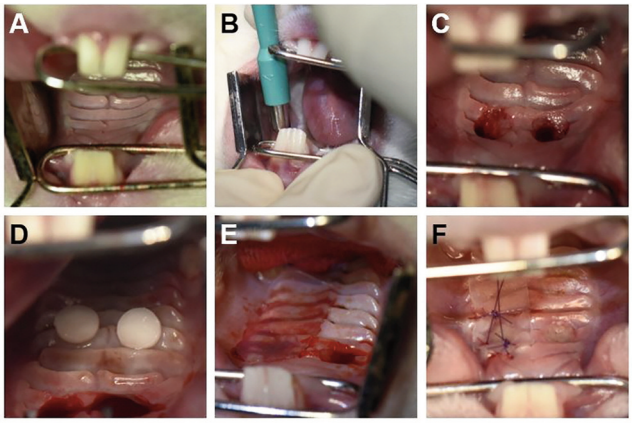

Figure 2. *Schematic representation of wound creation on the oral mucosa of a rabbit. A) The hard palate of the rabbit was fixed using a mouth gag. B and C) The excision wounds were induced using a 4 mm round biopsy punch on the rostral hard palate symmetrically. D) Chemical burn wounds were created by pressing a round filter paper soaked in acetic acid onto the oral mucosa of the rabbit. E) The oral wound dressing (OWD) film was applied on the left-hand side wound site. F) The OWD film was fixed using suturing.*

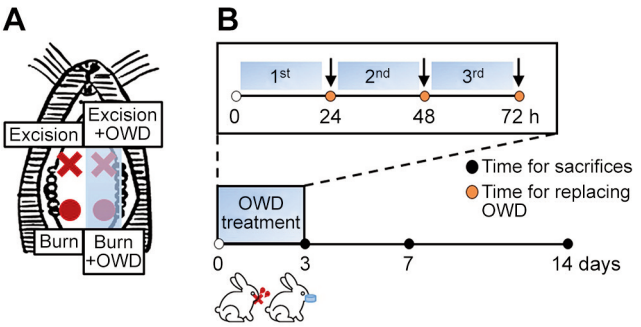

Figure 3. *Scheme of the oral wound site and experimental schedule. A) An excision wound was induced on the rostral surface and the burn wound was induced on the caudal surface of the hard palate of the rabbit. The oral wound dressing (OWD) film was applied on the left-hand side wound site. B) The OWD film was replaced every 24 h for the following 3 days. The rabbits were sacrificed at 3, 7, and 14 days after the operation.*

stained with Weigert's iron hematoxylin solution for 2 min, rinsed with tap water for 20 min, stained in Biebrich Scarlet Acid Fuschin solution for 15 min, and rinsed with distilled H_2O. The sections were placed in acid solution (mixture of phosphotungstic acid-phosphomolybdic acid-deionized H_2O at a ratio of 1:1:2, v/v) for 15 min, then stained with aniline blue dye (Sigma-Aldrich, St. louis, MO, USA) for 10 min, differentiated in a 1% glacial acetic acid solution for 3 min, washed in distilled water, dehydrated, and covered with xylene (13).

Immunohistochemistry. The hard palatal mucosa tissue sections were deparaffinized before being incubated in citrate buffer (0.01 M, pH 6.0) and heated in an autoclave for 10 min. All subsequent steps were performed at room temperature (25-30˚C). The sections were incubated with 0.3% [v/v] hydrogen peroxide in distilled water for 20 min to deactivate the endogenous peroxidase and blocked with 2% (v/v) normal goat serum (Vector Laboratories, Burlingame, CA, USA) in 0.3% (v/v) Triton X-100 for 1 h. Next, the sections were incubated with primary antibodies, rabbit anti-Ki-67 (1:200; Origene Tech, Rockville, MD, USA) in antibody dilution buffer (Invitrogen, Waltham, MA, USA) overnight at 4˚C. After washing, the sections were reacted with biotinylated goat anti-rabbit IgG (Vector Laboratories, Burlingame, CA, USA) for 1 h and then washed and incubated for 1 h with an avidin-biotin peroxidase complex (Vector Laboratories) prepared according to the manufacturer's instructions. After washing, the peroxidase reaction proceeded using a diaminobenzidine substrate (contained in the DAB kit; Vector Laboratories) prepared according to the manufacturer's instructions. To prepare controls, primary antibodies were omitted for a few test sections in each experiment.

Image analysis. Six representative microscopic images were taken for each sample stained with Masson's trichrome stain, using an Axio Scan.Z1 (Zeiss). Semi-quantification of the degree of fibrosis was performed digitally using ImageJ software according to the method described by Chen *et al*. (14). The "color deconvolution" plugin was used to measure the integrated density for the green color channel of the tissue samples.

Statistical analysis. The statistical significance of the values was analyzed using the Student's *t*-test through SPSS Statistics version 27.0 (SPSS Inc, Chicago, IL, USA). *p*-values <0.05 were considered statistically significant.

Results

OWD film treatment improves wound closure. The effect of the OWD film on oral wound healing was evaluated using histology to measure the epithelial gap across the wound (Figure 4). On post-excision day 3, the epithelial gap of the excision wounds in the OWD treatment group was significantly smaller than that of the excision wounds in the control group (EXCISION: 3.22±0.11 mm, EXCISION+OWD: 2.31±0.26 mm, $p<0.01$; Figure 4C). However, in the chemical burn wound model, the epithelial gap was larger, and the duration of spontaneous recovery was longer. However, there was no significant difference in the epithelial gap between the burn wound group and the OWD burn wound group on day 3 (BURN: 4.80±0.56 mm, BURN+OWD: 4.09±0.47 mm, $p>0.05$; Figure 4D). The OWD film treatment significantly reduced the ulcerated area in the oral dermis (BURN: 0.47±0.08 mm^2, BURN+OWD: 0.22±0.03 mm^2, $p<0.05$; Figure 4E).

OWD film treatment enhanced reepithelization by upregulating the proliferation of basal cells. Immunohistochemistry staining was used to count the proliferating cells in the excision and chemical burn wounds (Figure 5). Ki-67-

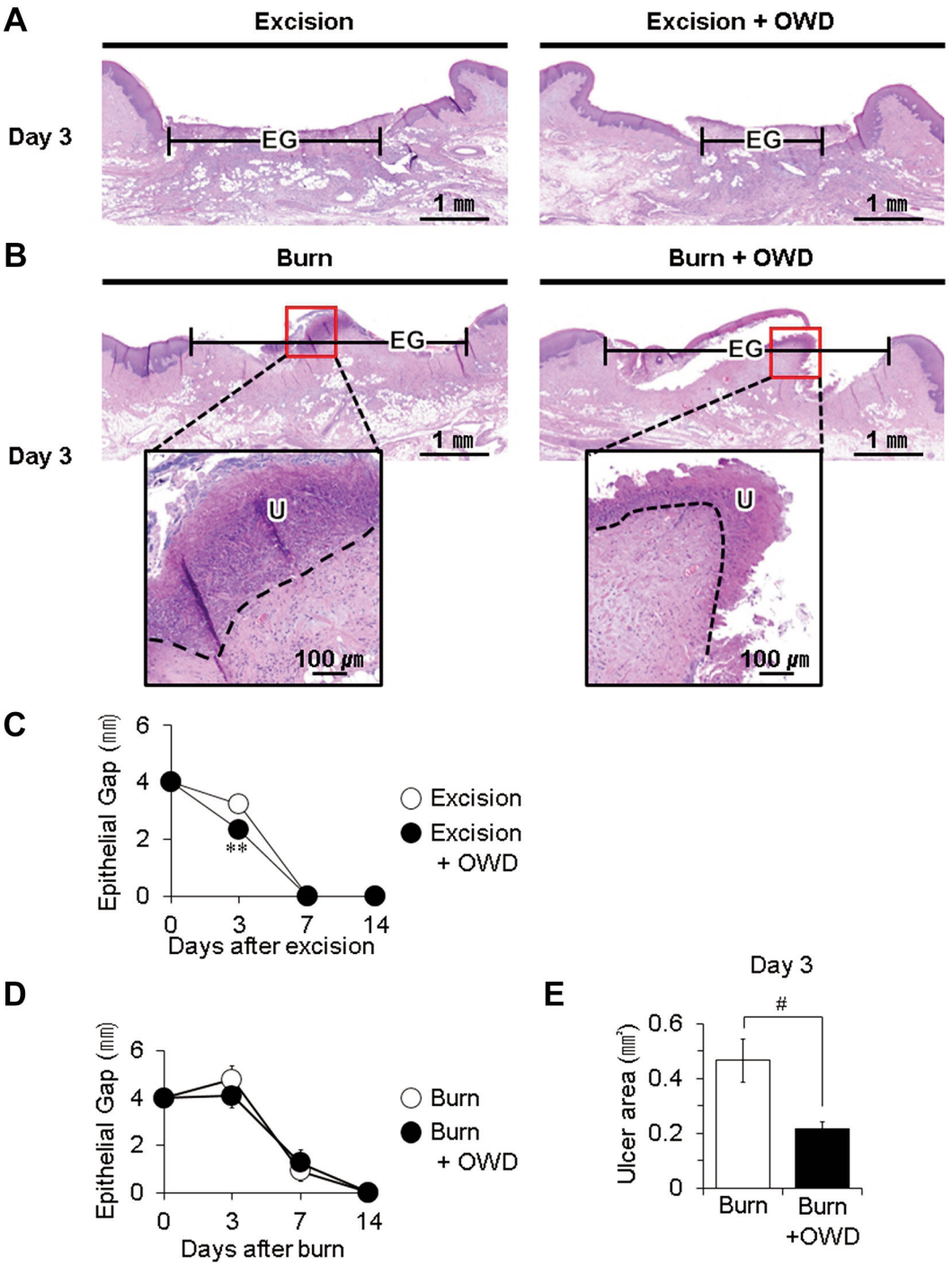

Figure 4. *Effect of the oral wound dressing (OWD) film treatment on wound closure. A) Re-epithelialization of the excision model. B) Re-epithelialization and ulcerated area of the chemical burn wound model. C) Epithelial gap in the excisional wound groups. D) Epithelial gap in the chemical burn wound groups. E) Ulcer area in the chemical burn wound group. Data are expressed as mean±standard error (SE). **p<0.01 excision controls, #p<0.05 vs. burn controls.*

positive cells were observed in the basal layer of the epidermis. On post-excision day 7, the number of Ki-67-positive cells in the OWD-treated excision wounds was significantly higher than that in the excision wound group (EXCISION: 72.17±5.41, EXCISION+OWD: 106.58±10.15, $p<0.05$; Figure 5C).

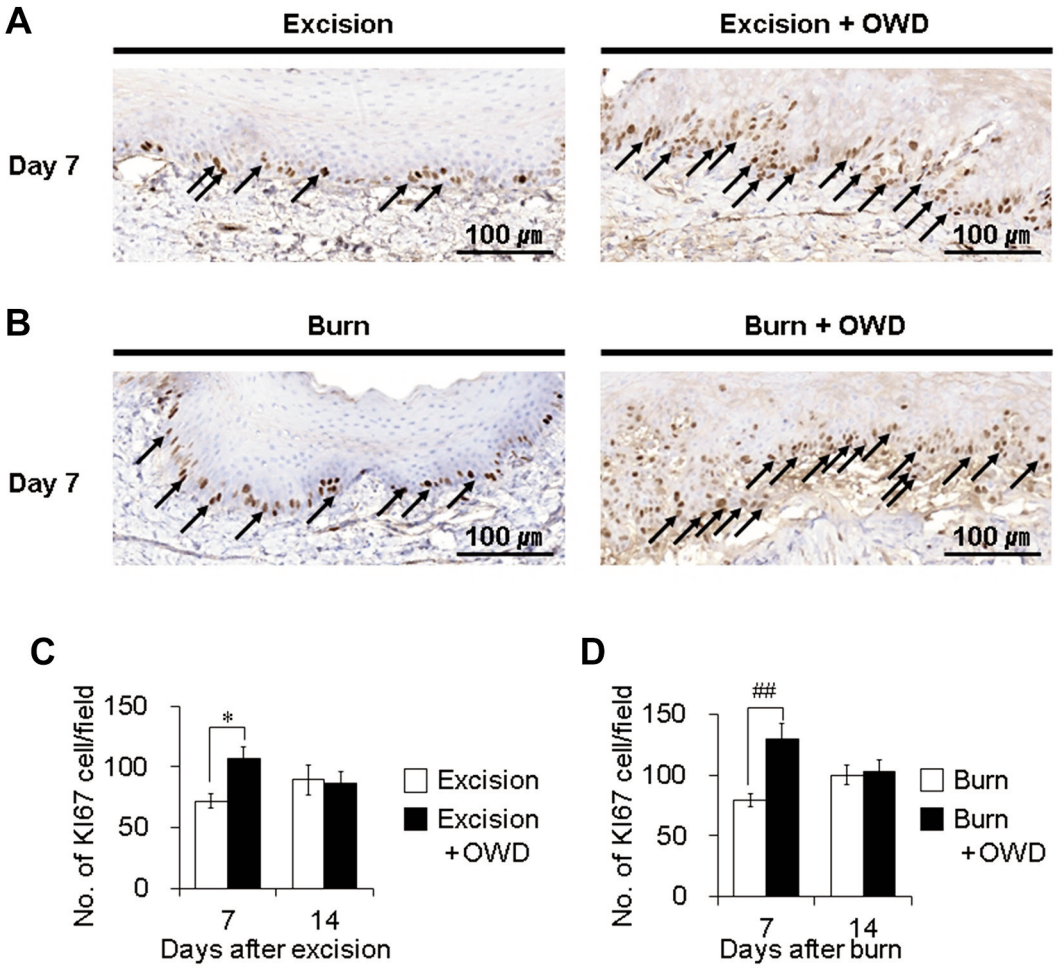

Figure 5. *Effect of the oral wound dressing (OWD) film treatment on the proliferation of basal cells. A) Expression of the proliferation marker Ki-67 in the wound edge epidermis of the excision wound model. B) Expression of the proliferation marker Ki-67 in the wound edge epidermis of the burn wound model. C) The number of Ki-67-positive cells in the excisional wound groups; D) The number of Ki-67-positive cells in the burn wound groups. Data are expressed as mean±SE. *p<0.05 excision controls, ##p<0.01 vs. burn controls.*

In the chemical burn wound model, the number of Ki-67-positive cells in the OWD-treated burn wounds was significantly higher than that in the burn wound group at day 7 (BURN: 78.83±5.43, BURN+OWD: 129.92±12.60, $p<0.01$; Figure 5D).

OWD film treatment promoted collagen accumulation during skin wound healing. Masson's trichrome staining was used to evaluate collagen deposition in the excision and burn wounds (Figure 6). On post-excision day 14, collagen deposition in the EXCISION+OWD treatment group accounted for 29.48±0.78%, which was significantly ($p<0.001$) higher than that observed in the EXCISION treatment group (21.56±0.89%) (Figure 6C).

In the chemical burn wound model, collagen deposition in the BURN+OWD treatment group accounted for 36.04±1.28%, which was significantly ($p<0.01$) higher than that observed in the BURN treatment group (28.36±1.30%) on day 14 (Figure 6D).

Discussion

The present study demonstrated that topical application of the OWD film, commercial name Curatick® or Ora-Aid®, improved wound closure and reconstruction following excisional and chemical burn oral wounds compared to the control injury groups.

The OWD film is a designed laminate consisting of an impermeable backing layer and a hydrophilic bioadhesive layer for mucosal attachment (10). The backing layer is a barrier that allows rapid wound closure, thus promoting wound healing and reducing scar formation (15). The inner

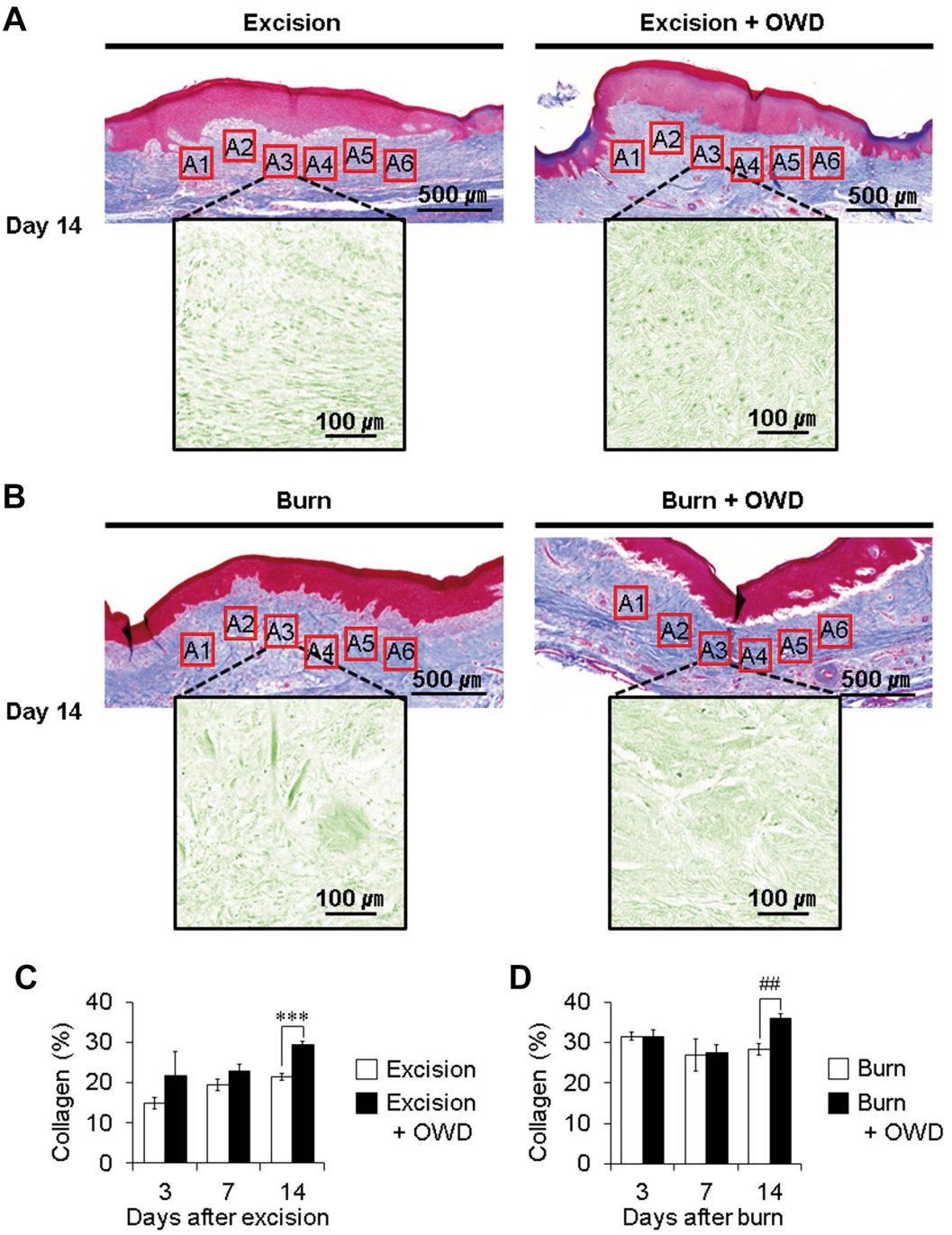

Figure 6. *Effect of the oral wound dressing (OWD) film treatment on collagen formation. A) Collagen deposition in the excision wound model. B) Collagen deposition in the burn wound model. C) Collagen fiber quantity in the excision wound model. D) Collagen fiber quantity in the burn wound model. Data are expressed as mean±SE. ***p<0.001 excision controls, ##p<0.01 vs. burn controls.*

layer, acting as the body glue, is converted into a gel and absorbs micro hemorrhages and wound exudates, maintaining a moist environment. Mucoadhesion results from the combination of several mechanisms. Appropriate mucoadhesion of the OWD film has good potential for reducing wound infections and improving the repair of damaged tissue (16, 17). However, a previous study revealed that excessive attachment of a bandage, continuously left on the wound for 12-14 days, delayed oral wound healing (18). Thus, the inner layer is designed with a hydrophilic

mucoadhesive feature and is automatically detached from the oral mucosa approximately 6-8 h after adhesion.

A clinical study conducted on 28 patients who underwent periodontal flap surgery examined the efficacy of Curatick® application and found it useful for reducing post-operative pain, bleeding, and dietary discomfort (9). For the first time, the present study evaluated the effects of this device on the various processes essential for soft tissue wound healing, including re-epithelization, epithelial proliferation, and matrix deposition.

Closure of the endothelial gap is crucial to achieving epithelial integrity during developmental and repair processes in wound healing. Histologically, we quantified the epithelial gap, one of the primary wound healing parameters (19, 20). The epithelial gap in the EXCISION+OWD treatment group showed a significant difference compared to the EXCISION treatment group on day 3. In contrast, there was no difference in the epithelial gap between the BURN+OWD and BURN treatment groups on day 3. In a previous study, an acetic acid-induced chemical burn wound model showed a temporally increased ulcer area as an acute-phase response (21). Similarly, our results showed a significantly increased epithelial gap compared with day 0 wound; however, the ulcer area significantly decreased during the acute phase (day 3).

For soft tissue wound healing, keratinocyte proliferation was previously studied (22, 23). In the present study, the number of basal keratinocytes positive for the endogenous cell proliferation marker Ki-67 in the neoepidermis and wound edge epidermis increased in the OWD treatment compared to that in the untreated groups on day 7. This effect only approached statistical significance on day 7.

Wound healing is a fundamental response to tissue damage, leading to restored tissue integrity, which is achieved by synthesizing the connective tissue matrix (24). Collagen is a major extracellular matrix protein and ultimately contributes to wound closure. Also, it is vital for strengthening and integrating the wound site (25, 26). In the present study, an increased quantity of collagen fiber was observed in the OWD groups; this increase was statistically significant on day 14. On the contrary, the increase was not noticeable in the untreated groups.

Previous studies evaluating the wound dressing film reported that the untreated wound dressing film was ineffective for treating excision and burn wounds (19, 27). The present study evaluated the effect of the OWD film on the treatment of excisional and chemical burn wounds and found that the OWD film, acting as a physical barrier of the wound site, improved the wound healing process.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Writing – original draft preparation, review and editing: S.K., E.J.J., S.E.K., and K.J.; Conceptualization: S.K., E.J.J., S.E.K. and K.J.; Investigation and formal analysis: H.M.J., S.S.K., M.S.L., S.Y.Y., K.M.S. All Authors contributed to the experiments and approved the designed experiments and study protocol.

Acknowledgements

This research was supported by the Basic Science Research Program through the NRF, funded by the Ministry of Education (Sejong, Republic of Korea) (NRF-2020R1C1C1009798).

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Received March 18, 2022
Revised April 8, 2022
Accepted April 11, 2022