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# Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

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Original research

## Experimental study and clinical application of polyglycolic acid sheet with fibrin glue for oral soft tissue surgery<sup>☆</sup>



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### ARTICLE INFO

#### Article history:

Received 14 October 2016

Received in revised form 17 February 2017

Accepted 25 February 2017

Available online 18 March 2017

#### Keywords:

Polyglycolic acid sheet

Fibrin glue

Oral surgery

Scar shrinkage

### ABSTRACT

**Objective:** The purpose of the present study was to examine the effects of a Polyglycolic acid (PGA) sheet with fibrin glue in the prevention of scar shrinkage.

**Methods:** A PGA sheet with fibrin glue was grafted into the tongue after partial glossectomy in 25 rabbits. The wounds were examined histologically and compared to those of animals without grafts at 1, 2, 4, and 8 weeks after surgery, with particular focus on the change in the shape of the tongue and scar shrinkage. Furthermore, a retrospective study was conducted for cases in which the material was grafted into the raw surface of the tongue after partial glossectomy in 20 patients with early tongue cancer or leukoplakia. Postoperative pain and bleeding, and functional disadvantages were compared between the patients with PGA grafts and 6 patients that received partial glossectomy followed by a collagen-based artificial dermis graft.

**Results:** In the animal experiment, less scar shrinkage was observed in rabbits receiving the graft of the PGA sheet with fibrin glue than in those with an open wound. Clinical application of the PGA sheet with fibrin glue indicated that the materials could prevent postoperative pain and functional disadvantages compared to collagen-based artificial dermis, although no statistical analysis was conducted on these results because of a historical controlled study with a small number of patients.

**Conclusions:** The results of this study suggest that a PGA sheet with fibrin glue is useful for treating an open wound after soft tissue surgery of the oral cavity.

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## 1. Introduction

In patients with a small defect after oral soft tissue surgery such as a partial glossectomy, the surgical wound is primarily sutured, whereas an extended defect generally requires reconstructive surgery using a vascularized free flap. In patients with a defect

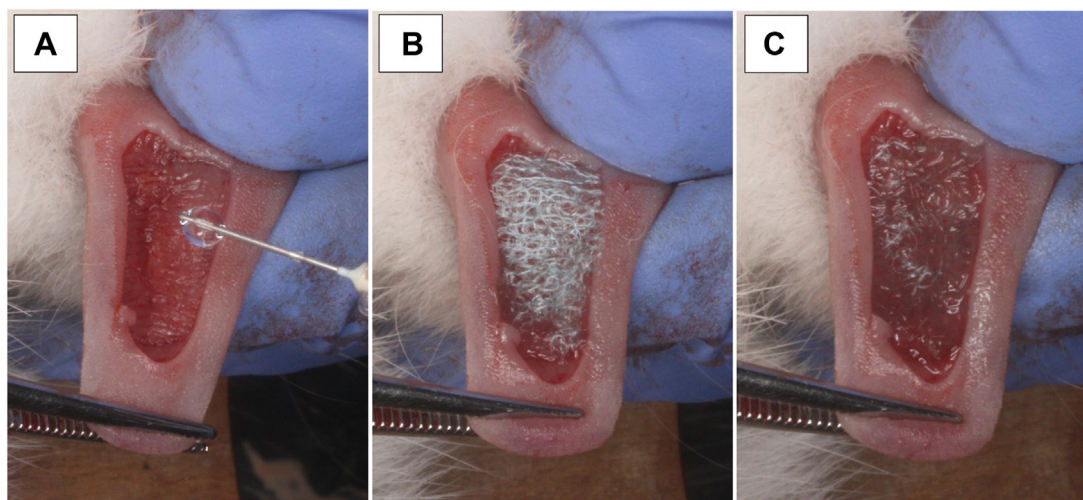
of an intermediate size, a skin graft is commonly used for covering the wound [1–3]. However, a skin graft has been associated with some problems such as causing damage to the donor site and partial or total necrosis of the grafted skin. A collagen-based artificial dermis (Terudermis<sup>®</sup>, Terumo Co., Ltd., Tokyo, Japan), in which collagen is combined with a silicone membrane allowing for suturing to the adjacent mucosa, has been widely used for an oral mucosal defect of intermediate size since the 1990s. Terudermis<sup>®</sup> is an excellent artificial material with good wound-healing and pain-relieving properties [4], but a tie-over dressing method is necessary because of the lack of adhesive ability to the surrounding tissue.

Recently, bio-absorbable polyglycolic acid (PGA) sheets with fibrin glue have been widely used for wounds during lung [5], liver [6], and gastrointestinal surgery [7] for the purpose of reinforcing the tissue and preventing leakage. Some investigators reported that these materials could also be used for coverage of a raw surface in oral surgery to decrease postoperative pain and bleeding.

<sup>☆</sup> AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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**Fig. 1.** Application of PGA sheet and fibrin glue. Fibrinogen solution is applied to the wound surface first (A), PGA sheet is attached (B), and mixture of fibrinogen and thrombin solutions is applied (C).

Takeuchi et al. [8] indicated that application of a PGA sheet with fibrin glue to the soft tissue wound after partial glossectomy may decrease functional disadvantages as well as prevent postoperative pain or bleeding; however, the efficacy of these PGA sheets in minimizing scar shrinkage has not been well investigated. Accordingly, the purpose of the current study was to investigate the effect of a PGA sheet with fibrin glue on the prevention of scar shrinkage after partial glossectomy in an animal model, and to retrospectively evaluate the clinical usefulness of this material in patients who had tongue cancer or a premalignant lesion and underwent partial glossectomy.

## 2. Methods

### 2.1. Animal experiment

A total of 43 New Zealand White Rabbits (SPF, male, 13 week-old, Biotek. Co.,Ltd, Saga, Japan) of approximately 2.0 kg in weight were used for the animal experiments. They were divided into two groups: PGA group (25 animals) and control group (18 animals). In the PGA group, a defect of approximately  $12 \times 10 \times 3$  mm was made on the dorsum of the tongue, and a 0.15-mm-thick PGA sheet (Neoveil<sup>®</sup>, Gunze Co., Ltd., Tokyo, Japan) with fibrin glue (Bolheal<sup>®</sup>, Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) was grafted to the surface of the open wound. After fluid-A (fibrinogen solution) was applied to the surface of the wound, the PGA sheet was attached, and a mixture of fluid-A and -B (thrombin solution) was further applied (Fig. 1). In the control group, the same defect was made but the wound was left open without any graft. Normal meal was given to the animals immediately after surgery.

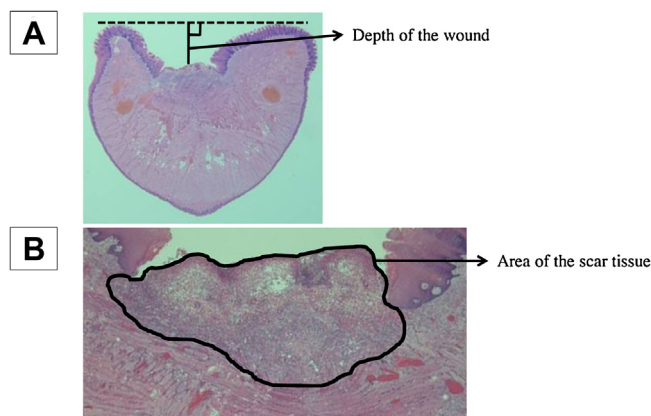
The animals were sacrificed at 1, 2, 4, and 8 weeks after the procedure, and the tongue was cut into the operative side half. The harvested tongue was fixed in formalin, and embedded in paraffin. The sections were stained with hematoxylin and eosin. Scar shrinkage of the wound was evaluated by measuring the depth of the wound and area of the scar tissue. Depth of the wound was measured on the specimen at the center of the wound relative to the line connecting the dorsum of the tongue at both ends of the wound to the deepest point of the wound, and area of the scar tissue was measured on the same specimen by freehand drawing using image-editing software (WinROOF ver.5.8, MITANI Co., Ltd., Fukui, Japan) (Fig. 2). The area of the scar tissue is expressed as the relative ratio, setting the area in the 1-week specimen as 100%.

Animal care and experimental procedures complied with the ARRIVE guidelines and were carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986.

### 2.2. Clinical application

Twenty-six patients that received partial glossectomy were examined retrospectively by the medical record (Table 1). The PGA sheet with fibrin glue was used in 20 patients (PGA group). The histologic diagnosis was leukoplakia in 13 patients and squamous cell carcinoma in 7 patients. After hemostasis of the surgical wound, fluid-A was applied to the surface of the wound, small pieces (10 mm) of PGA sheets were attached to cover the whole wound, and a mixture of fluid-A and -B was sprayed onto the PGA sheets using a double-syringe spray applicator. As a historical control, 6 patients who had undergone partial glossectomy followed by wound coverage with a collagen-based artificial dermis (Terudermis<sup>®</sup>) were also evaluated (collagen group). The distribution of patients in the two groups was not random owing to the retrospective nature of this study.

The area and depth of the wound, postoperative bleeding, use of postoperative non-steroidal anti-inflammatory drugs, and functional disadvantages were investigated and compared between the groups. The area and depth was measured by operation material.



**Fig. 2.** Evaluation of scar formation in an animal experiment. Depth of the wound (A) and area of the scar tissue (B) were measured on the specimen at the center of the wound.

**Table 1**  
Demographic factors of patients.

Group	Age	Sex	Diagnosis
PGA sheet	34–42 years (mean: 62.7)	male: 12 female: 8	leukoplakia: 13 squamous cell carcinoma: 7 (stage 1:5, stage 2: 2)
Terudermin	31–85 years (mean: 58.8 years)	male: 2 female: 4	leukoplakia: 2 squamous cell carcinoma: 4

Functional disadvantages were divided into 4 categories by medical record according to the complaint of the patient and objective findings: grade 0, no complaint nor objective findings; grade 1, mild complaint of disadvantage; grade 2, moderate complaint of disadvantage but no objective speaking or eating dysfunction; and grade 3, severe complaint of disadvantage with objective speaking or eating dysfunction.

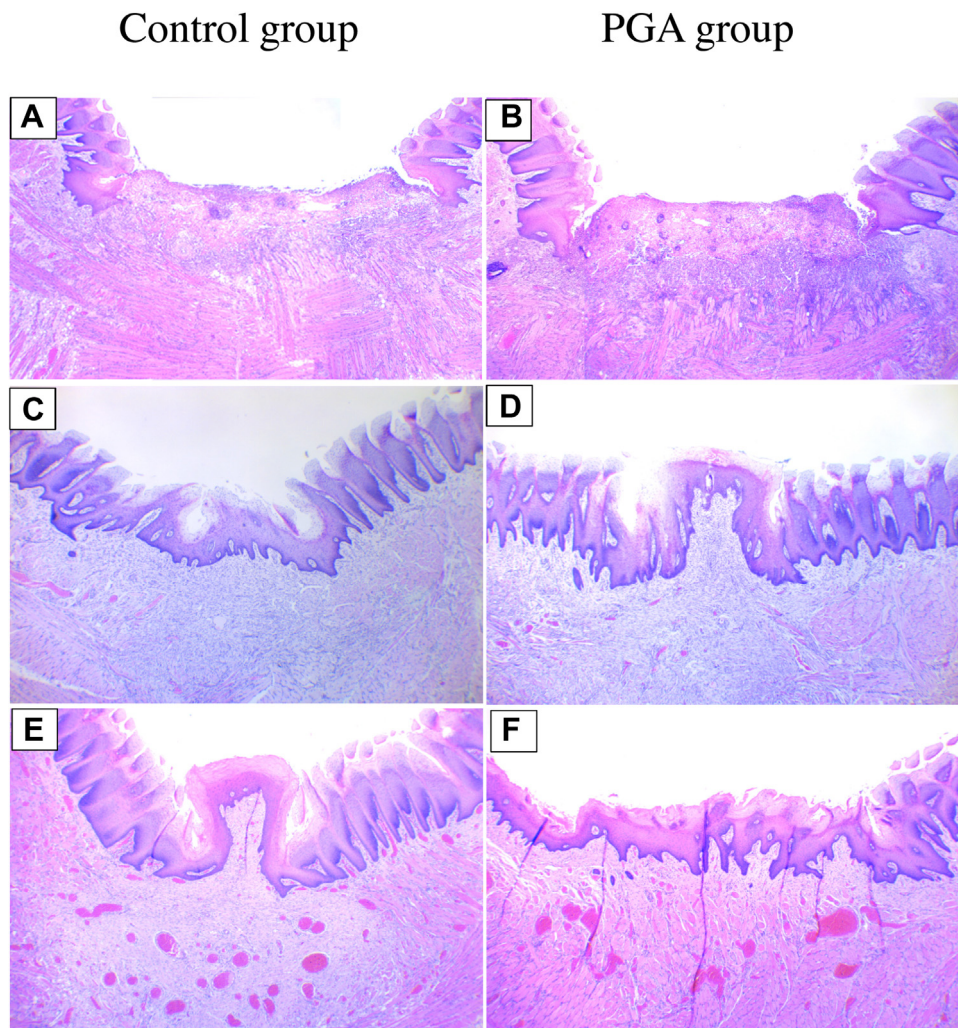
### 3. Results

#### 3.1. Wound healing in the animal experiment

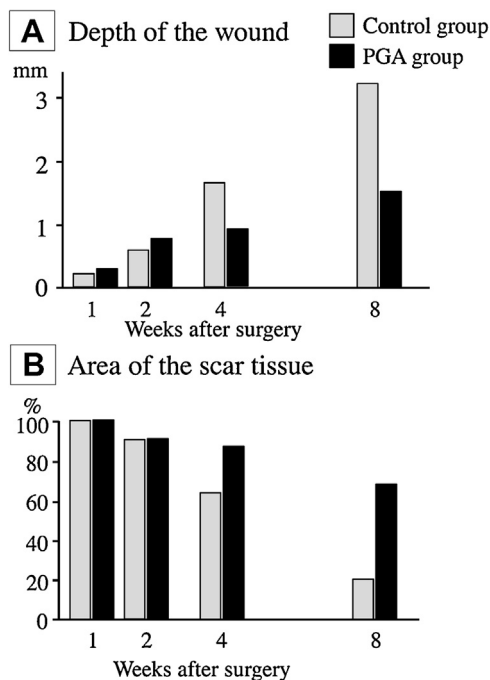
The histologic examinations of the control group at one week after defect formation showed a lack of the epithelial layer and

clear infiltration of inflammatory cells into the wound. The findings were similar between the PGA group and the control group. Remaining PGA fibers were evident, and the degree of inflammatory cells infiltration did not differ between the groups.

After 2 weeks, the specimens of control group and PGA group (Fig. 3A, B) exhibited partial repair of the epithelium, although the epithelial layer of the control group (Fig. 3A) was thinner than that of the PGA group (Fig. 3B). There was no difference in the degree of inflammatory cells infiltration between control group and PGA group (Fig. 3A, B). The PGA group (Fig. 3B) showed residual PGA fibers and macrophages were observed. Collagen fibers were found toward the center of the wound in the control group (Fig. 3A), suggesting that scar formation had begun, whereas those in the



**Fig. 3.** At 2 weeks after surgery, the specimens of both groups exhibited partial repair of the epithelium. The epithelial layer of the control group (A) was thinner than that of the PGA group (B). At 4 weeks after surgery, epithelialization was almost complete in control group (C) and PGA group (D). PGA was totally absorbed or detached (D). At 8 weeks after surgery, the specimens of the control group (E) showed more apparent recess of the tongue shape than that at 4 weeks, which indicated that scar formation had progressed. On the other hand, the PGA group (F) showed less deformation of the shape of the tongue.



**Fig. 4.** Scar formation after surgery in the animal experiment in the PGA (black) and control (grey) groups evaluated according to (A) depth of the wound and (B) area of scar tissue.

PGA group were running regularly across the whole surface of the wound (Fig. 3A, B).

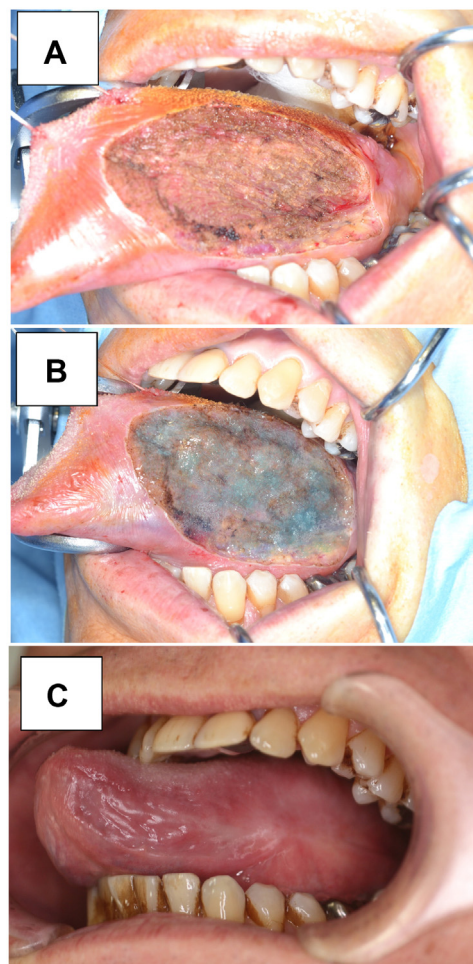
At 4 weeks after surgery, epithelialization was almost complete in control group and PGA group (Fig. 3C, D). PGA was totally absorbed or detached (Fig. 3D). The epithelium in the control group was thin and recessed (Fig. 3C), while that in the PGA group was as thick as the surrounding epithelial layer and flat (Fig. 3D). There was no infiltration of inflammatory cells in either group (Fig. 3C, D).

The histologic features of the specimens at 8 weeks post-surgery were similar to those of the specimens at 4 weeks post-surgery (Fig. 3E, F). Recess of the tongue shape in the control group (Fig. 3E) became more apparent than that at 4 weeks, which indicated that scar shrinkage had progressed. On the other hand, the PGA group (Fig. 3F) showed less deformation of the shape of the tongue.

The changes in the depth of the wound and area of the scar tissue in both groups are shown in Fig. 4. There were no apparent differences in the depth of the wound between the two groups within the first 2 weeks after resection. The 4-week control group specimens showed more recess in the shape of the tongue than the PGA group, and deformation of the tongue in the control group became more apparent after 8 weeks. The area of scar tissue in the control group at 8 weeks decreased to 21% of that at 1 week, in contrast to a 66% decrease in the PGA group (Fig. 4). These findings indicated that contracture in the control group was greater than that in the PGA group.

### 3.2. Clinical application of a PGA Sheet with fibrin glue after partial glossectomy

Table 2 shows a summary of patients who received a PGA sheet with fibrin glue or Terudermis® following partial glossectomy. The average postoperative days requiring a painkiller was 6.7 days in patients with PGA, and 12.1 days in those with Terudermis®. These findings indicate that a PGA sheet with fibrin glue has a better analgesic effect than Terudermis®. Postoperative bleeding did not occur in either group. The functional disadvantages were reduced in



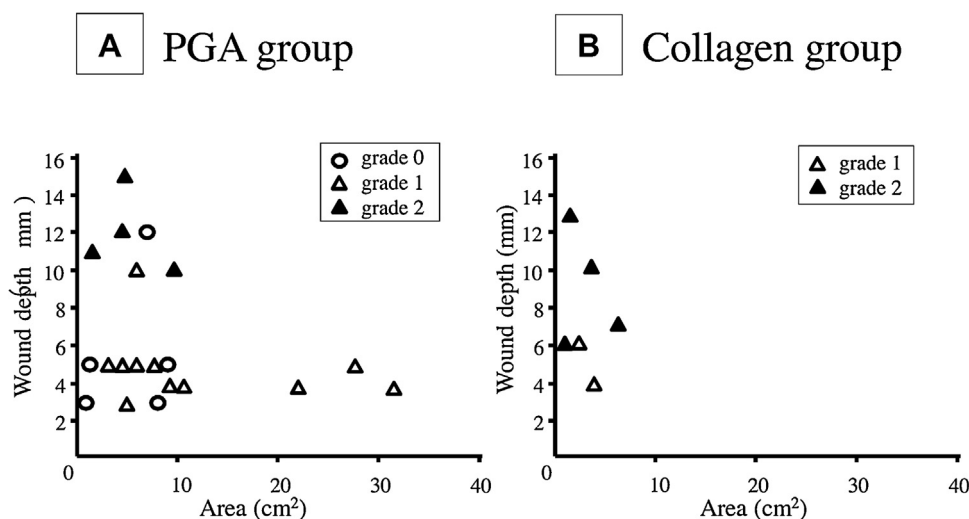
**Fig. 5.** Clinical application of a PGA sheet with fibrin glue. (A) Resection of leukoplakia of the tongue. (B) Attachment of the PGA sheet with fibrin glue. (C) Four months after surgery. There were no functional disadvantages observed.

patients with a PGA sheet than in those with Terudermis® (Table 2 and Fig. 5).

Fig. 6 shows the relationship between wound size and functional disadvantage in both groups. As the wound size increased, there were more functional disadvantages. Comparing the two materials, the PGA group seemed to show less disadvantages than the collagen group, although no valid conclusion could be drawn because of the small number of patients used as a histological control.

**Table 2**  
Comparison between patient groups for NSAIDs use, bleeding, and functional disadvantages.

Group	Patients	Mean days of NSAIDs use	Postoperative bleeding	Functional disadvantage
PGA sheet	20	6.7 days	0	grade 0: 5 grade 1: 11 grade 2: 4 grade 3: 0
Terudermis	6	12.1 days	0	grade 0: 0 grade 1: 2 grade 2: 4 grade 3: 0



**Fig. 6.** Relationship between wound area/depth and functional disadvantage after grafting of a PGA sheet with fibrin glue (A) or collagen-based artificial dermis (B). Note that patients with grade-3 functional disadvantage were not observed in the PGA group, and patients with grade-0 or grade-3 functional disadvantage were not observed in the collagen-based artificial dermis group.

#### 4. Discussion

A primary suture is generally performed in a small wound after resection of a premalignant or malignant lesion of the tongue. However, in cases with larger wounds, a primary suture causes deformation of the tongue. A free skin graft, which is sometimes applied to a moderately sized mucosal defect of the tongue, results in surgical damage of the donor site. A collagen-based artificial dermis has recently been used on the mucosal surface after soft tissue surgery of the oral cavity instead of a skin graft, but the surgical method requires a tie-over technique and thus becomes complicated.

A PGA sheet with fibrin glue has recently been used for treating wounds formed in lung, liver, or gastrointestinal surgery in order to reinforce the tissue and prevent leakage [5–7]. Takeuchi et al. [8] applied this material to the mucosal surface after partial glossectomy, and described that a wound covered by the PGA sheet with fibrin glue showed less scar contracture than a wound covered by a collagen-based artificial dermis. However, there have been no *in vivo* experimental studies on scar shrinkage of a PGA sheet with fibrin glue applied to the oral mucosa.

In the current animal experiment, there was no difference in the rate of wound repair between rabbits with a grafted PGA sheet with fibrin glue and those with an open wound, which suggests good biocompatibility of these materials. However, some notable differences were observed between the groups. First, the regenerated epithelial layer in the control group became thin, while that in the PGA group was as thick as the surrounding epithelium. Second, the shape of the tongue in both groups at 4 and 8 weeks was quite different. The epithelial layer in the control group was recessed, while that in the PGA group was flat. Further, the depth of the wound and the reduction of the area of scar tissue in the control group became larger than those of the PGA group. We also attempted to use a collagen-based artificial dermis in the animal experiment. Transplantation of a collagen-based artificial dermis needs tie-over dressing. However, it was difficult to perform this procedure to the tongue of rabbits because they could not keep their tongue resting after surgery and fixation of the dressing was easily loosened. These findings show that a PGA sheet with fibrin glue is a simple method and useful to minimize scar shrinkage compared to an open wound.

We have used a PGA sheet with fibrin glue for patients receiving a partial glossectomy, as reported previously [8–10]. In the present

study, the usefulness of this material was retrospectively compared to that of a collagen-based artificial dermis. The use of a PGA sheet with fibrin glue had some advantage with respect to relief from postoperative pain and less scar shrinkage, which appeared to minimize functional disorder of the tongue, although this study is retrospective one with a small number of patients. Takeuchi et al. [8] described that wound infection rarely occurred when PGA was attached to the open wound, because it could prevent invasion of bacteria by adhering strongly to the connective tissue, thereby minimizing scar contracture. We also consider that the main reason for the decreased use of painkillers in the PGA group is due to the strong adhesion of PGA to the surface of the wound by the fibrin glue. In addition, the PGA sheet may prevent scar shrinkage by providing a favorable environment for the regeneration of epithelial cells. However, no valid conclusion could be drawn because this was a preliminary, experimental study and a retrospective, historical controlled clinical study with a small number of patients, but direct comparison between PGA sheet and collagen-based artificial dermis by randomized clinical trial would be difficult for ethical aspects since it was suggested that PGA sheet is superior to collagen-based artificial dermis by the current study. Therefore, more clinical experiences of patients who received PGA sheet with fibrin glue for oral soft tissue surgery to clarify the usefulness of the materials.

#### 5. Conclusions

The results of this study suggest that a PGA sheet with fibrin glue is useful for treating an open wound after soft tissue surgery of the oral cavity. Future studies will focus on a larger clinical trial to evaluate the general usefulness of these materials in oral surgery.

#### Ethical approval

Owing to the retrospective nature of this clinical application study, it was granted an exemption of approval in writing by the Institutional Review Board of Nagasaki University Graduate School of Biomedical Sciences and complied with the standards of the Declaration of Helsinki.

**Conflict of interest**

None.

**Acknowledgement**

This work was supported by the experimental materials from Chemo-sero-therapeutic Research Institute (Kaketsuken), Kumamoto City, Japan.

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