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Original Article

Effect of basic fibroblast growth factor with collagen/gelatin fixture in a rabbit model of nasal septum perforation

Yuki Takizawa [a, b], Tsunetaro Morino [a, b], Ryo Takagi [a], Nobuyoshi Otori [b], Hiromi Kojima [b], Masayuki Yamato [a, *]

[a] Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan
[b] Department of Otorhinolaryngology, Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo, Japan

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ABSTRACT

Introduction: The treatment of nasal septum perforation solely by surgical intervention presents significant challenges. This study evaluated the effect of basic fibroblast growth factor (bFGF) in combination with collagen/gelatin on wound healing of nasal septum perforation in a rabbit animal model.
Methods: A nasal septum perforation rabbit model was created. bFGF was added to a collagen/gelatin fixture and placed adjacent to the perforation, which is a complete defect. The rabbits were divided into three groups: the sham group that underwent the surgical procedure only, bFGF (−) group that received collagen/gelatin fixture without bFGF, and bFGF(+) group that received collagen/gelatin fixture with bFGF. The dimensions of the perforations were measured after 4 weeks, and the septum was subjected to histological examination.
Results: All perforations remained open in the sham group (closure rate: 20.4%–83.1%). The closure rates of the bFGF(−) and bFGF(+) groups were 49.4%–68.8% and 72.7%–100%, respectively. No significant difference was noted in the closure rates between the sham and bFGF(−) groups; however, significant differences were observed between the sham and bFGF(+) groups, and the bFGF(−) and bFGF(+) groups ($p < 0.05$), indicating that bFGF promoted perforation closure.
Conclusions: The study demonstrated that bFGF with collagen/gelatin carrier promoted wound healing in a rabbit model of nasal septum perforation.

1. Introduction

A nasal septum perforation is a complete defect of the nasal septum. The etiology of nasal septum perforation includes iatrogenic causes, such as surgery, and other causes including tumors, collagen disease, trauma, medications, toxicity, infections, and foreign materials [1,2]. The main cause is nasal surgery especially septoplasty. Septoplasty is a surgical procedure used to correct nasal septum deviation by removing the deviated bone and cartilage, while leaving the mucosa on both sides intact. However, if the mucosa becomes injured during the surgery, it can result in the formation of a perforation. Most patients remain asymptomatic; however, frequent epistaxis, nasal pain, nasal congestion caused by airflow turbulence, and whistling have been reported by some patients, which drastically affect their quality of life. Surgical treatment is the only way to close the perforation, however, surgery is usually challenging [3,4]. Challenges arise due to unavailability of nasal mucosa in the nasal cavity for closure. Most symptoms of nasal septum perforation are caused by airflow turbulence. Small perforations do not typically cause symptoms, while larger ones which airflow turbulence occurs are reported to be symptomatic. Therefore, complete closure or reducing the size of the perforation is required to normalize the airflow, thus may lead to symptom improvement [5]. Based on the fact that septoplasty involves the removal of both cartilage and bone, there is no need for cartilage and bone reconstruction. Novel treatment strategies to accelerate wound healing that can be easily performed at many facilities are desired.

* Corresponding author.
E-mail addresses: ytakizawa@jikei.ac.jp (Y. Takizawa), morino.tsunetaro@twmu.ac.jp (T. Morino), takagi.ryo@twmu.ac.jp (R. Takagi), otori@jikei.ac.jp (N. Otori), kojimah@jikei.ac.jp (H. Kojima), yamato.masayuki@twmu.ac.jp (M. Yamato).
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Basic fibroblast growth factor (bFGF), also known as FGF2, is a growth factor encoded by the FGF gene. bFGF plays an important role in the proliferation and differentiation of various cells and tissues, which are required for angiogenesis, wound healing, and embryonic development [6]. The high efficacy and safety of bFGF have been proven in especially dermatological field [7,8]. However, bFGF decomposes within a few hours after administration. Therefore, combining materials such as gelatin and collagen to extend the effect have been considered recently [6,7,9]. Treatment of nasal septum perforation presents a significant challenge due to the complete three-dimensional defect it presents, requiring an essential approach to maintain medication efficacy. The approach of appropriately fixing gelatin with bFGF to the site of a tympanic membrane perforation, a condition that shares similarities with nasal septum perforation, has been reported to promote perforation closure [10].

We hypothesized that by appropriately applying bFGF in combination with other materials to the perforation site can assist the healing of nasal septum perforations. The application of bFGF with collagen/gelatin in an animal model of nasal septum perforation has not been reported before. This study examined the efficacy of a growth factor combined with a biomaterial on the healing of nasal septal perforations in a rabbit model.

2. Methods

2.1. Animals

All experimental protocols were approved by the Animal Welfare Committee of the Tokyo Women's Medical University (approval number: AE20-134,2020). Adult male specific-pathogen-free New Zealand white rabbits weighing 2.5–3.0 kg were used in this study. General anesthesia was induced using 2.0 mg/kg of midazolam (Astellas, Tokyo, Japan), 0.5 mg/kg of butorphanol (Meiji Seika Pharma, Tokyo, Japan), and 0.5 mg/kg of medetomidine (Zenoaq, Tokyo, Japan) administered intramuscularly to the hindlimbs of the rabbits.

2.2. Surgical procedure of rabbit nasal septum perforation model

The rabbits were placed in the prone position, and the region above the nasal dorsum was shaved. A vertical skin incision of approximately 5 cm was made over the center of the nasal dorsum. The periosteum of the nasal bone was incised laterally for full width to approximately 2.0 cm distal from the nasal apex, exposing the nasal bone. Two holes were created at the outermost point of the nasal bone in the lateral direction underneath the periosteal incision using a 2 mm diameter diamond drill. The two holes were then connected using surgical scissors, ensuring that no injury was caused to the nasal septum. A small incision was made with a scalpel on both sides, starting at the anterolateral side of the alar cartilage, close to the border of the maxillary bone and approximately 5 mm from the nasal apex. The incision was continued with surgical scissors toward the lateral incision made previously. The released nasal bone was gently elevated from the caudal side by incising the nasal septum along the nasal bone toward the alar cartilage with a scalpel. After flipping the nasal bone and alar cartilage forward, the nasal septum was exposed while retaining the nasal bone attached as a flap. The anterior part of the ventral nasal concha located externally on both sides of the septum was removed to ensure that sufficient space was available for the subsequent procedure. A perforation was created approximately 1.5–2.0 cm distal from the nasal apex using a 6 mm metallic circular perforator such that a distance of 2–3 mm was present from the upper septum edge. The flipped nasal bone was then placed in the original location after confirming hemostasis and removing the coagulum, followed by suturing of the periosteum and skin with a nylon thread (Fig. 1a–f).

2.3. Treatment with bFGF and collagen-gelatin fixture

The procedure for creating a perforation was the same as that described in the previous subsection. The dosage of bFGF (Trafermin, Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) was adjusted to 100 μg/mL. A collagen/gelatin fixture covered with a thin layer of silicone (Pelnaq G plus, Gunze Limited, Osaka, Japan) was used as the carrier for bFGF. The collagen/gelatin fixture was cut into an 8 × 8 mm square, and a total of 10 μg (0.1 mL) of bFGF was added (Fig. 1g). The fixture was then placed beside the perforation on the right side, followed by the addition of fibrin glue (BOLHEAL Tissue Sealant, KM Biologics, Tokyo, Japan). The fixture was sutured using a nylon thread at the upper and lower locations (Fig. 1h). The nasal bone was placed in the original location by flipping, and the periosteum of the nasal bone and skin were sutured using a nylon thread. The bFGF(−) group, wherein the collagen/gelatin fixture was placed without the application of bFGF, was prepared using the same procedure for comparison with the treatment model.

Twenty-two rabbits were divided into three groups: the sham group that underwent the surgical procedure only, bFGF(−) group that received a collagen/gelatin fixture without bFGF, and bFGF(+) group that received a collagen/gelatin fixture with bFGF. In addition, three rabbits from the treatment group were examined 7, 14, 21 days after the surgery.

2.4. Macroscopic assessments

All rabbits were euthanized via the intravenous administration of 150 mg/kg of thiopental sodium (Nipro ES Pharma, Tokyo, Japan) within 28–30 days. In addition, rabbits from the bFGF(+) group were euthanized 7, 14, and 21 days postoperatively to observe the macroscopic and histological changes over these periods. No additional procedures were performed during the observation period. The skin was removed after euthanization and the nasal and maxillary bones were incised. The exposed nasal septum was removed and photographed (Fig. 2). The areas of the remaining perforations were measured from the images using ImageJ (National Institutes of Health, Bethesda, MD, USA), and the closure rate was calculated (Fig. 3).

2.5. Histological assessments

All nasal septa were fixed in 4% paraformaldehyde for 1–2 days and subsequently dehydrated in ethanol, clarified in xylene, and embedded in paraffin (CT-Pro20 Cell & Tissue Processor; GenoStaff, Tokyo, Japan). Sections 4 μm thick were stained with hematoxylin and eosin, immunohistochemistry, and Alcian-blue staining. For immunohistochemistry, anti-pan-cytokeratin which is an epithelium marker was stained and Alcian-blue staining was used to stain goblet cells. The paraffin sections were deparaffinized, rehydrated, and incubated with proteinase K (S3020; Dako, Tokyo, Japan) or heated in a chamber at 125 °C for antigen retrieval. Blocking was performed by incubating the sections with a peroxidase-blocking solution (S2030; Dako) for 30 min after washing twice with PBS. The specimens were incubated with a blocking reagent (Blocking One Histo; Nacalai Tesque, Kyoto, Japan) for 1 h at room temperature to reduce non-specific antibody binding. Subsequently, the sections were incubated with an anti-pan-cytokeratin antibody (mouse monoclonal, 1:100; Abcam, ab27988) at 4 °C in a humidified chamber overnight. The sections were washed with PBS the

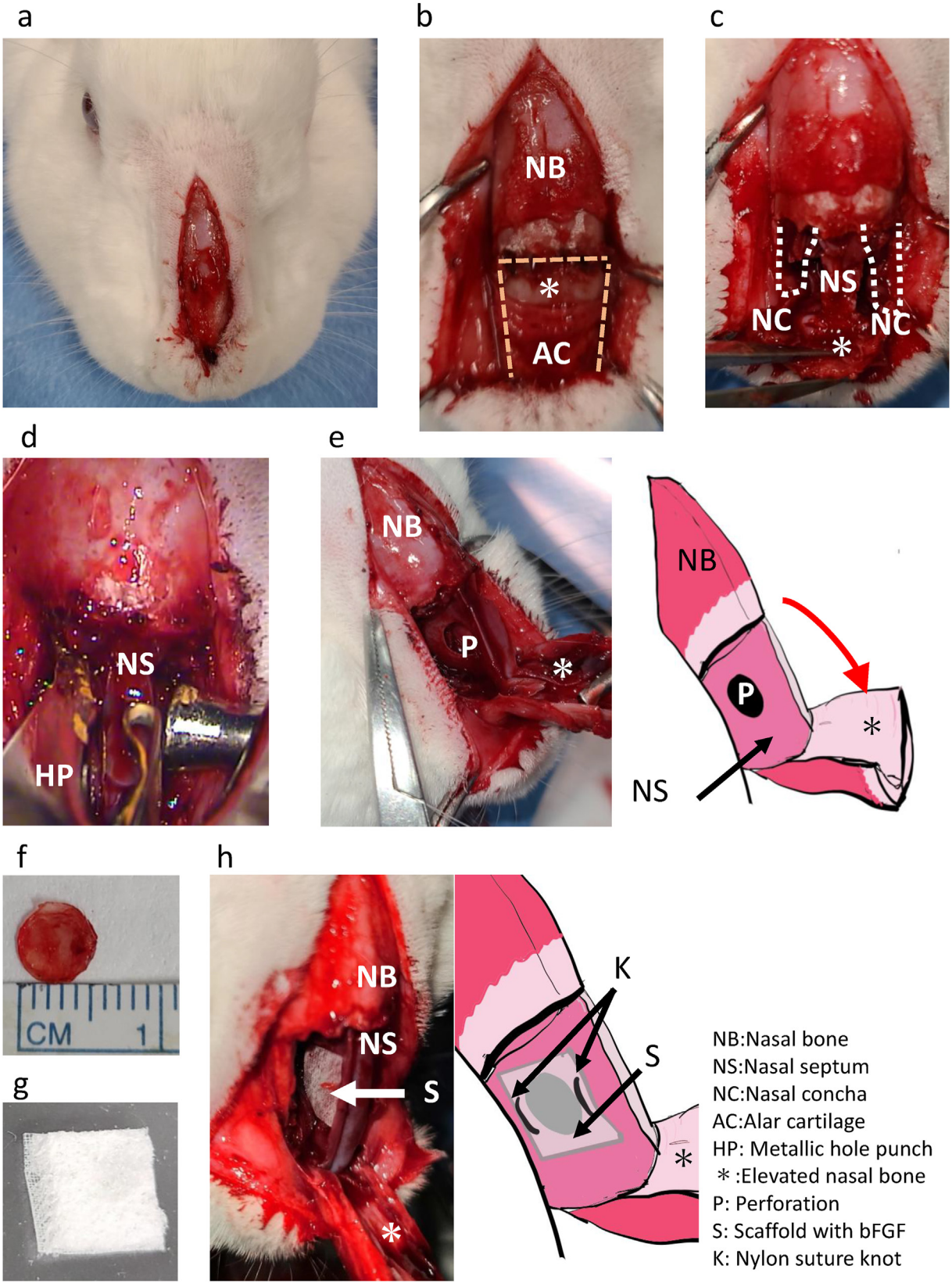

Fig. 1. (a) Vertical incision made on the dorsal aspect of the nose. (b) After incising the periosteum horizontally, one perforation is made on each side of the nasal bone horizontally and the perforations are connected by an incision with surgical scissors. Then an incision is made on both sides of the dorsal part of the alar cartilage, which joins the lateral incision previously made (dashed line). (c) The released nasal bone and alar cartilage are elevated forward together by disconnecting the nasal bone from the nasal septum with a scalpel. The anterior parts of both ventral nasal conchae are removed (dotted line). (d) A perforation is created using a 6 mm diameter metallic circular perforator. (e) View from the front right side of the perforation. (f) Perforated nasal septum tissue with a 6 mm diameter. (g) Collagen/gelatin fixture cut into 8 × 8 mm size. (h) bFGF is added to the collagen/gelatin fixture, placed beside the perforation, and sutured with two knots (right forward angle). bFGF, basic fibroblast growth factor.

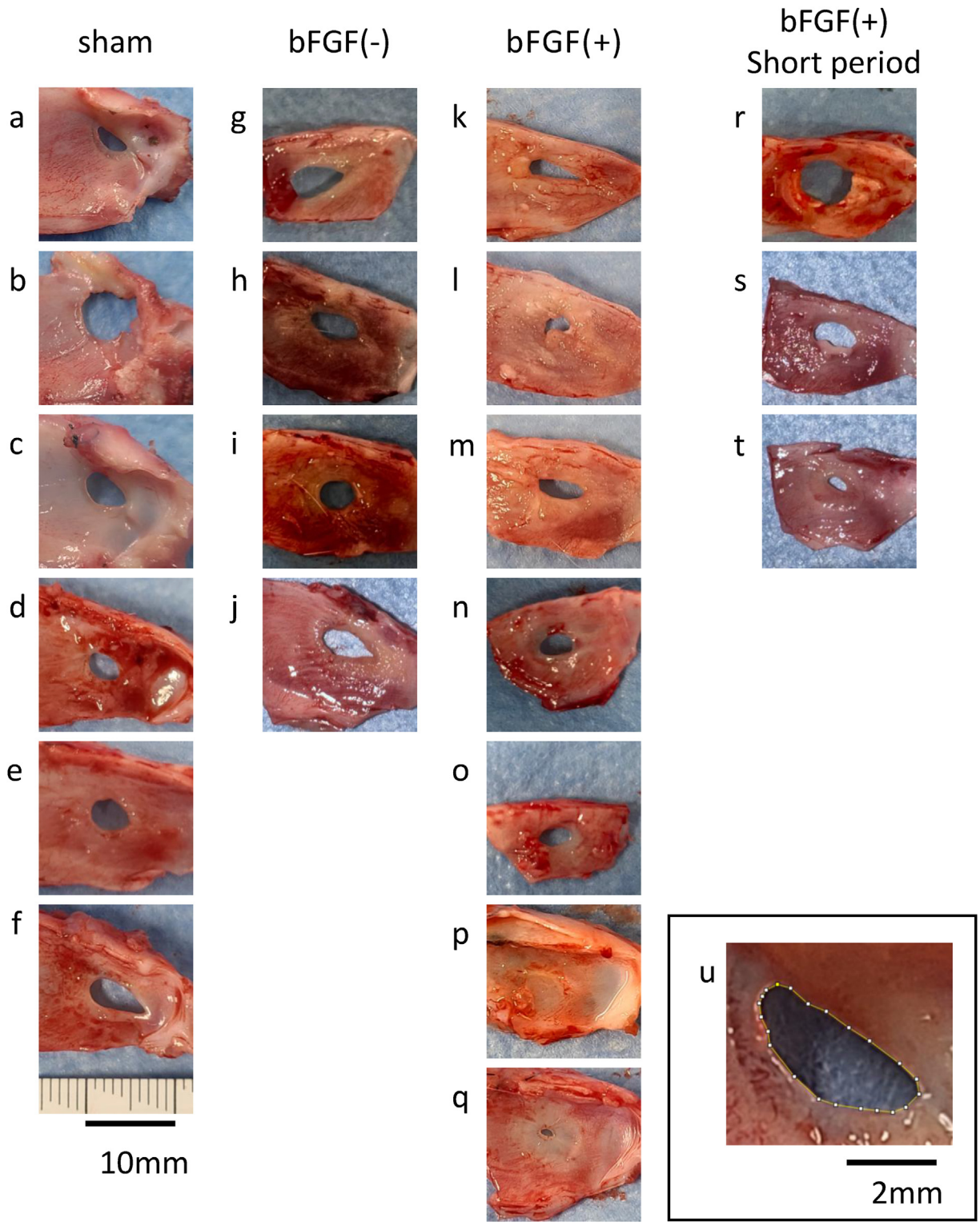

Fig. 2. Macroscopic image of the nasal septum collected 28 days (a–q), 7 days (r), 14 days (s), and 21 days (t) after surgery. The perforations are very evident in the sham and bFGF(−) groups (a–j). Perforations in the bFGF(+) groups appear to be smaller than in the other two groups (k–q) and completely disappeared in one case. The perforation size is gradually decreased post-operation (r–t). The perforation size was measured by outlining the perforation with Image J software (u). bFGF, basic fibroblast growth factor.

next day and incubated with a horseradish peroxidase-conjugated secondary antibody (EnVision Detection Systems, Peroxidase/DAB, Rabbit/Mouse; Dako) for 30 min at room temperature, followed by a diaminobenzidine solution (Dako) for 90 s. The nuclei were stained with hematoxylin. For Alcian-blue staining, the sections were deparaffinized, rehydrated in distilled water, and stained with Alcian blue (pH 2.5) for 20 min. Nuclear red staining was performed for 5 min to counterstain the cells.

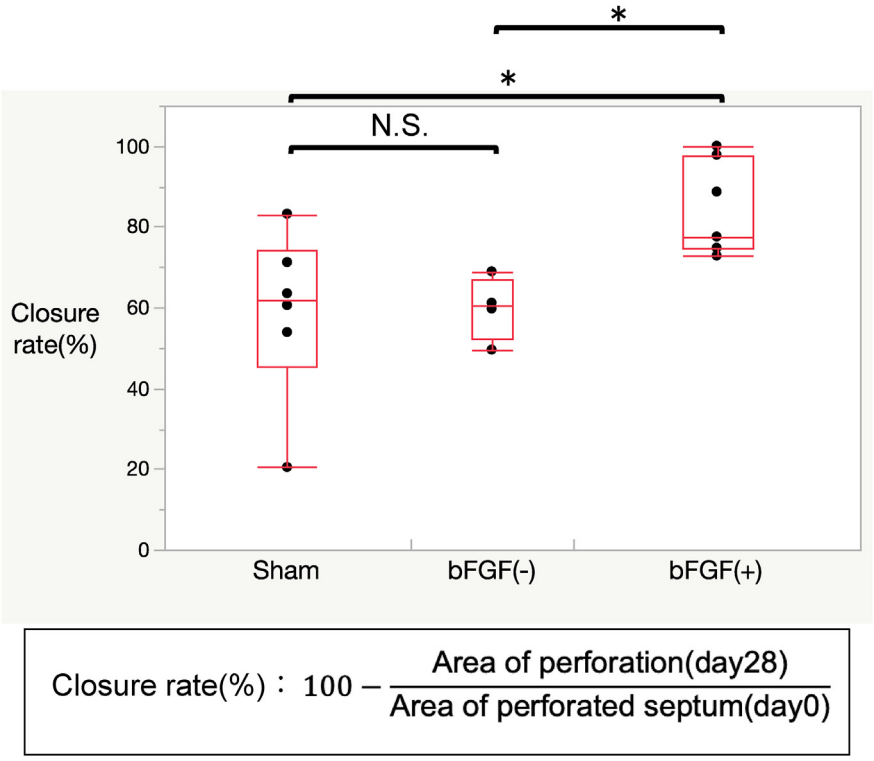

Fig. 3. Closure rate (%) comparison between the three experimental groups: sham, bFGF(−) groups, and bFGF(+). Data dispersion is represented by dots and boxes which indicate the first and third quartiles, whereas the lines represent median observations in each box. *p < 0.05; N.S., not significant. n = 6 (Sham), n = 4 [bFGF(−)], n = 7 [bFGF(+)]. bFGF, basic fibroblast growth factor.

2.6. Statistical analysis

JMP Pro 16 (SAS, Cary, NC, USA) was used for statistical analysis. The Wilcoxon test was used to compare the groups. Statistical significance was set at $p < 0.05$.

3. Results

Among the 22 rabbits used in this study, seven, seven, and five rabbits were included in the sham, bFGF(+)s, and bFGF(−) groups, respectively. Three rabbits were used to observe the histologic changes occurring 7, 14, 21 days after surgery. Two rabbits died because of deep anesthesia, one died during surgery and one died during observation; thus six and four rabbits remained in the sham and bFGF(−) groups, respectively. The rabbits in all three groups were euthanized 28–30 days postoperatively. In addition, one rabbit each from the bFGF (+) group was euthanized on 7, 14, and 21 days postoperatively to observe the histologic changes that occurred over a short period. An increase in body weight was observed in most rabbits; however, the body weight decreased to less than 10% of the initial weight in a few rabbits.

3.1. Comparison of the closure rate in the nasal septum perforation models

All perforations remained in the sham and bFGF(−) groups 4 weeks postoperatively (Fig. 2). Closure of one perforation was observed in the bFGF(+) group (Fig. 2p). The closure rates of the sham, bFGF(−), and bFGF(+) groups ranged from 20.4 to 83.1%, 49.4–68.8%, and 72.7–100%, respectively (Fig. 3). The closure rates of the sham and bFGF(−) groups showed no statistically significant difference. However, statistically significant differences were observed between the closure rates of the sham and bFGF (+) groups as well as the bFGF(−) and bFGF(+) groups ($p < 0.05$). The closure rates in the rabbits that were euthanized 7, 14, and 21 days postoperatively were 21.6%, 66.7%, and 91.6%, respectively.

3.2. Histological changes in the epithelium

Histological assessments for the perforations revealed differences in epithelial regeneration of the three groups. For comparison, normal nasal mucosa of nasal septum was stained (Fig. 4a, b, c). The regenerated nasal mucosa in the sham group comprised squamous epithelial cells instead of ciliated epithelial cells (Fig. 4d, e, f). The stratified squamous epithelium was thick and extensive. The mucosal change at the perforation edge was maintained even after a long period (Supplementary Fig. 1). Compared with that of those in the sham group, the epithelium of the rabbits in the bFGF(−) and bFGF(+) groups mainly comprised goblet cells consisting of mucus (Fig. 4g, h, i, j, k, l). Regeneration of the epithelium was observed in the three rabbits euthanized 7, 14, and 21 days postoperatively. The perforation edge was infiltrated with inflammatory cells and the epithelium had not yet regenerated by day 7 (Supplementary Fig. 2a). The perforation edge was slightly covered by the epithelium by day 14 (Supplementary Fig. 2b), whereas it was completely covered by epithelium consisting of many goblet cells by day 21 (Supplementary Fig. 2c).

4. Discussion

This study investigated the effect of bFGF with collagen/gelatin material on wound healing of nasal septum perforations in a rabbit model.

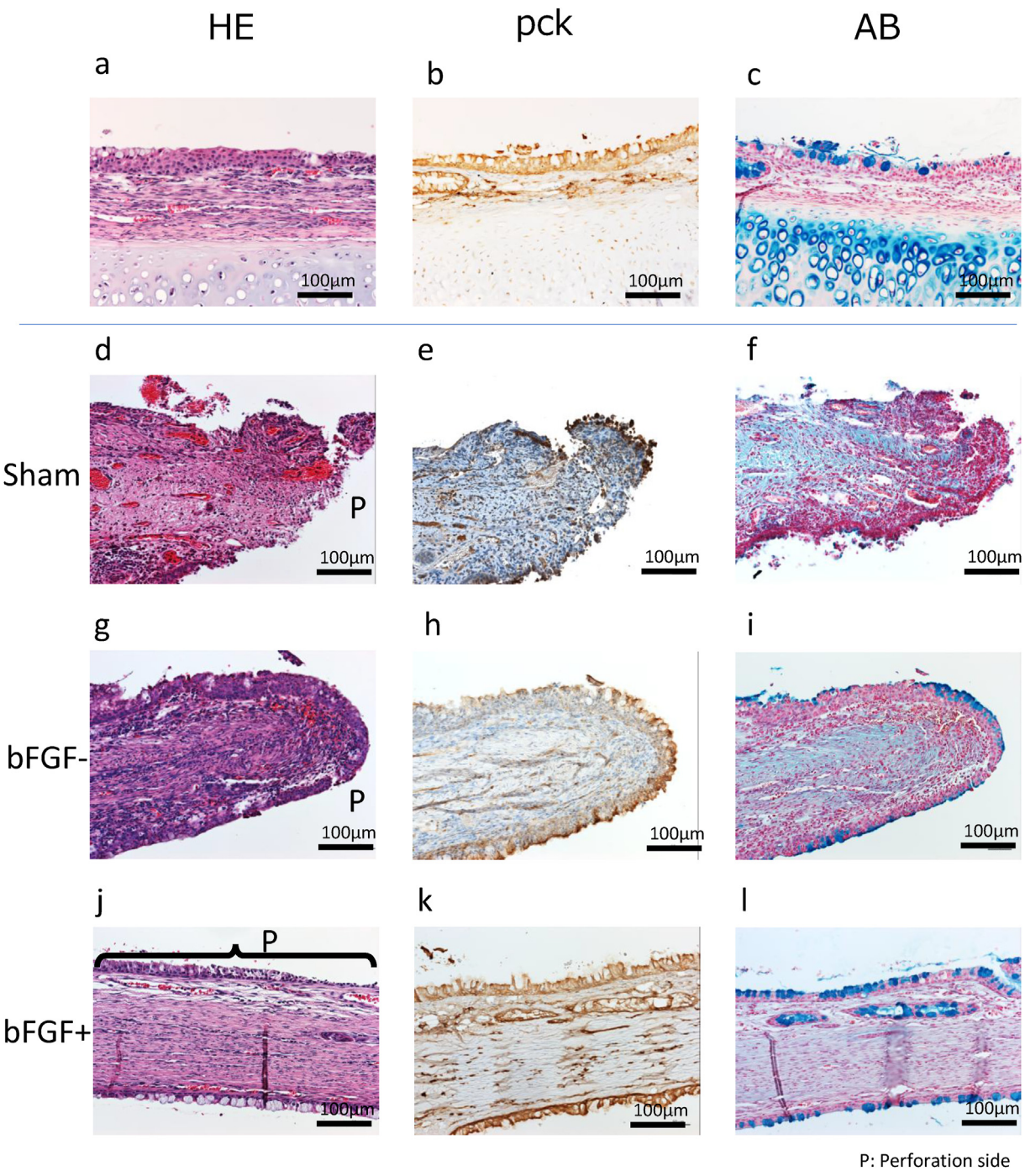

Fig. 4. Histological findings in the nasal septum 28 days after surgery. (a, d, g, j) Hematoxylin-eosin staining of the mucosa (× 200). (b, e, h, k) Pan-cytokeratin immunostaining of the mucosa (× 200). (c, f, i, l) Alcian blue and nuclear fast red staining of the mucosa (× 200). (a, b, c) Normal nasal mucosa of nasal septum. (d, e, f) The nasal mucosa in rabbits from the sham group are composed of squamous epithelium instead of normal ciliated epithelium. (g, h, i, j, k, l) The epitheliums in rabbits from the bFGF(−) and bFGF(+) groups consists of goblet cells (positive for Alcian-blue staining) which are not found in rabbits from the sham group. bFGF, basic fibroblast growth factor. P, perforation site.

Nasal septum perforation is frequently caused by nasal surgeries, such as endoscopic sinus surgery, septoplasty, septorhinoplasty, and skull base surgery, which are major surgeries performed by otorhinolaryngologists [1]. The perforation rate of septoplasty ranges between 1.3% and 4.2%, which is common considering the number of surgeries performed [11–13]. Progression of the pathological process involves multiple stages. An inflammatory response occurs in the local area initially, which leads to mucosal damage. This is followed by a decrease in vascularization, resulting in ischemia (reduced blood supply) of the cartilage and subsequent loss of mucosal tissue. Ulceration and necrosis are observed in the cartilage as the condition worsens. The affected areas are eventually covered by atrophic epithelium [2].

Surgery is required to close the perforation. However, surgery is performed only in a limited number of hospitals owing to the difficulties, which imposes a burden on the patient [1,3]. Small perforations often do not result in symptoms [5]. Thus, reducing the size of the perforation may lead to symptom improvement.

Therefore, several topical agents have been investigated for the healing of perforations in a rat or rabbit model [14–21]. However, effects vary, and no consensus has been reached regarding which agent and method are considered effective. In addition, these reports observed closure of the perforations in the control groups, which may have led to an overestimation of the actual effect. Conversely, in the present study, all control models maintained perforation at 4 weeks post operation, indicating reclosure rate of 0%. Moreover, most agents are applied to the nasal cavity daily in previous studies. However, this method may not be feasible for clinical application due to challenges in self-administration to the nasal septum by patients. Therefore, keeping the effect for a longer period with few doses for nasal septum perforation remains a challenge.

bFGF has been widely used in clinical practice and is involved in various biological processes, such as cell proliferation, differentiation, survival, and apoptosis [22]. It can accelerate wound healing and has been used mainly in the field of dermatology, with evidence of safety and effect [5–8]. However, bFGF decomposes within a few hours after administration. Therefore, patients must apply the medications daily. Several materials have been considered for use in drug delivery systems to extend the effect of a single dose for a longer duration. Kawai et al. [6] reported that the release time was extended to approximately 2 weeks with the use of gelatin and collagen. Zhang et al. [23] reported that poly lactic-co-glycolic acid (PLGA) microspheres effectively released bFGF over several weeks. The efficacy of bFGF in the treatment of tympanic membrane perforation in clinical practice has been reported [10]. bFGF was previously used for wound treatment adding on a layer of connective tissue. Therefore, utilizing it in a combination with a biomaterial to treat a three-dimensionally deficient space, such as tympanic membrane perforation, represents an innovative approach. The application of bFGF in combination with collagen/gelatin in a rabbit model of nasal septal perforation has not been previously reported. Although the nasal environment presents challenges to wound healing due to factors such as increased discharges and airflow compared to the ear, we hypothesized that this application of a biomaterial may be useful against nasal septum perforation. Kanemaru et al. [24] reported a high closure rate of tympanic membrane perforations following treatment with bFGF combined with gelatin. Another study reported the high efficacy of atelocollagen with bFGF [25]. Therefore, bFGF combined with collagen/gelatin was used in the present study to extend the effect of bFGF on perforation for a longer period. In addition, this material had a silicon film on the outer side, which helped the positioning of the material at the perforation site for a long period. The silicone film enabled the secure attachment by allowing suturing to the nasal septum, leading to the stable fixation of the collagen/gelatin fixture containing bFGF at the perforation site. Based on postoperative histological findings, mucosa regeneration was estimated to have occurred between 2 and 3 weeks after the operation. These findings indicate the need to maintain the effect of bFGF by adhering the material for a minimum of 2 weeks after the surgery, which can be achieved using this approach. A significant benefit of this method is that it is easy to apply and does not require frequent hospital visits, making it more convenient for patients.

The perforation site showed improved regeneration with application of the collagen/gelatin material soaked in bFGF. From macroscopic assessment, no granulations or elevations due to the proliferation of connective tissue which may contribute to airflow turbulence were observed in the regenerated mucosa. In general, the normal nasal mucosa is lined by either ciliated or non-ciliated columnar cells and goblet cells [26]. However, the epithelium of the sham groups consisted of stratified squamous epithelial cells. Conversely, the groups where the material was placed exhibited the regeneration of goblet cells and ciliated epithelium, closely resembling normal nasal mucosa. Squamous metaplasia of the respiratory epithelium occurs when exposed to airflow stimulation [27]. This suggests that turbulence from perforations may induce squamous metaplasia in the nasal septum, potentially causing crust formation and bleeding. Goblet cells produce mucus to protect the epithelium and facilitate the early stages of ciliated epithelial regeneration following damage [28,29]. Since the regeneration of goblet cells was also observed in the bFGF(−) groups, this may be due to the biomaterial protecting against airflow stimulation. However, bFGF has been reported to increase goblet cell proliferation [30]. Therefore, additional studies are required to determine the relationship between bFGF and mucosal homeostasis. The combination of bFGF with collagen/gelatin has enabled the promotion of mucosa regeneration that closely resembles its original physiological form, resulting in a reduction in the size of three-dimensional defects. In clinical research on tympanic membrane perforation that has already been applied in practice, success has been achieved in closing the tympanic membrane without resorting to traditional surgery by placing a gelatin sponge containing bFGF at the perforation site [24]. Our experimental results have demonstrated that the use of bFGF significantly increases the closure rate of nasal septal perforations. The findings suggest that the administration of bFGF affects fibroblasts and vascular endothelial cells, thereby promoting the proliferation of connective tissue and granulation. These processes are considered to be crucial factors for the successful closure of the nasal septum. Histological findings from the postoperative period have revealed that the proliferation of connective tissue occurred prior to the completion of epithelialization, which is achieved three weeks post-surgery. Consequently, it is important to accelerate the proliferation of connective tissue at the perforation site with the objective of filling the nasal septal defect before epithelialization is complete.

bFGF with collagen-gelatin material may promote healing of the nasal septum perforation. When used with septoplasty in cases with damage to the mucosa, this method has potential to prevent perforations. Additionally, this method can help reduce the risk of recurrence rate of nasal septum perforation surgeries. However, the limitation of this model is that perforation was created artificially and did not go through the usual pathologic stages. Moreover, clinicians encounter patients with nasal septum perforations whose margins have already healed. However, this model received treatment immediately after the perforations were created. Further studies wherein perforations are treated after a long duration postoperatively are required to evaluate their efficacy in permanent perforations which lays a challenge to treat. The concentration of bFGF used in the present study was equal to that utilized in other products. However, further studies are necessary to confirm the efficacy of bFGF at different concentrations.

The present study examined the effect of bFGF on nasal septum perforation. It utilizes a collagen/gelatin fixture to overcome the challenges in approaching this issue. The results indicate that bFGF used with collagen/gelatin fixture improved wound healing of nasal septum perforation in a rabbit model. Although further studies are required to confirm efficacy of bFGF with a collagen/gelatin fixture and to refine the method for clinical use, we hope this study provides valuable information for future studies.

5. Conclusions

bFGF in combination with collagen/gelatin material improved the wound healing of nasal septum perforation in a rabbit model. The effectiveness of combining collagen/gelatin fixture to prolong the impact of bFGF on a three-dimensional defect was demonstrated. We believe this method offers several advantages such as

the extended effect and ease of application with the potential for preventing postsurgical perforations.

Ethical statement

The animal studies were performed after receiving approval of the Animal Welfare Committee of the Tokyo Women's Medical University (approval number: AE20-134,2020).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.02.001.

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