Quality of Pediatric Second-degree Burn Wound Scars Following the Application of Basic Fibroblast Growth Factor: Results of a Randomized, Controlled Pilot Study

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Abstract
Pediatric burn wounds present unique challenges. Second-degree burns may increase in size and depth, raising concerns about healing and long-term scarring. Results of a clinical study in adults with second-degree burn wounds suggest that application of basic fibroblast growth factor (bFGF) may reduce time to second-intention healing and result in a more cosmetically acceptable scar. To evaluate the effect of this treatment on pediatric patients with deep second-degree burn wounds, 20 pediatric patients ranging in age from 8 months to 3 years (average 1 year, 3 months [± 6 months]) with a total of 30 burn wounds from various causes were allocated either the growth factor (treatment, n = 15) or an impregnated gauze treatment (control, n = 15). Wounds still exudative (not healed) after 21 days were covered with a split-thickness skin graft. All wounds were clinically assessed until healed and after 1 year. A moisture meter was used to assess scars of wounds healing by secondary intention. A color meter was used to evaluate grafted wounds. Five wounds in each group required grafting. Skin/scar color match was significantly closer to 100% in the treatment than in the control group (P <0.01). Wounds not requiring grafting were no longer exudative after 13.8 (± 2.4) and 17.5 (± 3.1) days in the treatment (n = 10) and control group (n = 10), respectively (P <0.01). After 1 year, scar pigmentation, pliability, height, and vascularity were also significantly different (P <0.01) between the groups. Hypertrophic scars developed in 0 of 10 wounds in the treatment and in three of 10 wounds in the control group, and effective contact coefficient, transdermal water loss, water content, and scar thickness were significantly greater in control group (P <0.01). Both the short- and long-term results of this treatment in pediatric burn patients are encouraging and warrant further research.

Keywords: comparative study, pediatrics, burns, fibroblast growth factor, scarring


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Pediatric burns may be the result of scalding, fire, electrical injuries, or parental abuse; tend to affect anatomically important areas such as the head, face, hands, and perineum; and can cause infection-related sepsis.1 Deep dermal burns (ie, partial-thickness wounds or second-degree burns reaching into more than half of the dermis) and third-degree burns require intensive treatment, including débridement and skin grafting. Deep second-degree pediatric burns are particularly challenging because without proper treatment, burn surface area and depth may worsen over time and accurate evaluation becomes more difficult due to immature skin organization and other factors.2 A case-controlled study3 of cytokine profiles in second- and third-degree pediatric burns has provided keys to the role of tumor necrosis factor-alpha (TNF-alpha) and its receptor within the cytokine system in inflammatory wound reaction; among cytokines, basic fibroblast growth factor (bFGF) demonstrated endogenous immunolocalization in the human dermis in partial-thickness burns from day 4 to day 11. In in vivo models,4 bFGF was shown to activate local macrophages up to the remodeling phase, which occurs several weeks after injury. A case series5 involving adult second-degree burn wounds has shown bFGF may be a presynthe-
sized mediator released locally from injury sites and thus may play an important role in early wound healing; in a comparative study, early administration of bFGF resulted in better scar quality and accelerated wound healing.

The purpose of this prospective, controlled study was to compare the effects of conventional treatment of second-degree burn wounds in a pediatric population to the use of conventional treatment and daily administration of bFGF.

Methods
Participants. Children 3 years of age or younger admitted to Nagasaki University Hospital, Department of Plastic and Reconstructive Surgery with second-degree burns and total burn surface area <15% between December 2010 and September 2011 were eligible to participate in the study. Burns were evaluated clinically by the authors and plastic surgery board-certified specialists and re-evaluated at 1 year after cessation of secretion from the wound (considered wound healing). Children with cancer, malnutrition, or total burn surface area exceeding 15% were not eligible to participate.

All investigations were performed with Internal Review Board approval (approved number 07073125, Cytokine effect on wound healing, August 26, 2007), which included the evaluation of wound healing time, use of the moisture meter, and color meter analyses. The parents of each patient received an explanation of the study and provided written, signed approval to participate.

Treatment. Participants were divided into two groups according to the date of the first visit or referral to the facility: patients presenting on even days received conventional (control) treatment, which consisted of the application of Ekzalb (Kade, Germany) ointment-impregnated gauze changed daily and standardized care that included daily gentle cleansing of the adjacent wound area with warm saline to avoid maceration and fixation and stabilization with splinting in burns in joint areas. Patients presenting on odd days received the bFGF treatment (Trafermin, Fiblast Spray®, Kaken Pharmaceutical, Tokyo, Japan). In the treatment group, standardized care was provided, along with daily application of the genetically recombinant human bFGF-containing clear solution, sprayed over the wound. The concentration of bFGF was 30 μg of bFGF per 6 cm² area or at a concentration of 1 μg/cm² as 100 μg of freeze-dried bFGF dissolved in 1 mL of solution of benzalkonium chloride, with 300 μL sprayed once a day 6 cm² area from a distance of 5 cm. The bFGF was sprayed immediately after thorough debridement and hemostasis or cleansing of the wounds. The ointment-impregnated gauze used in the control group also was applied to wounds in the treatment group 30 seconds following the application of bFGF. The bFGF application was repeated daily and continued until complete wound healing occurred. In both treatment groups, the ointment-impregnated gauze was covered with nonadhesive wound dressings.

Wound assessment. Because pediatric burn wounds tend to become unstable and sometimes worsen as a factor of external pathogens or insufficient systemic tissue perfusion, and according to protocols of using bFGF, wound assessment was done daily. Scars were assessed using the Vancouver Scar Scale to grade pigmentation (0 = normal, 1 = hypopigmented, 2 = mixed, and 3 = hyperpigmented); pliability (0 = normal, 1 = supple, 2 = yielding, 3 = firm, 4 = ropes, and 5 = contracture); height (0 = flat, 1 = <2 mm, 2 = 2 mm to 5 mm, and 3 = >5 mm); and vascularity (0 = normal, 1 = pink, 2 = red, and 3 = purple). This scale has/have not been validated for use in adults/children.

Wound variables were assessed daily to determine whether the wound healed (ie, presence of exudate) or if local infection was present when the wound was persistent. The Vancouver Scar Scale was applied for the scar not for the wound, and the moisture meter is not applied when a wound is completely healed. In both treatment groups, if wound exudate was still present after 21 days, a split-thickness skin graft was applied. For dermateuse use, the thickness and donor sites of split-thickness in both groups were set as equal.

All wounds were covered with nonadhesive wound dressings regardless of bFGF use or split-thickness grafting. Conservative therapy included dressing changes before and then every 2 to 3 days post grafting if grafting was performed.

Moisture meter. A moisture meter (ASA-M2, Asahi Biomed, Co. Ltd, Yokohama, Japan) was used to measure transepidermal water loss (TEWL), water level, and the thickness of the corneal keratinocyte layer of the skin, as well as the effective contact coefficient, which is determined by electrolytes in the corneal layer. The meter records and analyzes the susceptibility of conductance using low-frequency (160 Hz) alternate current and detects the occurrence of conductance using high-frequency (143 KHz) alternate current, using the formula:

\[ \text{Skin conductance (μS)} = \text{effective contact coefficient (μS)} \times \text{water level (μS)} \]

To enable the use of all formulary factors, low- and high-
frequency electric voltages were applied to the scar. The better the barrier function of the skin (a measure of healing), the lower the TEWL.

The moisture meter consists of round probe, 5 mm in diameter, and the detection was set 5 seconds after probe contact with the patient to stabilize electrodes and the skin condition. The measurements were performed at least 1 year after cessation of wound secretion for wounds that healed either with or without bFGF or following skin grafting. A case controlled study by Akita et al. showed this instrument is useful for patients as young as 11 months.

Color meter. At least 1 year after healing, a hand-held color meter (NF-333; Nippon Denshoku Co., Ltd., Osaka, Japan) was used to assess scar clarity (L), red (a), and yellow (b) in all wounds. The differentials of each polarized color criterion parameter (L, a, and b) were standardized with the surrounding intact skin. The delta ratio of each parameter then was compared and analyzed. The measurement of each point was always perpendicular to the scar and was repeated five times immediately after touching the scar surface.

The color meter is well-correlated with clinical color change after adult split-thickness skin grafting. Clinical consensus regarding the relevance between clinical assessment and color meter readings was obtained among the experts in the department before use in this study.

Data analysis. All moisture and color meter data were directly transferred to a personal notebook computer and converted to Excel file (Microsoft, Tokyo, Japan). Patient demographic, wound baseline variables, and the results of scar (color) and moisture analysis were analyzed descriptively once the wound formed a scar. All variables were compared using unpaired t-tests, and P <.05 was considered statistically significant.

Results

Twenty (20) pediatric patients were enrolled in the study. Ten (with 15 burn wounds) received the control treatment and 10 patients with 15 burn wounds were in the treatment (bFGF) group (all patients with multiple wounds were in the bFGF group and received the same treatment). In each group, five patients subsequently received a split-thickness skin graft.

Ages for all patients in the study ranged from 8 to 32 months. The average total burn surface area (TBSA) was 7.0 (± 2.6)% for bFGF-treatment and 8.3 (± 2.9)% for non-bFGF treatment. Burns were located on the upper extremities (five in the bFGF group and six in the nonbFGF group), lower extremities (three in each group), trunk (four in each group), and face (three bFGF and four nonbFGF) (see Table 1): no significant differences among locations were noted. Burns in the bFGF group included contact (two out of 15, 13.3%), scald (10 out of 15, 66.7%), and flame (three out of

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**Table 1. Patient and wound variables**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=10 patients)</th>
<th>Control (n=10 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female:male)</td>
<td>4:6</td>
<td>4:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.7±2.8</td>
<td>0.7±2.9</td>
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<tr>
<td>Total burn surface area (%)</td>
<td>7.7±2.6</td>
<td>8.3±2.9</td>
</tr>
<tr>
<td>Wound location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extemity</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Face</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Trunk</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cause of burn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Scald</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Flame</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Average (SD) time between injury and absence of wound exudate (days)</td>
<td>13.8±2.4*</td>
<td>17.5±3.1*</td>
</tr>
</tbody>
</table>

*P<0.01
Correlation between the effective contact coefficient and was also significant ($y = -0.38x + 8.78$, $r^2 = 0.76$, $P < 0.01$).

The number of days from the start of treatment to secretion cessation was significantly different between the two groups (treatment = 13.8 [± 2.4], control 17.5 [± 3.1] treatment days, $P < 0.01$).

Clinical evaluation of the scars after 1 year in patients who did not receive split-thickness grafting showed significant differences between the treatment and control group: pigmentation, 0.8 (± 0.6) versus 1.7 (± 0.6); pliability, 1.2 (± 0.72) versus 2.4 (± 0.79); height, 0.6 (± 0.7) versus 1.5 (± 0.7); and vascularity, 0.7 (± 0.61) versus 1.8 (± 0.72), in the treatment and control groups, respectively ($P < 0.01$).

No significant differences in Vancouver Scar Scale variables by burn wound location were seen. One year post-healing, clinical hypertrophic scars were observed in one out of three upper extremity, one out of three lower extremity, and one out of two trunk burn wound scars in the control group only (see Table 2).

The moisture meter analysis results also were significantly different between groups. The effective contact coefficient was 11.3 (± 2.1)% in the control group compared to 17.8 (± 1.34)% in the control group ($P < 0.01$), and TEWL in the treatment group was significantly lower than that in nonbFGF treatment (12.7 [± 3.9] g/m²/hour, 20.8 [± 3.9] g/m²/hour, $P < 0.01$). The correlation between the effective contact coefficient and TEWL was also significant ($y = -0.38x + 8.78$, $r^2 = 0.76$, $P < 0.01$).

Average water content in the control group was 46.3 (± 3.3) µS compared to 24.7 (± 3.8) µS in the treatment group ($P < 0.01$). The thickness of corneum in treatment group was 10.2 (± 1.8) µm, compared to 17.6 (± 2.2) µm in the control group ($P < 0.01$) (see Figure 1).

Color meter analysis. Five wounds in each group were evaluated after split-thickness skin grafting for three factors — clarity, redness, and yellowness — in terms of matching the surrounding (nonburned) skin. The treatment group scars were closer to 100% match than the control group scars in red and yellow, but not in clarity (for red, average 109.6% [± 13.0%] and 180.3% [± 30.8%], $P < 0.01$; for yellow, 121.1% treated with standard impregnated dressings compared to burns treated with daily bFGF applications. Use of the moisture meter facilitated an objective evaluation of the corneal layer (stratum corneum) by measuring the effective contact coefficient, together with TEWL, water content, and layer thickness.

Abnormal functioning of corneal layers was well demonstrated in a randomized, controlled pilot study as evidenced by increased TEWL, decreased water content, and increased skin thickness. According to a controlled case study, adult atopic skin may have reduced intercellular phospholipid ceramides, which may account for the damaged function of the corneal layers.

In a prospective cohort study, both TEWL and high-frequency conductance remained high in hypertrophic scars and keloids, and the stratum corneum in the lesion showed a faster turnover time than that of adjacent normal skin in adults. These data also suggest that proliferative changes in the dermis may affect the corneal layers. In the current study, the bFGF-treated group had significantly lower TEWL after 1 year than the control group, while water content was significantly higher. The authors hypothesize that scars following bFGF treatment may be in the process of better skin remodeling, thus avoiding the development of the fibroproliferative disorders.

This study evaluated the nature of wound healing in terms of hardness and barrier function mainly from the reconstructed epidermis. However, clinically, pigmented skin discoloration may cause patient concern, especially when it occurs on the face and visible extremities. Split-thickness skin grafting is widely used for primary wound coverage after the debridement of extensive burns, because donor site morbidity is lower and wider skin grafts are available. After wound healing, the site of split-thickness skin grafting can result in discoloration when compared to surrounding skin due to profound differences in the degree and extent of melanization (either hyperpigmentation or hypopigmentation in the melanocyte-melanosome complex) between donor and recipient sites, as noted in adult histological samples. Objective analysis of the scars in this study showed that wounds treated with bFGF before grafting were significantly closer in color to adjacent skin in the red and yellow spectrum than wounds in the control group (see Figure 2).
The authors hypothesize that accelerated wound healing in nongrafted wounds, maintenance of complex system of melanization, and diminishing activity of erythema following bFGF treatment may lead to a better clinical color match. In a case controlled study of split-skin grafts in adults, the amount of yellowness and redness was an average of 1.52 times greater in nonbFGF than in bFGF treated wounds. In this study, the difference in yellowness and redness averaged 1.53.

Among second-degree burn wounds, the time until burn wounds were no longer exudative was also significantly shorter in the bFGF than in the control group; in adults, the average time to healing second-degree burn wounds was 17.9 days in the bFGF treatment and 19.6 days in the control group. A randomized large-scale clinical trial is needed to substantiate the findings of this pilot study.

Limitations
The small sample size and the fact that the study was not blinded limit the ability to generalize results to additional populations. Also, some patients had more than one wound, which affects the independence of the sample.

Conclusion
The results of this study suggest that exogenous daily application of bFGF covered with impregnated gauze may facilitate healing of deep, second-degree burn wounds in a pediatric population when compared to impregnated gauze alone. In wounds that did not require grafting, time until they were no longer exudative was significantly shorter in the treatment than in the control group. After at least 1 year, hypertrophic scarring was observed in 0 of 10 wounds in the treatment and 3 of 10 wounds in the control group, and scars in the treatment group were rated better for pigmentation, pliability, height, and vascularity. Moisture meter analysis was also significantly different between the two groups. For the wounds that were covered with a split-thickness graft (five in each group), color meter analysis after 1 year showed that bFGF treated wounds had significantly lower red and yellow color scores than control treated wounds, a closer match to adjacent skin. Future controlled clinical studies using a larger sample size are needed to confirm these results in young patients.

References