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Original Research Article

Effect of the combination of composite skin grafting and recombinant human basic fibroblast growth factor on plastic surgery for extensive scars after burns

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Abstract

Purpose: *To investigate the effect of combined use of composite skin grafting and recombinant human basic fibroblast growth factor (rh-bFGF) on plastic surgery for extensive burn scars, and its influence on wound healing and inflammatory responses in patients.*
Methods: *Hospital records of 120 patients who underwent extensive scar plastic surgery after burns in Hanchuan People's Hospital from February 2019 to February 2020 were retrospectively analyzed. The patients were equally assigned to study group (STG) and control group (COG), based on the order of admission. All patients received composite skin grafting surgery and post-surgery topical silver sulphadiazine cream regularly, while those in study group (STG) received additional treatment with rh-bFGF spray on the wound surfaces. Scar scores, degree of wound healing, populations of fibrocytes and capillaries, levels of vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1), and activities of lactate dehydrogenase (LDH) and succinate dehydrogenase (SDH) were evaluated.*
Results: *Patients in STG had significantly better scar scores, shorter mean wound healing time, higher mean degree of wound healing, higher scores on inflammatory reactions near the wounds, and higher populations of fibrocytes and capillaries, when compared with patients in COG group ($p < 0.001$). After surgery, there were lower levels of VEGF and TGF-β1, and lower levels of activities of LDH and SDH in STG than in COG group ($p < 0.001$).*
Conclusion: *Rh-bFGF accelerates the proliferation of wound tissue, improves local microcirculation, regulates inflammatory response, and enhances wound healing in burn scar patients when used in combination with composite skin grafting. Therefore, Rh-bFGF has a potential for enhanced management of burn scars.*

Keywords: *Composite skin grafting, Recombinant human basic fibroblast growth factor (rh-bFGF), Plastic surgery, Burns, Scar*

INTRODUCTION

Burns are generally caused by exposure of the skin to hot liquids, hot air and flames. In mild cases, the mucosa is damaged, but in severe cases, the muscles and joints are damaged, thereby triggering a series of morphological and pathological changes in the skin, all of which result in scars [1]. The incidence of extensive scars caused by burns has been increasing yearly [2]. The rough appearance of the surface, with different degrees of skin pigmentation greatly influences the self-esteem and daily lives of burn patients. Laser, conservative treatment, and surgery are frequently used for treating burns in clinics [3]. Skin grafting is a treatment method often used for extensive scars. Based on differences in skin source, skin grafting is divided into three types: autologous, heterodermic and composite skin grafting. Autologous skin grafting hardly meets the needs in multiple wound repairs [4]. Heterodermic skin grafting leads to hyperplasia and contracture due to the lack of dermal components [5]. In contrast, composite skin graft which combines split-thickness skin graft with allogeneic dermal scaffold, alleviates inflammatory reactions near the wound *via* the acellular allogeneic dermis, accelerates fibroblast proliferation, and enhances rate of wound healing [6]. It has been reported that combined use of silver sulphadiazine, a broad-spectrum antibiotic, with composite skin grafting significantly improved scar revision and reduced the possibility of adverse reactions caused by composite skin [7]. However, the healing of burn wounds is affected by various factors, and the use of silver sulphadiazine alone does not produce the optimal effect of composite skin grafting.

A study has revealed that burn wound healing is significantly enhanced by application of silver sulphadiazine and rh-bFGF [8]. The reason for this is that rh-bFGF induces mobilization of fibroblasts and vascular endothelial cells to the wound area, accelerates fibroblast proliferation, improves local microcirculation, and reduces inflammatory reactions. At present, not much is known about the effect of combined use of composite skin grating and rh-bFGF. However, rh-bFGF enhances the repair of burn wounds. Thus, it may be beneficial for acceleration of percentage healing due to composite skin grafting. Based on this, this study was carried out to investigate the effect of combined application of composite skin grafting and rh-bFGF on plastic surgery for extensive scars after burns.

METHODS

Study design

This study is a retrospective analysis conducted based on patient records at Hanchuan People's Hospital from February 2019 to February 2020 to investigate the effect of combined use of composite skin grafting and rh-bFGF on plastic surgery for extensive scars after burns, as well as the influence of the combined treatment on wound healing and inflammatory response in patients. The study was approved by the ethics committee of Hanchuan People's Hospital, Hanchuan, China (approval no. 20181270). It was carried out in line with the guidelines of the Declaration of Helsinki [9]. After enrollment, the patients were informed about the purpose, significance and scope of the study, as well as maintenance of confidentiality regarding the study subject. All the included patients submitted signed consent forms.

Patients and grouping

The data of 120 patients who underwent plastic surgery for extensive scars after burns in Hanchuan People's Hospital, Hanchuan, China from (February 2019 to February 2020 were retrospectively analyzed. The patients were equally divided into study group (STG) and control group (COG), based on the order of admission.

Inclusion criteria

Patients who met the diagnostic criteria of 2nd degree or 3rd degree burns in *Recommended Guidelines for Clinical Management of Keloids in China* [10], those aged 18-60 years, and patients with complete clinical data, were included in this study.

Exclusion criteria

The excluded patients were those with mental problems or patients unable to communicate with others, as well as patients with malignant tumors, coagulation abnormalities, and liver and kidney dysfunctions [11]. Moreover, malnourished patients, subjects with a history of drug dependence and patients who were using hormonal and immunosuppressive drugs, were excluded [12]. Patients with incomplete medical records, and those who withdrew halfway from the study were also excluded.

Withdrawal criteria

The medical records of patients in the following categories were not used for data analysis: patients who experienced adverse events or serious adverse events, those whose disease conditions deteriorated during the study, patients with severe comorbidities or complications, those who requested to be withdrawn on account of their unwillingness to continue with the clinical trial, and those who were considered unfit to continue in the study.

Treatments

All patients were treated with composite skin grafting. The patients were made to lie in appropriate positions based on the burn sites, after which the scar tissues were completely removed under general anesthesia. Then, the contracture was relaxed, the functional position was restored, and the resection site was washed repeatedly with normal saline to arrest bleeding. Acellular dermal matrix (ADM) was washed with normal saline, and the preservation solution was removed, after which the mesh was prepared. The already prepared dermal papilla layer was grafted upwards on the wound, and the razor-thin graft fit for the wound was used to cover the layer, followed by suturing with absorbable thread. The surgical area was bandaged under pressure, and the joint was fixed with a plaster holder, followed by disinfection with iodophor every 2 days. Silver sulphadiazine cream (Henan Tongyuan Pharmaceutical Co. Ltd.; NMPA approval no. = H41021844) was applied on the wound in the COG patients, and the dressing was replaced. In STG patients, rh-bFGF was sprayed on the wound surface. In essence, every 2 days after surgery, rh-bFGF (Longtime Pharmaceutical Co. Ltd; NMPA approval no. = S20143008) was dissolved in 0.9% sodium chloride (Fuzhou Neptunus Fuyao Pharmaceutical Co. Ltd; NMPA approval no. = H35020178) and sprayed on the wound surface. The wound surface was covered with a layer of sterile gauze, and silver sulphadiazine cream was coated on the gauze. Finally, the gauze was fixed with a covering of sterile dressing.

Evaluation of parameters/indices

Scar scores

The severity of scar was evaluated at 1 week after surgery (T_1), 3 weeks after surgery (T_2) and 6 weeks after surgery (T_3), based on the *Scar Cosmesis Assessment and Rating* (SCAR) scale [13] and the *Patient and Observer Scar Assessment Scale* (POSAS) [14]. The SCAR scale comprised six parameters (scar spread, erythema, dyspigmentation, suture marks, hypertrophy/atrophy, overall impression) and two questions for patients, and the total score ranged from 0 to 15 points, with a minimum score of 0 for the best condition, and a maximum score of 15 for the worst condition. The POSAS scale comprised *Observer Scar Assessment Scale* (OSAS) and *Patient Scar Assessment Scale* (PSAS). It covered patients' subjective evaluation of symptoms and doctors' evaluation in terms of scar color, height, hardness and degree of hyperemia. There were 5 parameters in OSAS, with scores ranging from 5 to 50, while PSAS had 6 parameters, with scores between 6 and 60. In both scales, the lower scores indicated normal skin, while higher scores indicated poor scar appearance.

Wound healing

The mean wound healing time, mean rate of wound healing, and scores for inflammatory reactions near the wound were recorded for the two groups as in Eq 1.

$$AHR = \frac{WAI - WAE}{WAI} \times 100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where *AHR* is mean wound healing rate, *WAI* is wound area measured immediately after injury; *WAE* is wound area measured at each time point.

Fasting venous blood (5 ml) was collected from each patient in the morning at T_1, T_2 and T_3. After standing for 0.5 h at normal temperature, the blood was centrifuged at 4000 rpm to obtain serum. Then, levels of inflammatory factors were measured using enzyme-linked immunosorbent assay (ELISA) kits (Beijing Kewei Clinical Diagnostic Reagent Co. Ltd; NMPA approval no. S20060028), and scores on inflammatory reactions near the wound were calculated.

Number of fibrocytes and capillaries

At 3, 7 and 12 days after surgery, the bandage was unwrapped to expose the skin graft. A biopsy was taken, and capillary growth differentiation under the grafted skin and number of fibroblasts were examined microscopically (×1000/field), after which the grafted skin was re-bandaged.

Levels of VEGF and TGF-β_1, and activities of LDH and SDH

Fasting venous blood (5 ml) was collected from patients in the morning at 3, 7 and 12 days after surgery, and centrifuged at 4000 rpm to obtain the sera after standing for 0.5 h at room temperature. Then, the VEGF and TGF-β_1 levels were measured using ELISA, and scores on inflammatory reaction near the wound were calculated. At 3, 7 and 12 days after surgery, granulation tissues were collected in PBS

(Zhongshan Aoquan Medical Technology Co. Ltd.; pH = 7.2 ± 0.1; Central Guangdong Medical Products Administration certified No. 20180007). Following thorough mixing and centrifugation, the activities of LDH and SDH levels were measured using ELISA.

Statistical analysis

Data were processed using SPSS 20.0, while graphics were done with GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration and measurement data were analyzed with χ^2 test and *t*-test, respectively. Differences were considered statistically significant at $p < 0.05$.

RESULTS

There were no statistically significant differences in general profile between the two groups ($p > 0.05$). These data are shown in Table 1.

Scar scores

Compared with COG, the scar scores of STG were better after surgery ($p < 0.001$).

Table 1: Comparison of general profile of patients between the two groups

Group	STG (n = 60)	COG (n = 60)	χ^2/t	*P*-value
Gender			0.034	0.854
Male	34	33		
Female	26	27		
Age range (years)	26-48	27-50		
Mean age (years)	35.12±2.56	35.26±2.14	0.325	0.746
Mean body mass (kg)	56.98±2.15	56.88±2.10	0.258	0.797
BMI (kg/m^2)	22.54±2.22	22.17±2.68	0.824	0.412
Average course of disease (days)	4.10±0.56	4.05±0.45	0.539	0.591
Cause of injury				
Hydrothermal scald	25	24	0.035	0.853
Flame burn	23	24	0.035	0.852
Chemical burn	8	7	0.076	0.783
Electric burn	4	5	0.120	0.729
Degree of burn			0.058	0.810
II	50	49		
III	10	11		
(TBSA) of a burn (%)				
Range	35%-89%	32%-93%	0.040	0.841
Mean area	55.21±2.15	55.26±2.68	0.113	0.910
Area of skin defect cm^2)				
Range	4.0×8.2-15.2×16.9	4.0×8.2-15.2×16.9	0.040	0.841
Mean area	11.89±1.20	11.90±1.23	0.045	0.964
Residential area			0.135	0.714
Urban	34	32		
Rural	26	28		
Marital status			0.046	0.831
Married	45	46		
Unmarried, divorced or widowed	15	14		
Monthly income (Yuan)			0.135	0.714
≥4000	28	26		
<4000	32	34		
Smoking history	35	32	0.304	0.581
History of drinking	28	29	0.033	0.855
Education degree			0.035	0.853
≥ *High school degree*	25	24		
≥ *University degree*	35	36		

Note: TBSA = total body surface area

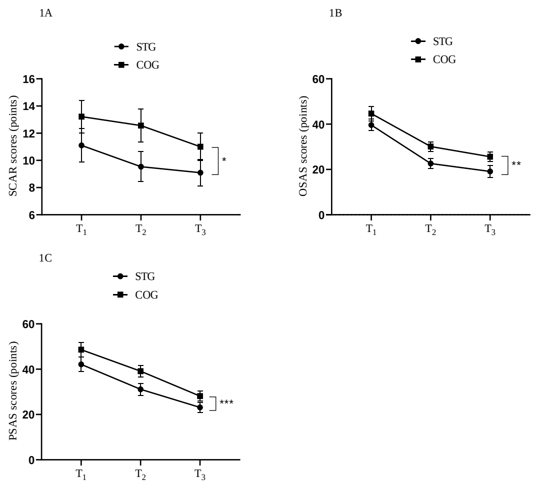

Figure 1: Comparison of scar scores (mean ± SD, points). A: SCAR scores; B: OSAS scores; C: PSAS scores. *$P < 0.001$, SCAR scores at T_1, T_2 and T_3 in STG vs SCAR scores at T_1, T_2 and T_3 in COG; **$p < 0.001$, OSAS scores at T_1, T_2 and T_3 in STG vs OSAS scores at T_1, T_2 and T_3 in COG; ***$p < 0.001$, PSAS scores at T_1, T_2 and T_3 in STG vs PSAS scores at T_1, T_2 and T_3 in COG

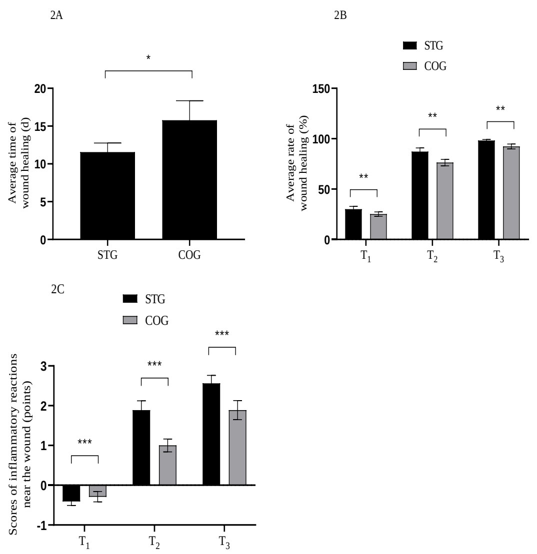

Figure 2: Comparison of wound healing (mean ± SD, points). A: Mean time of wound healing; B: mean rate of wound healing; C: inflammatory reaction scores near the wound. *$P < 0.001$, mean time of wound healing in STG vs mean time of wound healing in COG; **$p < 0.001$, mean rate of wound healing at T_1, T_2 and T_3 in STG vs the mean rate of wound healing at T_1, T_2 and T_3 in COG; ***$p < 0.001$, scores of inflammatory reactions near the wound at T_1, T_2 and T_3 in STG vs scores of inflammatory reactions near the wound at T_1, T_2 and T_3 in COG

Fibrocytes and capillaries

As shown in Figure 3, the numbers of fibrocytes and capillaries in STG group after surgery were significantly higher than the corresponding numbers in the COG group ($p < 0.001$).

Levels of VEGF and TGF-β_1, and activities of LDH and SDH

The levels of VEGF and TGF-β1, and activities of LDH and SDH were higher in STG patients than in COG patients after surgery ($p < 0.001$; Figure 4).

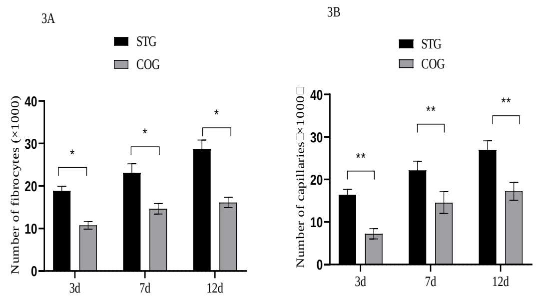

Figure 3: Comparison of numbers of fibroblasts and capillaries between the 2 groups. Data are mean ± SD. A: Number of fibrocytes; B: number of capillaries. *$P < 0.001$, number of fibrocytes at 3, 7 and 12 days after surgery in STG vs number of fibrocytes at 3, 7 and 12 days after surgery in COG; ** $p < 0.001$, number of capillaries at 3, 7 and 12 days after surgery in STG vs numbers of capillaries at 3, 7 and 12 days after surgery in COG

Levels of VEGF and TGF-β_1, and activities of LDH and SDH

The levels of VEGF and TGF-β1, and activities of LDH and SDH were higher in STG patients than in COG patients after surgery ($p < 0.001$; Figure 4).

DISCUSSION

At present, with increasing incidence of scars caused by burns, the elimination of extensive scars has become the focus of research in plastic surgery.

Composite skin grafting which involves combination of split-thickness skin graft with the allogeneic dermal scaffold, has been widely used in clinical practice to effectively reduce graft rejection and improve wound healing. In a previous study, it was reported that the mean wound healing rates of patients with composite skin grafting at 2 and 4 weeks post-surgery were significantly higher than the corresponding rates in patients with autologous skin grafting [15]. This suggests that the acellular allogeneic dermis in the composite skin induced proliferation of epithelial cells and accelerated the formation of fibrocytes.

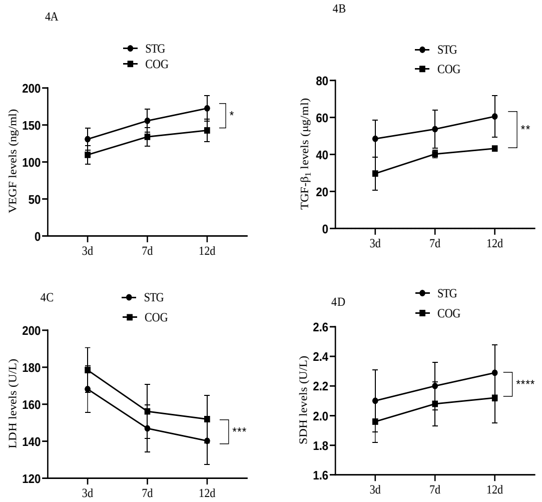

Figure 4: Comparison of levels of VEGF and TGF-β1, and activities of LDH and SDH between the 2 groups. Data are expressed as mean ± SD. A: VEGF levels; B: TGF-β_1 levels; C: LDH levels; 4D: SDH levels. *$P < 0.001$, VEGF levels at 3, 7 and 12 days after surgery in STG vs VEGF levels at 3, 7 and 12 days after surgery in COG; ** $p < 0.001$, TGF-β_1 levels at 3, 7 and 12 days after surgery in STG vs the TGF-β_1 levels at 3, 7 and 12 days after surgery in COG; ***$p < 0.001$, LDH activities at 3, 7 and 12 days after surgery in STG vs LDH activities at 3, 7 and 12 days after surgery in COG; ****$p < 0.001$, SDH activities at 3, 7 and 12 days after surgery in STG vs SDH activities at 3, 7 and 12 days after surgery in COG

This study showed that patients with composite skin grafting had higher average healing rate at 3 weeks after surgery, possibly because of the simultaneous application of silver sulphadiazine cream. The main components of silver sulphadiazine cream are silver nitrate and sulfadiazine, which not only reduced levels of inflammatory factors near the wound surface, but also absorbed exudates, thereby keeping the wound surface dry and providing favorable growth conditions for granulation tissues. Thus, silver sulphadiazine cream is often used in the treatment of burns [16].

Previously, some researchers used silver sulphadiazine and rh-bFGF as therapeutic drugs for healing of burn wounds. It was found that the wound healing times of superficial 2nd degree burn and deep 2nd degree burn were shorter than that of silver sulphadiazine alone [17]. This study showed that the mean time of wound healing was shorter in STG patients than in COG patients, indicating that the use of rh-bFGF in combination with silver sulphadiazine also resulted in shortened wound healing time. This is due to the fact that rh-bFGF is a multifunctional cell growth factor that stimulates the proliferation of cells derived from mesoderm and neuroectoderm; it induces the migration of fibroblasts and vascular endothelial cells to the wound surface, and enhances the establishment of collateral microcirculation at the wound surface.

The levels of VEGF and TGF-β_1, and activities of LDH and SDH were better in STG than in COG. Lactate dehydrogenase (LDH) reflects the degree of anaerobic metabolism in a tissue, while SDH is the rate-limiting enzyme in aerobic metabolism. The increase in SDH activity and decrease in LDH levels indicate improvement of microcirculation in the wound surface, which enables the skin grafting tissue to obtain nutrients through stable oxygen flow. In a previous study, it was found that rh-bFGF enhanced the survival of grafted skin, and boosted the population of fibroblasts and capillaries [18]. Moreover, it improved the growth of the grafted skin through enhanced nutrient supply, repair of the wound surface, and enhancement of the structure and strength of the repaired tissues [18]. Similar results were obtained in this study

It has been reported that when combined with the antibacterial effect of silver sulphadiazine, rh-bFGF also activated the immune function of phagocytes and inhibited microbial infection, thereby reducing the probability of wound infection and mitigating scar hyperplasia [19]. Therefore, scar score in STG after surgery was higher than that in COG. In an earlier study on plastic surgery patients treated with rh-bFGF, there was a marked decrease in score on the Vancouver Scar Scale (VSS) [20]. Thus, rh-bFGF not only prevented pigmentation by regulating microcirculation, but also suppressed the formation of pathological scars by inhibiting excessive collagen precipitation. In this way, the healing of incision was improved, the physical and psychological pressure on the patients were alleviated and their quality of life was enhanced.

Limitations of the study

It is worth noting that this study used a small number of samples. Therefore, there is need for more controlled studies using larger size of samples to investigate the effect of combined use of composite skin grafting and rh-bFGF on plastic surgery for extensive scars after burns.

CONCLUSION

Composite skin grafting is frequently used in plastic surgery for extensive burn scars. The findings of this study show that the combined use of silver sulphadiazine and rh-bFGF stabilizes the grafting effect, improves local microcirculation, regulates inflammatory reaction, and enhances wound healing. Therefore, this therapeutic strategy has a potential for use in clinical practice but further clinical trials are required.

DECLARATIONS

Acknowledgements

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Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jiadong Liu and Xiaojun Zhang conceived and designed the study, collected, analyzed and interpreted the experimental data, drafted the manuscript and revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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