ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2025.108.5.325
Annals of Surgical Treatment and Research

The efficacy of skin soft tissue expansion and recombinant human epidermal growth factor in the repair of second-degree scald scars: a prospective single-blind randomized controlled trial

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Purpose: This research observed the efficacy and safety of soft tissue expansion combined with recombinant human epidermal growth factor (rhEGF) in repairing second-degree scald scars.
Methods: This study conducted a prospective, single-blind, randomized controlled trial. Eighty-four patients with deep second-degree scald scars were evenly divided into the control and observation groups. The control group was treated with soft tissue expansion, and the observation group was additionally treated with rhEGF. The skin expansion and wound healing times were compared. The changes in wound exudate and inflammation around the wound were observed after first-stage surgery. The hydroxyproline (OHP) and collagen I/III ratios were compared during the second stage of surgery. The complications and repair effects during treatment were evaluated.
Results: The observation group exhibited lower expansion time, immediate retraction rate, and wound healing time, higher skin expansion rate, higher wound exudate score and inflammation score, higher OHP, lower collagen I/III, lower complication rate, and higher total effective rate than the control group (all $P < 0.05$).
Conclusion: Skin soft tissue expansion combined with rhEGF is more effective in repairing second-degree scald scars, which can effectively increase skin expansion area and reduce wound infection and complications.
[Ann Surg Treat Res 2025;108(5):325-330]

Key Words: Burns, Cicatrix, Epidermal growth factor, Tissue expansion, Treatment outcome

INTRODUCTION

Scalds are among the most frequently encountered injuries and rank as the fourth leading cause of trauma worldwide [1]. Second-degree scald, which is frequently encountered in clinical settings, poses significant challenges in management [2]. Scars are prevalent and persistent issues following the healing of scalded wounds [3]. As a localized manifestation arising from severe physical, biological, or chemical trauma to the skin and soft tissue, scars alter both the appearance and function of the affected area, as the damaged tissue cannot fully heal normally, and is instead replaced by fibrous tissue. Patients with scars, particularly those resulting from burns, scalds, or severe trauma, may experience physical discomfort and psychological distress [4]. The scar proliferation phase can last for several years, causing considerable hardship for patients. Following this, the atrophy period may lead to facial disfigurement and functional impairment, resulting in significant physical and

Received October 4, 2024, **Revised** January 9, 2025,
Accepted January 28, 2025

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mental suffering. Hence, scar repair holds immense clinical significance for these patients [4].

In plastic surgery, tissue expansion is a commonly employed technique for skin defect repair [5]. Soft tissue expansion is a fundamental and widely adopted technique in plastic surgery for acquiring extra skin for diverse medical applications [6]. This expansion offers skin tissue that closely matches the recipient area in color and texture, making it a highly suitable option for repairing superficial defects [7]. However, soft tissue expansion encounters numerous challenges, including lengthy treatment duration, suboptimal skin quality, a high incidence of retraction, and potential complications [6]. It is well known that growth factors such as epidermal growth factors (EGFs) are essential for wound healing and tissue homeostasis by regulating cell survival, migration, proliferation, and differentiation [8]. However, the use of EGFs alone fails to adequately address this scar tissue. Prioritizing the stabilization of EGFs and facilitating wound healing without scars is of utmost importance [3]. Additionally, recombinant human EGF (rhEGF) has shown promise as a potential treatment option for accelerating wound healing and reducing scar development [9]. The use of rhEGF can shorten wound healing duration, reduce wound bacterial positivity rates, reduce adverse reactions, and improve wound healing [10].

There have been few studies exploring the combined application of skin expansion and rhEGF. Therefore, the aim of this study was to investigate the impact of soft tissue expansion and rhEGF on patients with second-degree scald scars, while also considering the clinical efficacy of both methods in promoting scar repair.

METHODS

Ethics statement

The study was approved by the Ethics Committee of The First People's Hospital of Jiangxia District (No. 20190107) and the patients gave informed consent.

Research patients

This study was a prospective, single-blind, randomized controlled trial. Eighty-four cases of patients with deep second-degree scald scars admitted to The First People's Hospital of Jiangxia District from April 2019 to January 2021 were selected and divided into the control group (n = 42) and the observation group (n = 42) by using the randomized numerical table method. The control group was treated with soft tissue expansion, and the observation group was coadministered with rhEGF on the basis of the control group. In the control group, there were 22 male and 20 female patients aged 36.52 ± 5.09 years. The scar locations were 28 cases on the limbs, 7 cases on the chest, and 7 cases on the head and neck, with a scald area of 6.57% ± 1.31%. In the observation group, there were 24 male and 18 female patients aged 35.88 ± 4.73 years. The scar locations were 31 cases on the limbs, 5 cases on the chest, and 6 cases on the head and neck, with a scald area of 6.61% ± 1.40%. General information of patients in the 2 groups, such as gender and age, was not statistically significant ($P > 0.05$).

Inclusion criteria were as follows: (1) patients with a clear medical history of scars formed after scald wound healing; (2) patients whose wounds have healed for ≥3 weeks with no significant spontaneous regression of scars; (3) patients aged >18 years; (4) patients with complete clinical data; (5) patients who can understand and cooperate with the study. Exclusion criteria were as follows: (1) patients with abnormal coagulation function; (2) patients with acute and chronic infection; (3) patients with allergy to therapeutic drugs; (4) patients with other skin diseases; (5) patients with serious organic lesions.

Randomization and blinding

The study involved using a random number table to assign patients into 2 groups. We randomly selected the treatment method for each patient from a box containing 84 sealed envelopes with codes 1 and 0. To reduce bias in the results, this study employed a single-blind design. This means that the physician assessing the outcomes and the members analyzing the data were blinded to the patient's treatment methods, but the trial implementers were not blinded.

Treatments

The control group was treated with soft tissue expansion in 2 stages of surgery. The location and size of the scar were rationally analyzed in the first-stage surgery, and an appropriately sized skin expander was selected. The site and number of expander insertions were determined. After local anesthesia, the expansion site and injection were accurately marked in the repair area. An incision parallel to the expander edge was made at the junction between the scalding scar and normal skin, with a length of 1–2 cm. Blunt dissection was performed to separate the subcutaneous tissue and muscles. After hemostasis at the incision site, the expander was inserted. After sufficient hemostasis, negative pressure drainage was applied, and the subcutaneous soft tissue and skin were sutured in layers. After 3–5 days, 15–30 mL of sterile 0.9% sodium chloride was injected into the balloon (injections were performed 1–2 times a week accordingly). The injection volume was determined according to the size of the balloon and the skin tension of the patient, and 4–10 injections were generally required. Subsequently, the expanded tissue was observed after 1–3 months. After the expanded tissue met the surgical requirements, the second-stage surgery was performed. Two weeks after stopping the injection of saline, the expander was removed, the scar was excised, and the expanded skin flap

was advanced to repair the defect. Postoperative compression dressing was applied.

The observation group was treated with rhEGF (S20010094, Haohai Biological Technology) in combination with the control group. Before the soft tissue expansion surgery, the lyophilized powder was dissolved by 0.9% sodium chloride injection and then prepared into a 5,000 IU/mL solution for massage treatment (2 times/day until 1 day before soft tissue expansion).

Observation indicators

Time to completion of expansion, soft tissue expansion rate, immediate retraction rate, and wound healing time were compared. Time to completion of expansion is the time from the beginning of the implantation of the skin expander to the completion of the expansion of the skin donor area. The area was marked at the expander placement site before the first injection and the area was measured after the expansion capacity was reached.

Skin expansion rate = (measured area – original area)/original area × 100%

Immediate retraction rate was calculated by marking the area at the top of the expanded area before the second-stage surgery and measuring the marked area again after the end of grafting.

Immediate retraction rate = (preoperative area – postoperative area)/preoperative area × 100%

After the first-stage surgery, changes in trabecular exudate and periwound inflammation were noted. Specifically, the score for traumatic exudate was assigned as follows: 0 for no change, 1 for a decrease, 2 for a significant decrease, and 3 for wound dryness. Similarly, the score for periwound inflammation change was determined as: 0 for no change in periwound swelling, 1 for a decrease in periwound swelling, and 2 for complete subsidence of periwound swelling.

An appropriate amount of soft tissue was left during second-stage surgery to detect hydroxyproline (OHP) by chemical colorimetric method and collagen I and III. Collagen I and III were extracted adopting the acetic acid-pepsin method and then determined using enzyme-linked immunosorbent assay kits.

The occurrence of complications, including skin infection, scarring, skin redness, and pigmentation changes, was documented in the patients. Skin infection presented clinically as purulent secretions on the skin, local pain, redness, swelling, or fever in the affected area. Antigen detection for specific pathogens in drainage fluid or infected tissue from the infected site was positive.

The repair effects of the 2 groups were compared. Significantly effective: the surgical wound healed completely, the scar disappeared completely, and there was no difference between the implanted tissue and the normal skin; effective: the surgical wound healed well, some scars disappeared, and the implanted tissue was different from the normal skin color, but the difference was not obvious; ineffective: the surgical wound did not heal or even ulcerated, the scar did not improve, and the color of the normal skin was significantly different.

Total effective rate = (number of significantly effective + number of effective)/total number of patients × 100%

Statistical analysis

GraphPad Prism ver. 6.0 software (Graph Pad Inc.) was applied to process the experimental data, and the experimental data were first tested for normality and chi-square, if the test was consistent with normal distribution and chi-square, the measurement data were expressed as mean ± standard deviation ($\bar{x} \pm SD$), and comparisons between the 2 groups were analyzed by t-test. Enumeration data were expressed as percentages and analyzed by chi-square test. The test level was $\alpha = 0.05$, and $P < 0.05$ was regarded as a statistically significant difference.

RESULTS

Skin expansion

Compared to the control group, the observation group exhibited shorter expansion time, and immediate retraction rate, while their skin expansion rate was considerably greater ($P < 0.05$) (Table 1).

Table 1. Comparison of skin expansion between the 2 groups of patients

Variable	Control group (n = 42)	Observation group (n = 42)	P-value
Time to completion of expansion (day)	37.12 ± 4.12	28.98 ± 3.37	<0.001
Skin expansion rate (%)	86.73 ± 10.26	121.58 ± 16.80	<0.001
Immediate retraction rate (%)	34.94 ± 6.82	22.48 ± 4.25	<0.001
Wound healing time (day)	17.24 ± 2.73	14.93 ± 1.20	<0.001

Values are presented as mean ± standard deviation.

Table 2. Comparison of peritraumatic changes in the 2 groups of patients

Variable	Control group (n = 42)	Observation group (n = 42)	P-value
Traumatic exudate score	1.48 ± 0.63	2.07 ± 0.78	<0.001
Peritraumatic inflammation score	0.93 ± 0.51	1.19 ± 0.45	0.020

Values are presented as mean ± standard deviation.

Table 3. Comparison of OHP and collagen I/III ratio between the 2 groups

Variable	Control group (n = 42)	Observation group (n = 42)	P-value
OHP (μg/mg)	2.46 ± 0.54	3.39 ± 0.87	<0.001
Collagen I/III ratio	2.95 ± 0.51	2.13 ± 0.27	<0.001

Values are presented as mean ± standard deviation.
OHP, hydroxyproline.

Table 4. Comparison of complication rates between the 2 groups of patients

Variable	Control group (n = 42)	Observation group (n = 42)	P-value
Skin infection	2 (4.76)	0 (0.00)	
Scarring	6 (14.29)	0 (0.00)	
Skin redness	1 (2.38)	2 (4.76)	
Pigmentation	1 (2.38)	1 (2.38)	
Total effective rate	10 (23.81)	3 (7.14)	0.035

Values are presented as number (%).

Table 5. Comparison of repair effects between the 2 groups of patients

Group	Control group (n = 42)	Observation group (n = 42)	P-value
Significantly effective	19 (45.24)	25 (59.52)	
Effective	12 (28.57)	15 (35.71)	
Ineffective	11 (26.19)	2 (4.76)	
Total effective rate	31 (73.81)	40 (95.24)	0.007

Values are presented as number (%).

Peritraumatic changes

The wound exudate score and periwound inflammation score of patients in the observation group were significantly higher than those of the control group ($P < 0.05$) (Table 2).

Hydroxyproline and collagen I/III ratio

The OHP content of patients in the observation group was significantly higher, and collagen I/III ratio was significantly lower compared to the control group ($P < 0.05$) (Table 3).

Complication rates

Patients in the observation group (7.14%) experienced fewer complications compared to those in the control group (23.81%) ($P < 0.05$) (Table 4).

Repair effect

In the observation group, the total effective rate (95.24%) exceeded that of the control group (73.81%) ($P < 0.05$) (Table 5).

DISCUSSION

The formation of scars after scalds affects not only the aesthetics of the patient but also the function of the limbs. As living standards and aesthetic preferences rise, there is an increased demand for superior outcomes in post-scald scar plastic surgery, driving advancements in plastic and cosmetic surgery [6]. This study probed the therapeutic efficacy of soft tissue expansion combined with rhEGF in the repair of second-degree scald scars among patients.

The results of this study indicated that compared to the control group, the observation group had a shorter skin expansion duration, a higher immediate retraction rate, and a significantly higher skin expansion rate. This suggests that soft tissue expansion combined with rhEGF can effectively increase epidermal growth speed and enhance tissue repair capabilities. As mentioned earlier, soft tissue expansion offers skin tissue that closely matches the recipient area in color and texture, making it a highly suitable option for repairing superficial defects [7]. Moreover, it has been confirmed that rhEGF has a wide range of physiological activities such as stimulating cell proliferation, increasing skin blood flow, improving epidermal microcirculation, and preventing stasis of metabolic wastes, and has achieved remarkable results in the clinical treatment of scalds [11]. It has a close relationship with cell proliferation, which can promote cell migration in wounds and stimulate the secretion of collagen fibers and hyaluronic acid in the granulation tissues, which in turn accelerates the growth of tissues. rhEGF also has the effect of accelerating wound repair and healing while stimulating epithelial cell growth [12]. Meanwhile, the study also found that patients in the observation group had higher wound exudate scores and periwound inflammation scores, suggesting that skin expansion combined with rhEGF can reduce wound secretions and control wound infection. Furthermore, we also observed a significant increase in the level of OHP in the observation group, along with a notably lower collagen I/III ratio compared to the control group, suggesting that rhEGF can promote the increase of neoplastic collagen, accelerate the reconstruction of extracellular matrix, and improve skin expansion rate. As reported, proliferative scarring is a fibrotic reaction of the skin

based on the deposition of extracellular matrix such as collagen, whereas OHP, a raw material for the synthesis of collagen, is maintained at constant levels in normal tissues [13]. Collagen III increases dramatically in the process of wound repair and also promotes the proliferation of epidermal cells. When the skin synthesizes collagen vigorously, collagen I/III ratio shows a decreasing trend [14,15]. Notably, as compared to other techniques like skin grafts, tissue expansion permits improved skin matching, reduced scarring, and reduced donor site complications. In addition, it is not dependent on microsurgery skills and infrastructure or its complications, and the expanded skin also offers more vascularity than delayed flaps [16]; rhEGF is a chemokine and mitogen for glial cytochemistry, and it can promote the differentiation and migration of epithelial cells and fibroblasts and accelerate the formation of neoplastic granulation tissue [17,18]. Furthermore, compared to the control group, patients in the observation group exhibited a lower incidence of complications and a higher overall effective rate. This indicates that the combined use of soft tissue expansion and rhEGF can reduce the incidence of complications among patients with second-degree scald scars.

In summary, soft tissue expansion combined with rhEGF demonstrates superior efficacy in repairing second-degree scald scars. It can effectively increase epidermal growth speed and skin expansion area, reduce wound secretions and wound infections, decrease the incidence of complications, and promote the increase of newly formed collagen and skin expansion, thereby enhancing tissue repair capabilities. The findings of this study provide new ideas and methods for the treatment of second-degree scald scars. However, the results of this study are limited to second-degree scald scars. In the future, with continuous advancements and innovations in medical technology, research can be conducted to further explore the application effects of soft tissue expansion and rhEGF in other types of scalds.

ACKNOWLEDGEMENTS

Fund/Grant Support

None.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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