Outcomes of the Recombinant Human Epidermal Growth Factor Addition to Chloramphenicol Ointment for Facial Burn Wound Healing

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ABSTRACT

Objective: Delayed healing of facial burns can result in scarring and psychological morbidity. Epidermal growth factor may promote wound granulation and angiogenesis to enhance wound healing. We compared the effect of Chloramphenicol ointment alone with Recombinant Human Epidermal Growth Factor (rhEGF) plus chloramphenicol on facial burn wound healing.

Methods: A randomized controlled trial was conducted in patients admitted to the Burn Unit. Subjects aged 18 to 65 years with acute second-degree facial burn wounds that did not require surgical treatment were enrolled. Subjects were divided equally and randomized to receive either topical chloramphenicol ointment twice daily (control) or rhEGF ointment once daily and chloramphenicol ointment twice daily. Wounds were assessed at frequent intervals. Wound size, complete healing day, pain score, infection, side effects, Vancouver Scar Scale and the cost of treatment were recorded.

Results: Twenty-six wounds were enrolled. The mean wound size was similar in both groups (rhEGF plus chloramphenicol treated group 38.5±18.2 cm^2 vs control group 42.1±19.4 cm^2). Burn wounds in the rhEGF group healed more rapidly, though the difference was not statistically significant (8.5 ± 3.4 days vs 9.3 ± 4.4 days, p=0.3). No difference was observed in the Vancouver scar scale. Mean post-treatment pain scores were the same in both groups. There were no infections or side effects in either group. The rhEGF-treated group was more expensive (1463.1 ± 142.6 vs 19.2 ± 1.9 baht).

Conclusion: There are no difference in outcomes of acute facial burn wound healing treated with rhEGF and chloramphenical ointment compared to chloramphenicol treatment alone. The further study to evaluate the effect of rhEGF in patients who have some factors that delay wound healing should be done.

Keywords: Burn; wound healing; epidermal growth factor (Siriraj Med J 2019; 71: 446-449)

INTRODUCTION

Facial burns represent 27-60% of all burn patients[1-3] and may result in physical and psychological morbidities. Burn scar contracture can cause difficulty with mastication, breathing, facial expression, and pronunciation. Furthermore, patients may develop keratopathy from ectropion, making it difficult to breathe due to depression of the nasal bridge and chondritis.[4] Facial appearance affects many social outcomes such as personal identification, interpersonal communication. Facial deformities may lower

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Received 21 August 2019 Revised 15 October 2019 Accepted 18 October 2019
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http://dx.doi.org/10.33192/Smj.2019.66

self-confidence and self-esteem that can lead to social anxiety and mental illness.

Burn wound healing is a complex process. Previous studies have described new drugs that can promote wound healing without infection and decrease scar formation.[5-8] Epidermal growth factor (EGF) is secreted by platelets, monocytes and fibroblasts, and stimulates epidermal cells, fibroblasts, smooth muscle cells and endothelial cells to promote wound granulation and angiogenesis. Recombinant human epidermal growth factor (rhEGF) has been reported to improve wound healing in diabetic foot ulcer and radiation-related oral mucositis without major side effects.[9-13] rhEGF can also decrease inflammation and scarring in the murine mode.[14]

The chloramphenicol ointment is one of the topical ointments that has been used as standard treatment of facial burn wounds in some clinics because it provides an optimal environment for effective wound healing and reduces the risk of infection. Previous literatures reported its efficacy for infection prophylaxis and infection treatment purposes.[15] The chloramphenicol shows broad spectrum which covers both gram positive and gram negative bacteria.[16] Moreover, an ointment preparation mainly contains oil base so it can adhere to the wound bed more effective than cream and solution. It provides occlusive property so it is a good option in topical antibiotics. The combination of rhEGF with chloramphenicol might improve healing efficacy. We aimed to compare the effect of chloramphenicol ointment and recombinant human epidermal growth factor (rhEGF) therapy with chloramphenicol ointment alone for facial burn wound healing. We hypothesized that the addition of rhEGF would enhance the rate of wound healing, and decrease scar formation without side effects or infection.

MATERIALS AND METHODS

A prospective randomized controlled trial was conducted at the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. From July of 2017 to September of 2018, patients aged 18 to 65 years with facial burn wounds were enrolled. According to Guo et al (2010), the sample size was calculated based on healing time between EGF-treated group and control group.[17] Patients with an acute (< 48 hours) second-degree facial burn wound that was expected to heal without surgical treatment were eligible. Subjects with burns involving the eyelids, those with compromised immunity, renal disease, diabetes and pregnant or lactating women were excluded. Informed consent was obtained. Data were collected on sex, age, underlying diseases, cause of burn, and burn wound characteristics.

The wound was cleaned and debrided to evaluate the size and degree of burn by surgeons and experienced burn unit nurses. Subjects were evaluated with the eKare inSight™ 3D Wound Assessment (Daewoong Pharmaceutical Co. Ltd, Seoul, South Korea) tool which measures the area (cm^2) of the wound.

Wounds were equally allocated by simple random sampling method into a rhEGF-treated group (study group) and chloramphenicol group (control group). The control group defined as the wound was applied with topical chloramphenicol ointment twice each day. The study group or rhEGF-treated group was received topical recombinant human epidermal growth factor ointment (Easyef® Ointment Daewoong Pharmaceutical Co. Ltd, Seoul, South Korea, 1g contains rhEGF 1 μg) once daily in the morning combine with chloramphenicol ointment twice each day. In case the area of wound could not be divided to two groups, it would be assigned to receive either rhEGF plus chloramphenicol ointment or chloramphenicol ointment alone. Burn unit nurses and patients dressed the wound and were blinded to the intervention.

The wound was assessed at every other day by a single, experienced burn unit nurse who has responsibility to evaluate all wounds in this study. Size of the wound, infection, pain score and side effects were recorded until complete wound healing was achieved. Complete healing was defined as full epithelialization of the wound with absence of discharge. The pain score was evaluated using a numerical scale. The Vancouver Scar Scale (VSS) was used to evaluate the post-burn scar after two months. The costs of treatment including medicines and other dressing materials were evaluated after complete wound healing.

Statistical analysis

Statistical analysis was performed using SPSS version 21 statistical software and Microsoft excel. Each measurement is shown as mean ± standard deviation. The differences between group measurements such as wound area, healing time and cost of treatments were examined by T-test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Twenty-six wounds from fourteen patients (five men and nine women) who aged between 18 to 57 (mean 36.8±13.6 years) were enrolled in this study. No subject had underlying medical illness. Nine cases were thermal burns, three were scalds, and two were electrical burns. The size of wounds in each group was similar. The average

wound size in the rhEGF-treated group was 38.5±18.2 cm^2 compared to 42.1±19.4 cm^2 in the control group (p = 0.31).

The results comparing between study and control group were shown in Table 1. Wounds in rhEGF-treated group healed faster, but the difference was not statistically significant. The complete healing day in the rhEGF-treated group was 8.5±3.4 days compared to 9.3±4.4 days in the control group (p Value = 0.3). Scar formation after two months was similar. The Vancouver scar scale (VSS) ranged from 0 to 3 with a mean in both groups was 1.6 ± 0.8. The mean pre-treatment and 30-minutes post-treatment pain scores were the same in both groups, and decreasing post-treatment pain scores were observed overall (pre-treatment 3.7±2.9; post-treatment 2.8±2.1). Fig 1 showed the efficacy of rhEGF plus chloramphenicol compare to chloramphenicol alone at 0, 2 weeks and 2 months after injury.

All wounds in both groups healed without infection or complications such as rash, swelling or urticaria. The total cost of study group was higher than the control group. The mean cost of EGF-treated group was 1463.1±142.6 baht and chloramphenicol group was 19.2±1.9 baht (p ≤ 0.05). (Table 1)

DISCUSSION

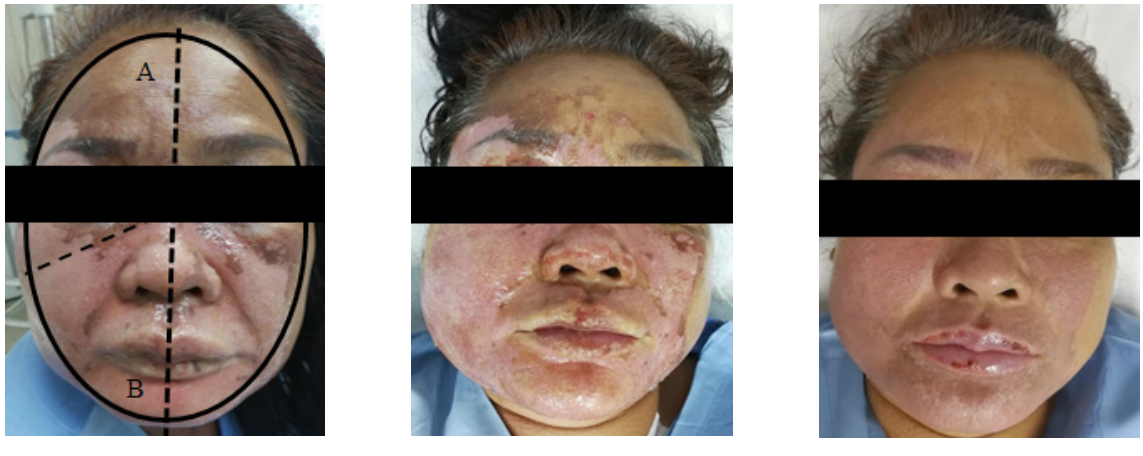
Burn wound healing is a complex process. Due to the ability of rhEGF that can stimulate epidermal cells, fibroblast, smooth muscle cells and endothelial cells to promote wound granulation and angiogenesis. This growth factor was effective using in chronic wounds such as diabetic foot ulcer, and radiation ulcer.[11-13]

Complete healing occurred more rapidly in the rhEGF-treated group; however, the rhEGF plus chloramphenicol cannot accelerate facial burn wound healing effectively compared with chloramphenicol alone. Without surgical treatment, an acute second-degree facial burn wounds usually heal spontaneously within two weeks.[18]

Treatment with rhEGF plus chloramphenicol did not increase post-burn hypertrophic scar formation or

TABLE 1. Comparison results between study group (rhEGF+Chloramphenicol group) and control group (Chloramphenicol group).

	Study group	Control group	P-value
Complete healing day (Days)	8.5 ± 3.4	9.3 ± 4.4	0.30
Vancouver scar scale at 2 months	1.6 ± 0.8	1.6 ± 0.8	> 0.05
Pre-treatment pain score	3.7 ± 2.9	3.7 ± 2.9	0.17
Post-treatment pain score	2.8 ± 2.1	2.8 ± 2.1	0.17
Side effects	No	No	-
Total cost (Baht)	1,463.1 ± 142.6	19.2 ± 1.9	< 0.05



Day 0 Day 14 Day 60

Fig 1. Facial burn wound treated with chloramphenicol (A) and rhEGF+ chloramphenicol (B).

facial scar contracture compared with chloramphenicol alone. The Vancouver Scar Scale at two months was the same in both groups. Although there was no significant in scar reduction, previous animal study has already proved the efficacy of rhEGF in visible external scars formation over control group.[14] Moreover, the second degree dermal layer burn wound usually create the scar less than deep layer wound because it most likely to heal by spontaneous epithelial wound healing.

Treatment with rhEGF and chloramphenicol did not increase pain, infection or result in any side effects, suggesting that this therapy is safe to use in facial burn wounds. Our study showed, there was similar outcome about decreasing pain score after treatment of both rhEGF-treated and chloramphenicol group but no statistical significance. It is possibly that the facial wound is a small area which presents many sensory nerves, it is difficult to differentiate the pain feeling between these two areas.

Finally, the cost of rhEGF treatment is greater than chloramphenicol. Due to insignificant effect to accelerate burn wound healing, we might consider rhEGF just as an alternative drug in facial burn wound or challenge in patients who have some factors that might delay wound healing.

Further studies are needed to evaluate the efficacy of rhEGF in deeper facial burn wounds which might not spontaneously heal, and in patients who have risk factors that could delay wound healing. Deep layer facial burn wounds cause more cellular dysfunction and post-burn scar formation. rhEGF might demonstrate the benefit of treatment in those patients.

CONCLUSION

There are no difference in outcomes of acute facial burn wound healing treated with rhEGF and chloramphenical ointment compared to chloramphenicol treatment alone. The further study to evaluate the effect of rhEGF in patients who have some factors that delay wound healing or in deeper burn wounds with less chance of spontaneous epithelialization healing should be done. There were no increases in hypertrophic scar, scar contracture, infection or other side effects after using rhEGF. Therefore, rhEGF is safe to use just as an adjunct therapy in dermal facial burn wounds.

ACKNOWLEDGMENTS

We thank Daewoong Pharmaceutical Company for Support Easyef® Ointment and eKare inSight™ 3D Wound Assessment in this study. The financial relationships did not pose a conflict of interest to authors.

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