Book Chapter

Effective Treatment of Hard-to-Heal Surgical Wound with Recombinant Human Epidermal Growth Factor

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Abstract

A facile protocol, which involves topical application of recombinant human epidermal growth factor (rhEGF), was previously developed by our group and shown to be effective in treating diabetic foot ulcers, when working in conjunction with debridement surgery. In this communication, using the same approach of rhEGF application, despite the absence of debridement, our findings showed that the protocol worked equally well on a hard-to-heal wound, which remained unhealed subsequent to surgical removal of the great saphenous vein from the left thigh of a diabetic patient. After treating with rhEGF for 10 days, the wound was shown to heal readily and finally achieved complete healing. The success of rhEGF in the healing process is concluded to be attributable to both the fine quality and sufficient dosage of rhEGF.

Keywords

Recombinant Human Epidermal Growth Factor; *Escherichia coli*; Excretion; Hard-to Heal Wounds; Topical application; Diabetes Mellitus

Abbreviations

DFU-Diabetic foot ulcers; rhEGF-Recombinant human epidermal growth factor employed in this study; Hegf-Human epidermal growth factor produced by other protocols; VT-Designation of the diabetic patient concerned in this study; CAD- Coronary artery disease; CABG-Coronary Artery Bypass Grafting; EVH-Endoscopic vein harvesting; SJS-Steven Johnson Syndrome

Introduction

Patients suffering from diabetes mellitus are potentially afflicted with many health threatening complications. Among them, the presence of diabetic neuropathy and peripheral vascular damage may lead to the development of diabetic foot ulcers (DFU),
which results in a 5 to 50 folds of higher risk of non-traumatic amputation when compared with normal individuals. In case abnormal growth of new blood vessels occurs in the retina accompanied by macular edema, loss of vision or even blindness may occur. When vascular damage results in cardiovascular or coronary artery disease, thereby leading to accelerated atherosclerosis, myocardial infarction or “heart attack” appears to be an inevitable outcome.

My group has pioneered the application of recombinant human epidermal growth factor (rhEGF) to the treatments of DFU and complex wounds. In the early 2000s, employing rhEGF prepared from an engineered *Escherichia coli* excretion system [1-4], we reported the use of rhEGF to successfully enhance the healing rate of DFU [5]. In our protocol, rhEGF resuspended in aqueous cream was demonstrated to be able to dramatically improve the efficacy of complete recovery of DFU wounds, from a rate of 42.1% obtained using only debridement surgery to a much increased efficiency of 95%, achieved through first debridement and subsequently topical treatment with 0.04% (wt/wt) rhEGF [5]. Since then, patent protection has also been obtained for the findings reported in this facile treatment process [6-10].

In addition to treating DFU [5], rhEGF has also been applied successfully to cure other severe wounds including Steven Johnson Syndrome [11] and bedsores [10]. All these applications support the view that rhEGF is not only an effective means for wound healing, but it may be highly versatile in managing widely different hard-to-heal wounds. In this communication, the application of rhEGF to an effective treatment of a recalcitrant wound, which resulted from the surgical removal of the great saphenous vein of the left thigh of a diabetic patient, is reported. Prior to the curing process, the wound suffered bacterial infections, thus rendering the development of gangrenes, which might lead to life-threatening conditions if delays in treatment occurred.
Results and Discussion

The patient was a 64 years old male, designated VT, who had suffered from type II diabetes mellitus for 7 years. By taking prescribed drugs: metformin and glyburide, VT’s blood sugar readings varied between 6 and 10 mmol l\(^{-1}\) before he was diagnosed with coronary artery disease (CAD). To cure this potentially fatal heart disease, VT, who had never received any cardiac surgery previously, was recommended to undertake the treatment of Coronary Artery Bypass Grafting (CABG), in which three coronary arteries were required to be bypassed during surgery. To attain three vessels required in CABG, a 48 cm great saphenous vein was harvested from VT’s left thigh (Figure 1), using the endoscopic method [12], and then employed for the surgical bypass. As a result of operations, four incisions, spreading from the groin to the knee and with each wound measured 4-6 cm X 0.8 cm or so, were left on his left thigh (Figure 1).

![Figure 1: Four incisions resulting from endoscopic harvesting of the great saphenous vein from VT’s left thigh. Labels 1\(^{st}\) to 4\(^{th}\) indicate positions of the 4 incisions. The 2\(^{nd}\) wound (boxed) refused to heal and was then subjected to treatment with 0.04% (w/w) rhEGF.](image)

The CABG surgery progressed favorably well. VT recovered swiftly from CAD after treatment and was discharged home 4 days after the surgery. At that point, despite his diabetic complications, all four incision wounds located on VT’s left thigh appeared to heal well.
However, probably due to movements of the left leg, in about the 3rd week or so after VT returned home from the hospital, the 2nd wound from the knee (Figure 1) cracked open. While recovery of the remaining three wounds progressed readily well, the 2nd wound did not show any improvement in healing. In another 4 weeks, while the 1st, 3rd and 4th wounds almost completely healed, the 2nd wound remained not only unhealed, but also started to develop gangrenes, despite being treated with cloxacillin, an antibiotic prescribed by VT’s family doctor for him to take to prevent bacterial infections.

Despite taking cloxacillin and being monitored by doctor, the 2nd wound on VT’s left thigh refused to heal and the gangrenes there showed signs of deterioration (Figure 2). It appeared that further delays in treating the wound might bring about life threatening ulceration, which might lead finally to leg amputation. VT and his family were worried and they approached us for assistance 7 weeks after endoscopic vein harvesting (EVH).

**Figure 2:** Healing of the unhealed wound (2nd one shown in Figure 1) treated with 0.04% (w/w) rhEGF. Day 0 to Day 60 stand for the stages of healing of the wound at various times: Day 0 (before treatment); Day 2 to Day 10 (treatment with rhEGF for 2 to 10 days). The treatment was stopped after day 10; Day 16 and Day 60 reveal the progress of healing of the wound on day 16 and day 60, respectively. Gangrene symptoms in the wound are indicated.
With our previous experience and success in healing DFU, a facile protocol (Figure 3) was promptly designed to treat VT’s unhealed 2\textsuperscript{nd} wound on his left thigh [5]. Just like treating DFU, a simple topical procedure was proposed to be employed for the unhealed wound (Figure 3). However, unlike DFU, VT’s wound was relatively “clean”; it appeared to be only mildly infected, despite the diagnosis of early onset of gangrene symptoms. Moreover, there was not much dead tissue in or around the wound, thus precluding the requirement of a debridement procedure for wound cleansing. VT’s wound was treated twice a day with an aqueous cream containing 0.04\% (w/w) rhEGF (Figure 3), which was previously employed successfully in treating DFU, bedsores and SJS [5,10-11]. The result was unexpectedly effective. VT’s wound showed efficient recovery, and thus rhEGF application was stopped after the 10\textsuperscript{th} day of treatment. Over the next six days or so, despite the absence of rhEGF treatment, VT’s wound continued to recover and subsequently achieved complete healing (Figure 2). Another point worth noting is that the wound healed not only efficiently, but apparently also quite smoothly, thus avoiding the formation of a hypertrophic scar on the skin (Figure 2).

\textbf{Figure 3:} A facile protocol for treating the unhealed wound (2\textsuperscript{nd} one shown in Figure 1). Five simple steps (1-5) are involved in the protocol. In step (1), the dilutions are done according to the manufacturers’ recommendations. In step (3), the 0.04\% (w/w) rhEGF film should cover the wound completely. In step (4), tape the gauze pad to fix its position.
Previously, we reported that rhEGF was employed successfully in treating various complex wounds including DFU, bedsores and SJS [5, 10-11]. In the current study, it was again well demonstrated that rhEGF was effective in promoting treatment of a seriously deteriorating wound of a diabetic patient (Figure 1) which refused to heal 7 weeks after the surgical process. The high efficacy of rhEGF in wound healing was likely attributable to two important factors, firstly, to the high concentration, 0.04% (w/w) rhEGF, which was revealed to be above the minimum effective dosage in treating DFU [5]. Secondly, the fine quality of rhEGF might also play a crucial role. The excretion system engineered by our group has been employed to efficiently produce rhEGF, which has been shown to possess not only potent bioactivity, but also superb purity [3]. Both the high levels of bioactivity and purity of rhEGF were concluded to have critical impact on curing the recalcitrant wound on VT’s thigh (Figure 2).

A big variety of expression systems have been developed for the production of hEGF [13-14], which comprised a collection of structurally heterogeneous products [13-14]. In fact, many of these systems were able to produce only structural derivatives of mature native hEGF [13-14], which might not be as active or stable as rhEGF [1-4]. The latter product was characterized to possess an authentic structure, hence sharing the same primary sequence as mature native hEGF of human origin [3]. Moreover, hEGF produced by majority of the protocols, which were designed essentially for intracellular protein production, were likely contaminated by endogenous proteins and/or endotoxins of the host cells. These contaminants could seriously hamper the bioactivity and stability of hEGF. As a matter of fact, it has been criticized that many of these protocols have resulted in even non-active hEGF [15]!

**Conclusion**

CAD, like DFU, is a common side effect of diabetes. CABG is often considered a solution to treat CAD. When an incision resulting from CABG refused to heal, gangrenes may develop...
and lead to life threatening complications. In this report, as demonstrated previously by our group in treating DFU, topical treatment with 0.04% (w/w) rhEGF is shown to be equally effective in promoting healing of a hard-to-heal surgical wound derived from EVH.

References


