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Topical epidermal growth factor spray for the treatment of chronic diabetic foot ulcers: A phase III multicenter, double-blind, randomized, placebo-controlled trial

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ABSTRACT

Aims: This study was conducted to evaluate the efficacy and safety of a novel spray-applied growth factor therapy containing recombinant human epidermal growth factor (rhEGF) for the treatment of chronic diabetic foot ulcers (DFU).

Methods: This study was a phase III double-blind, randomized, placebo-controlled trial. 167 adult patients at six medical centers were randomized to receive routine wound care plus either topical spray treatment with 0.005% rhEGF (n = 82) or an equivalent volume of saline spray (n = 85) twice a day until ulcer healing or for up to 12 weeks.

Results: Demographics, medical status, and wound characteristics were comparable between rhEGF and placebo groups. More patients in the rhEGF group significantly had complete wound healing compared to placebo (73.2% versus 50.6%, respectively; P = .001). Wound healing velocity was faster in the rhEGF group (P = .029) regardless of HbA1c levels. The rhEGF group had a shorter median time to 50% ulcer size reduction (21 versus 35 days; hazard ratio = 3.13, P < .001) and shorter time to complete ulcer healing (56 versus 84 days; hazard ratio = 2.13, P < .001).

Conclusions: This study confirms that application of spray-applied rhEGF in DFU patients results in faster healing velocity and higher complete healing rate regardless of HbA1c levels.

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1. Introduction

Individuals with diabetes are prone to the development of chronic diabetic foot ulcers (DFUs). The annual prevalence of chronic DFUs is estimated to be between 7 and 10% in adults. As the person with diabetes is expected to substantially increase in size over the next several decades, the burden of disease attributable to DFUs is also likely to further increase [1]. Most DFUs are triggered by trauma, which may be trivial and therefore go unrecognized initially until an ulcer develop [2,3]. Among patients affected by diabetes, impaired sensation and vision can further increase the risk of experiencing a lower extremity injury leading to ulcer development. In addition, persons with diabetes often have other associated medical issues that can further complicate wound healing, including peripheral vascular disease, peripheral neuropathy, and reduced tissue regenerative capacity. Persons with diabetes may therefore experience delayed ulcer healing, and chronic lower extremity ulcers are common among persons with diabetes despite the use of advanced wound dressing modalities [4–7].

Recently, several growth factors including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF), and epidermal growth factor (EGF) have been introduced as potential adjunctive therapies to promote ulcer healing [8–10]. In particular, treatments using EGF have attracted attention for use during diabetic foot ulcer management [11,12]. Since Cohen discovered EGF in 1962 [13], a number of researchers have sought to characterize its primary role during wound healing. In a previous study, Nanney reported that EGF interacts with the EGF receptor on epidermal cells and fibroblasts [14]. And several studies have shown that EGF stimulates epithelial cell growth across the wound surface, enhances epidermal regeneration, and accelerates epithelialization [14,15]. Currently, only a few studies have reported clinical outcomes for DFUs treated with EGF, but these results are promising [16–19]. Among these studies, Hong et al. reported complete healing in 76% (52/68) of chronic DFU patients treated with topical recombinant human EGF (rhEGF) applied with an advanced dressing in their observational study [19]. And Tsang et al. found that rhEGF cream decreased the median time to complete healing of DFUs in a single-center trial [17]. Accordingly, the treatments using EGF showed better outcomes for DFUs in the previous studies. Building on previous clinical results, this trial is the first multicenter, double-blind, randomized, placebo-controlled trial to investigate the efficacy and safety of spray-applied rhEGF for the treatment of DFUs. In this multicenter study, the daily application of rhEGF spray was compared with that of saline spray during the treatment of DFUs in persons with diabetes of various HbA1c level.

2. Materials and methods

2.1. Patients and study design

This study was a phase III, prospective, multicenter, randomized, double-blind, placebo-controlled study. Diabetic patients with foot ulcers were consecutively recruited from January 2011 to June 2012 at six medical centers and the number of patients were relatively equal across the medical centers. The clinical study protocol and informed consent process were approved prior to study initiation by the Institutional Review Board at each participating center.

Patients were eligible for study inclusion if they met the following criteria: medical diagnosis of type 1 or 2 diabetes mellitus; foot ulcer size $\geq 1\ cm^2$; ulcer persisting for more than four weeks without signs of healing; Wagner ulcer grade I or II; and adequate distal extremity arterial flow, defined as either transcutaneous partial pressure of oxygen ($TcPO_2$) $\geq$ 30 mm Hg or palpable pulses at either the dorsalis pedis artery or the posterior tibial artery of the ankle. Patients were excluded if they had any infection, osteomyelitis, or other disorder that could interfere with wound healing (such as deep venous thrombosis, rheumatoid arthritis, systemic lupus erythematosus, or any other systemic inflammatory disease). Patients were also excluded if they were pregnant or if they were being treated with corticosteroids, immunosuppressive drugs, or chemotherapy. Other conditions for which patients were excluded were the presence of any systemic wasting disease (e.g. chronic obstructive pulmonary disease, sickle cell disease, chronic heart failure, or malignant tumor); Charcot arthropathy of the foot; or severe malnutrition (defined as serum albumin < 3.0 g/dL). Prior or ongoing treatments with growth factors or bioengineered tissue products in the past 14 days were also used as exclusion criteria. Patients eligible for study inclusion were identified based on physical examination and review of medical records at an initial visit. At the screening visit, eligibility was further assessed based on general laboratory tests (complete blood count, serum chemistry screen, and urinary analysis). After informed consent for participation was obtained by clinical research coordinator, enrolled patients were randomized to one of the two study groups in a 1:1 ratio. The randomization code was generated using a permuted-block method with a block size of four or six implemented using the SAS system (Version 9.2, SAS Inc., Cary, NC). Randomization was stratified by clinical center. This trial was registered with ClinicalTrials.gov (NCT01629199).

2.2. DFU evaluation and wound care procedures

Prior to wound assessment and before each spray therapy application, each patient's ulcer was thoroughly cleaned with saline solution to remove debris and necrotic tissue and to expose healthy tissue. During the study period, depending on the assigned treatment group, either 0.005% (50 μg/ml) of recombinant human EGF spray (rhEGF, Daewoong Pharmaceutical Co., Seoul, South Korea) or normal saline spray (placebo) was applied topically over the wound bed twice a day. After spraying, wounds were covered with polyurethane foam dressings (Medifoam, Genewel Co., Seoul, South Korea). Both spray solutions were distributed in identical packaging, with the same label to ensure double-blinding. Offloading devices used were preapproved by the clinical research coordinators and selected by the investigators at patient enrolment. Patients were taught that it was important to wear the offloading device at all times. Initial DFU evaluation included