Randomised placebo-controlled trial of use of topical recombinant bovine basic fibroblast growth factor for second-degree burns

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Summary

Background Wound healing is a dynamic process that could be accelerated by growth factors. We investigated the effect of recombinant bovine basic fibroblast growth factor (rbFGF) on burn healing in a randomised placebo-controlled trial.

Methods We recruited 600 patients with superficial or deep second-degree burns. Patients received 150 AU/cm^2 daily topical rbFGF (n=300) or placebo (n=300) plus vehicle. We assessed healing by photography, punch-biopsy, and clinical examination.

Findings All patients treated with rbFGF had faster granulation tissue formation and epidermal regeneration than those in the placebo group. Superficial and deep second-degree burns treated with rbFGF healed in a mean of 9·9 (SD 2·5) days and 17·0 (4·6) days, respectively, compared with 12·4 (2·7) and 21·2 (4·9) days (p=0·0008 and p=0·0003, respectively). No adverse effects were seen locally or systemically with rbFGF.

Interpretation rbFGF effectively decreased healing time and improved healing quality. Clinical benefits would be shorter hospital stays and the patient's skin quickly becoming available for harvesting and grafting.

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Introduction

Wound healing is a dynamic process involving complex mechanisms that manifest in various stages: from blood clotting to inflammation, cellular proliferation, formation of new blood vessels, and reconstruction of extracellular matrices.[1,2] Healing of skin wounds has three general biological stages: inflammation, proliferation and repair, and remodelling. The interaction of growth factors and some of tissue-repair cells, such as fibroblasts, epithelial cells and endothelial cells, have a key role. Wound healing can be accelerated by the action of growth factors,[3–5] because of the biological characteristics of wound healing and function of growth factors.

Epidermal growth factor stimulates keratinocyte division in vitro and epidermal regeneration in vivo, and the residual epithelial cells in wound sites proliferate in an integrated way to regenerate intact epidermis.[6,7] Fibroblast growth factors stimulate proliferation and differentiation of neuroectodermal and mesodermal tissues (eg, endothelial cells and fibroblasts), and have a key part in regeneration of granulation tissues.[3,4,8] Based on this knowledge and our pilot study of patients with burns,[9] we did a prospective, randomised, double-blind multicentre trial to assess the effect of topical recombinant bovine basic fibroblast growth factor (rbFGF) on the healing of burns.

Methods

Patients

We enrolled 600 patients with burns in 32 hospitals across China between Jan 1, 1996, and June 1, 1996. We obtained informed consent, and the protocol was approved by the Institutional Review Boards of National Drug Administration and the scientific committees of each hospital. The study was supervised by the Advisory Committee of Growth Factor Clinical Trials. The doctors involved in data collection were visiting doctors experienced in burn management who worked to the protocol.

Methods

According to the trial profile, we used random numbers to assign the 600 patients rbFGF treatment or placebo (figure 1, table 1) in each hospital's burns unit. The randomisation codes remained in the burns units during the trial and were not available to the

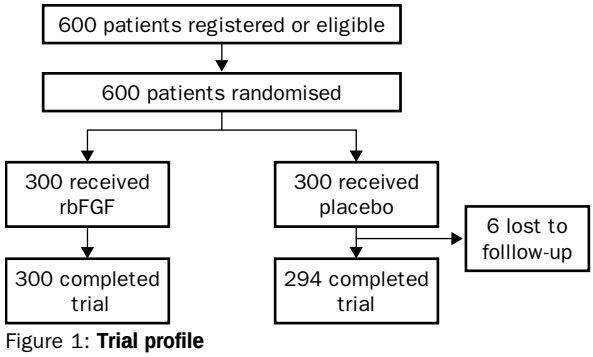

Figure 1: **Trial profile**

Groups	n	Male	Female	Mean (SD) age (years)	Superficial second-degree burns	Deep second-degree burns
rbFGF group	300	157	143	35·28 (12·75)	168	132
Placebo group	294	155	139	33·17 (11·58)	165	129

Table 1: **Characteristics of patients**

investigators. rbFGF and placebo were administered from identical numbered vials provided by the manufacturer. Patients, surgeons, and nursing staff were masked to nature of the treatment.

Eligible patients had burns of partial thickness (through a portion of the dermis and epidermis), classified as superficial (n=333) and deep second-degree burns (n=267), covering 1–10% of total body surface area. The depths of burns were judged by the visiting doctors by clinical examination[10] or punch biopsy. We excluded patients with known cancer, pregnancy, collagen, vascular diseases, immunosuppressive disorders, or severe burns (>10% total body surface area), third-degree burns, or burns in special areas such as the face.

150 AU/cm² rbFGF (Torita Bio-Pharma, Industry Co, Zhuhai, China) or a placebo of normal saline containing 0·1% heparin plus vehicle were applied to wounds, starting within 5 days of injury. Immediately before treatment, all wounds were cleaned with normal saline and after treatment were covered with sterile cotton dressings, which were removed the next day with saline irrigation. If necessary, topical antibiotics were used. Treatment was repeated daily at about the same time until the burn wounds were closed, which was confirmed by a experienced doctor masked to treatment status.

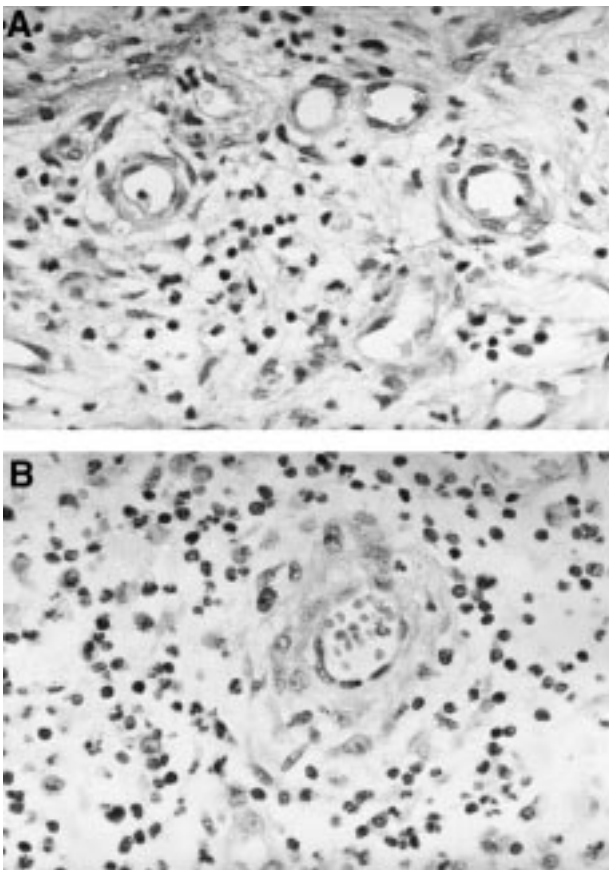

Figure 2: **Histology of biopsy samples from deep-second degree burns 7 days after treament**
A=rbFGF: shows differentiated regenerated granulation tissues several new capillary sprouts or tubes. B=placebo: shows scanty capillary tubes and poorly organised and differentiated fibroblasts. Magnification X160.

Groups	n	Effective	Non-effective
Superficial second-degree burns	168	161 (95·8%)	7 (4·2%)
Deep second-degree burns	132	125 (94·7%)	7 (5·3%)

Table 2: **Rate of treatment effectiveness by group**

We defined patients who received rbFGF but had a longer healing time than patients in the placebo group as non-effective. High fever, abnormal liver and renal function, local pain, and infections were defined as side-effects. To assess the systemic toxic effects and the side-effects of rbFGF, we assessed liver and renal function in all patients before and after treatment.

Wound sites were assessed daily and photographed. On days 3 and 7, punch-biopsy samples were obtained from all wounds. The biopsy samples were fixed in 10% buffered formalin, embedded in paraffin, sectioned, stained with haematoxylin and eosin, and assessed with light microscopy. According to the protocol, 160 samples were used for assessment of granulation tissue in the rbFGF group and 160 in the placebo group. We defined healed wounds as burns that were totally closed.

Statistical analysis

We did all analyses with SDAS (version II). All data are presented as mean (SD). We used one-way analysis of variance and the *t* test where appropriate. Significant differences were defined as $p<0·05$.

Results

Of the 600 patients included, 594 were followed up; six patients in the control group were excluded because of pregnancy (two) and a new injury (four, figure 1). Healing time was shorter in the rbFGF group (mean 9·9 [SD 2·5] days superficial second-degree burns, 17·0 [4·6] days deep second-degree burns) than in the placebo group (12·4 [2·7] days and 21·2 [4·9] days, respectively, p=0·0008 and p=0·0003).

Histological assessment of biopsy samples from some deep second-degree burns showed that in the rbFGF group the epidermis and dermis were almost completely regenerated, and regenerated epidermis consisted of stratified squamous epithelium. In regenerated granulation tissues 7 days after treatment, histological assessment showed more abundant capillary sprouts or tubes in rbFGF-treated wounds than in placebo-treated wounds (12·56 [3·45] *vs* 8·35 [2·43], p=0·0004, figure 2). The fibroblasts were differentiated in rbFGF-treated wounds. By contrast, wounds in the placebo group typically lacked a continuous epidermis and dermis and the regenerated cells were scant, less organised, and poorly differentiated (figure 2). No metaplasia or neoplasia was seen in any biopsy sample.

14 patients in the rbFGF group were defined as non-effective. Treatment with rbFGF was effective in 161 (95·8%) of 168 of superficial second-degree burns and in 125 (94·7%) of 132 of deep second-degree burns (table 2).

There were no complications in the two groups. Also, more than 1·5 years after treatment stopped there were no complications and no clinical evidence of neoplasia in the healed wounds.

Discussion

Although many advances have been made, consensus on the best treatment to hasten healing of burns has not been reached.[1,2,10] For some minor injuries, wounds will heal readily with granulation formation and re-epithelialisation. In large thermal injuries or severe

trauma, however, open wounds promote a hypermetabolic response, and provide sites for bacterial infection.[10,11] Acceleration of the rate of tissue regeneration in wounds or donor sites has, therefore, become an important area for study.[1,2,10] In the 1980s, many investigators studied acceleration and whether the duration of wound healing could be shortened.[12,13] Some studies have shown that exogenous application of growth factors or growth hormone may decrease the healing time and improve healing quality.[14–16] Epidermal growth factor and recombinant human growth hormone (rhGH) accelerate healing in burns and donor sites. Brown and colleagues[14] found that epidermal growth factor shortened the time and improved the quality of healing in burns and donor sites. Gilpin and colleagues[15] showed that rhGH decreased healing times at donor sites. Although fibroblast growth factors have been studied in vivo and in vitro and their effects on stimulation of granulation tissue formation and acceleration of wound healing confirmed,[9,16,17] data from multicentre clinical trials are not available. We showed with rbFGF decreased wound healing time, accelerated epidermal regeneration, and stimulated granulation tissue formation.

The exact mechanisms by which exogenous fibroblast growth factor promotes wound healing are not clear. Biologically, basic fibroblast growth factor (bFGF), a 146 aminoacid polypeptide, has mitogenic effects on cells from tissues of neuroectodermal and mesodermal origin.[16–18] Some studies showed that bFGF stimulates mRNA, DNA, and protein synthesis in many cell types, such as fibroblasts and epithelial cells. In addition, bFGF stimulates fibroblast, vascular endothelial cell, and keratinocyte division in vitro and granulation tissue formation and epidermal regeneration in vivo.[16,19–22] Exogenous basic fibroblast growth factor may also stimulate wound healing indirectly by increasing the production of other growth factors, such as epidermal or transforming growth factors, or increasing the action of growth factors delivered to wounds by platelets or macrophages.[23–25] We have shown previously that the expression of the bFGF gene and the secretion of bFGF protein in damaged tissues were significantly impaired and that the local high concentration of fibroblast growth factor promoted granulation tissue formation and re-epithelialisation.[26–28] In some impaired wounds, such as diabetic foot ulcers and venous ulcers, a local deficiency of growth factors, an access of growth-inhibiting factors, or alteration in growth-factor receptors may lead to delayed wound healing.[13] These findings support the hypothesis that growth factors, including FGF, epidermal growth factor, growth hormone, and their receptors may play important parts in wound healing in impaired and unimpaired wounds.

Because of the extensive distribution and multiple function of bFGF and its receptors,[18] the side-effects or toxic effects of bFGF are of concern because of high concentrations in the local wounds.[29,30] Abnormal cell transformation may become permanent in the regenerated tissues after application of epidermal growth factor and bFGF[14,29,30] Another concern is the possible action of bFGF in hypertropic scar formation, but histological assessment of regenerated tissues from animal experiments or biopsy samples from patients in clinical trials has shown no evidence of metaplasia, and none of our patients had hypertropic scarring or malignant changes after use of rbFGF. Finally, the concentrations of rbFGF in local topical applications are many times higher than those found normally in tissues and blood. Such high concentrations of bFGF could be absorbed into the blood and damage the liver and renal function. We found no evidence, however, of impaired liver and renal function after treatment with rbFGF. The biological effects of this treatment do, however, require further elucidation.

Use of rbFGF accelerated wound healing, which is of clinical benefit because burn wounds can be closed rapidly and the patient's own skin soon become available for harvest and autografting. Decreased healing time can also shorten the length of stays in hospital. Future work should investigate suitable doses for different types of wounds and assess biological effects.

Contributors

Zhiyong Sheng was the advisor for the study and helped with the writing of the paper. Zuyao Shen and Mingliang Zhang, in charge of the trial in Jishuitan Hospital, Yulin Chen, in charge of the trial in Chanhai Hospital, Junhe Xie, in charge of the trial in Zhongshan Medical Hospital, and Zhenrong Guo and Xiaobing Fu, in charge of the trial in 304th Hospital, were all members of the advisory committee. Xiaobing Fu also prepared the manuscript.

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Differences in sexual risk behaviour between young men and women travelling abroad from the UK

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Summary

Background Identification of people who most frequently engage in sexual risk behaviour while travelling abroad would be useful for the design and targeting of health education and promotion campaigns.

Methods Eligible participants were people living in the UK aged 18–34 years who had travelled abroad without a partner in the previous 2 years. Respondents were first screened for eligibility as part of representative face-to-face and telephone surveys by a market research company. Eligible individuals who agreed to take part then underwent a computer-assisted telephone interview. Reinterviewing continued until 400 eligible people had been contacted. We also interviewed a control group of 568 young people who had travelled abroad without a partner in the previous 2 years but who did not report a new sexual relationship during their travels.

Findings One in ten of the eligible participants reported sexual intercourse with a new partner. Travellers who reported a new sexual relationship abroad were also likely to report large numbers of sexual partners at home. Of the 400 people who had a new sexual partner abroad, 300 (75%) used condoms on all occasions with the new partner. Logistic regression modelling showed differences between men and women in those factors linked to the practice of unsafe or safer sex while travelling. For men, patterns of condom use abroad with casual partners ($p<0{\cdot}001$) reflected patterns of use at home ($p<0{\cdot}001$), whereas for women, patterns of condom use varied according to their partners' backgrounds ($p<0{\cdot}001$).

Interpretation Condoms are widely used among young travellers, but patterns of use vary by sex. Campaigns about sexual health targeted at international travellers should continue, not least because young people who meet new sexual partners abroad may be a convenient proxy group for that minority of the population who report most sexual partners at home. Such campaigns should be designed differently for men and women.

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Introduction

Sexual risk behaviour among international travellers has become an important issue because of the HIV-1 epidemic.[1] A common assumption is that people are more likely to engage in high-risk sexual behaviour when travelling than when they are at home. Of the several national European studies on sexual behaviour,[2] the Swiss national survey is the only one that collected data