



Guideline

Clinical guideline on topical growth factors for skin wounds

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Abstract

An increased number of patients with skin wounds have been witnessed in the past decades. Among the various kinds of treatments for skin wounds, topical exogenous growth factors are indispensable and have been used in many countries. However, whether they have reliable effects remains controversial, and their application for skin wound treatment needs to be further standardized and optimized in terms of socio-economic considerations. Thus, the Chinese Burn Association developed this guideline indicating efficacy, application details, adverse reactions and precautions of five clinically common topical growth factors using the Grading of Recommendations Assessment Development and Evaluation method to promote the rational application of topical exogenous growth factors in skin wounds and to benefit more patients.

Key words: Growth factor, Skin wound, Wound healing, GRADE method, Guideline

Background

With the rapid development of the economy, the great changes in people's lifestyles and the accelerated aging of the population, problems caused by various kinds of skin wounds have multiplied during the past decades. The treatments for these wounds include surgical and non-surgical ones. As a non-surgical treatment, the application of exogenous growth factors (eGFs) is one of the indispensable methods to promote wound healing or to provide healthy wound beds for surgical treatments. eGFs have been used in many countries all over the world and the first report on the successful treatment of wounds with commercial eGFs was published as early as 30 years ago. To date, no obvious toxicity or severe adverse reactions have been reported in the treatment of wounds with eGFs. However, whether the eGFs have reliable effects remains controversial, and the application of eGFs for wound

treatment needs to be further standardized and optimized in terms of socio-economic considerations.

The process of wound healing generally consists of three stages, inflammatory reaction, proliferation and tissue reconstruction. It is an elaborate biological process involving multiple factors such as repairing cells, proteins and biotic factors, among which growth factors play a vital role. The growth factors not only promote the proliferation, differentiation and migration of repairing cells such as keratinocytes, fibroblasts and vascular endothelial cells (VECs), but also regulate apoptosis of the repairing cells, the composition of the extracellular matrix (ECM), the synthesis of DNA, RNA and proteins, the process of glycolysis, as well as the remodeling of damaged tissues. It is suggested that decreased activity and/or quantity of growth factors and their receptors is a potential and important pathophysiological basis of refractory non-healing

wounds [1]. This lays a theoretical foundation for topical application of eGFs to promote wound healing in various kinds of cases. In order to promote the rational application of eGFs in skin wounds and to benefit more patients, the present guideline was developed after much discussion by writing group of growth factor guideline on behalf of Chinese Burn Association under the guidance of the academician Xiaobing Fu.

Methods

This guideline has been registered in the International Practice Guidelines Registry Platform with the registration number IPGRP-2020CN127. It was developed based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) [2–3]. The recommendations were aimed at indicating the efficacy, application approaches and doses, concentration and treatment course of topical eGFs on skin wounds, and adverse reactions and precautions. The process of guidelines development was as follows (Figure 1). (1) Search the Chinese CNKI, CQVIP and WANFANG databases using the key words “basic fibroblast growth factor (bFGF)”, “acidic fibroblast growth factor (aFGF)”, “epidermal growth factor (EGF)”, “granulocyte macrophage colony stimulating growth factor (GM-CSF)”, “platelet-derived growth factor (PDGF)”, “wound”, and “healing/repair” both in Chinese and in English. Meanwhile search PubMed, Web of Science and EMBASE databases using the above key words in English. (2) The guideline supporting group, under the guidance of the experts, reviewed the titles, abstracts and full texts of the obtained literature, determined the articles that should be included in the later literature evaluation based on the inclusion criteria and exclusion criteria, and used an artificial method to grade the quality of evidence forming “high”, “moderate” or “low” classifications. (3) The expert panel reviewed the included literature and, based on comprehensive consideration of benefits and harms, patient values and preferences, economic costs and clinical practice related factors, put forward their own recommendations with “strong” or “weak” as different recommendation strengths.

The inclusion criteria are as follows: (1) clinical trials of topical eGFs for the treatment of skin wounds, or *in vitro* and *in vivo* studies involving dose–effect investigations; (2) published from the establishment year of each aforementioned database to 31 July 2019; (3) written in Chinese or English; (4) subjects were patients with skin wounds or *in vivo* and/or *in vitro* experimental models; (5) the experimental group was treated with eGFs, while the control group was treated with placebo or standard/routine therapies; (6) outcome index mainly included wound healing data such as wound healing time and wound healing rate. The exclusion criteria include: (1) studies exclusively on non-skin wounds (e.g. oral mucosa); (2) *in vitro* studies or experimental animal studies which do not involve dose–effect investigations; (3) observational studies with a small sample ($n < 30$) in each group.

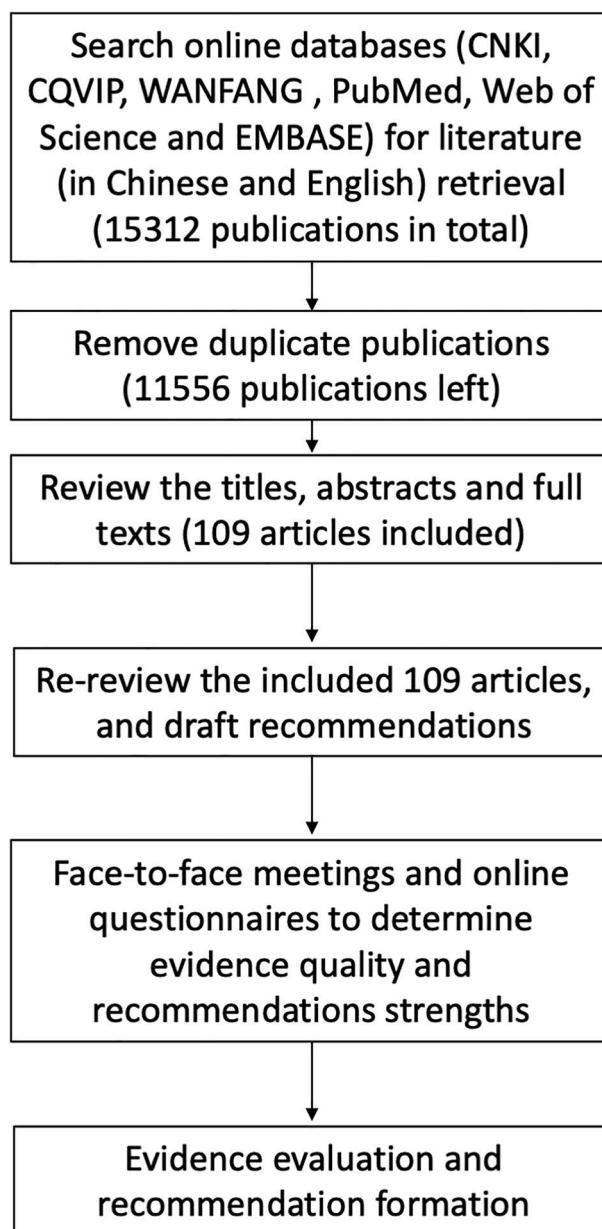


Figure 1. Diagram of the development of clinical guideline on topical growth factors for skin wounds using the Grading of Recommendations Assessment Development and Evaluation method

A total of 4253 articles in Chinese and 11 059 articles in English were retrieved, including 3333 articles in Chinese and 8223 in English obtained after repeated examination. After review of the titles, abstracts and full texts, 109 articles were included, of which 78 were in Chinese and 31 in English. Among these, 40 were on bFGF, of which 33 were in Chinese and 7 were in English; 7 were on aFGF, of which 6 were in Chinese and 1 was in English; 44 were on EGF, of which 35 were in Chinese and 9 were in English; 11 were on GM-CSF, of which 4 were in Chinese and 7 were in English; 7 were on PDGF, all of which were in English.

Table 1. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of basic fibroblast growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Superficial partial-thickness burns	High	Strong	4–11
Deep partial-thickness burns	High	Strong	4–14
Fresh traumatic wounds	Moderate	Strong	4, 15–19
Donor sites	Moderate	Weak	4, 6, 7, 20–23
Chronic wounds	Moderate	Weak	4, 5, 20, 24–29
Diabetic ulcers	Moderate	Weak	30–32
Pressive ulcers	Moderate	Weak	33–36
Grafted wounds	Low	Weak	37, 38
Redidual granulation wounds after burns	Low	Weak	4, 7, 39
Chronic ulcers after burns	Low	Weak	39
CO ₂ laser treated wounds	Low	Weak	40
Radiative dermatitis wounds	Low	Weak	41

Table 2. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of basic fibroblast growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Deep partial-thickness burns	Moderate	Weak	42,43,44
Redidual granulation wounds after burns	Low	Weak	45
Diabetic foot ulcers	Low	Weak	46

Recommendations and rationale

Effectiveness of topical growth factors for skin wounds

FGF FGF is a class of significant growth factors in organisms. It has a wide range of biological effects on tissues and cells derived from mesoderm and neuroectoderm, and is involved in wound repair, nerve repair, metabolic regulation, angiogenesis and embryonic development. In the family of FGFs, topical bFGF and aFGF have been used widely. The possible biological functions of bFGF in promoting wound healing are as follows. (1) bFGF can significantly promote angiogenesis *in vivo* and *in vitro*, exert chemotaxis of various kinds of cells involved in angiogenesis, and promote their proliferation and migration, which is one of the main angiogenetic factors. (2) Injury-induced bFGF promotes the aggregation of monocytes, neutrophils, macrophages and fibroblasts via chemotaxis in the injured tissues. It can also promote the formation of granulation tissue, cell division and proliferation related to injury repair and tissue reconstruction, playing a vital role in the repair of tissue damage. aFGF can promote the proliferation and migration of fibroblasts and other skin repair related cells to promote wound healing. Its underlying mechanisms include mitogenic activity, which mainly demonstrates promotion of cell proliferation and division, and non-mitogenic activity such as reducing local ischemia. aFGF is a mitogen in a variety of cells and thus participates in multiple processes of tissue repair. The evidence grades and expert recommendations for FGF to promote the healing of different types of wounds [4–46] are shown in Tables 1 and 2.

EGF EGF can be found in almost all kinds of body fluids, secretions and most tissues. EGF receptor (EGFR) is mainly expressed by keratinocytes. Other EGFR-expressing cells

include fibroblasts, glial cells, smooth muscle cells (SMCs) and chondrocytes.

EGF exerts chemotaxis and mitogenic effects mainly by binding to receptors on the cell membrane and forming a complex metabolic network during its intracellular transmission, resulting in the regulation of cell metabolism, differentiation and other biological activities. Based on the literature, experts suggest that EGF can promote the healing of various kinds of skin wounds. The evidence grades that EGF promotes healing of different types of wounds and recommendations [47–78] are shown in Table 3.

GM-CSF GM-CSF is a family of specific cytokines. Not only can it promote the proliferation of skin repairing cells through autocrine, it also plays a role in promoting wound healing by mediating several other cytokines. Before 2008, GM-CSF had been applied mainly by injection as a general clinical drug for nearly 15 years. It could be used for more than 7 days at a safe dose of 3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Subsequently, recombinant human GM-CSF (rhGM-CSF) gel was developed and applied to clinical wound therapy.

In 1992, Kaplan first reported the introduction of GM-CSF into the treatment of acute skin wounds. It was proved that rhGM-CSF injection could promote wound healing [79]. GM-CSF is involved in a series of processes of wound repair, including activation of T lymphocytes, dendritic cells, macrophages, endothelial cells and fibroblasts, etc. GM-CSF can enhance the function of many kinds of cells necessary for wound healing, such as activation of neutrophils and macrophages, increased migration and proliferation of epithelial cells, regulation of fibroblasts phenotypes, etc. The grades of evidence and expert recommendations for GM-CSF

Table 3. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of epidermal growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Superficial partial-thickness burns	Moderate	Weak	47–59
Deep partial-thickness burns	Moderate	Weak	47–62
Donor sites	Moderate	Weak	47–51
Redidual granulation wounds after burns	Moderate	Weak	48,50,51,53
Diabetic foot ulcers	High	Strong	47,63–70
Venous ulcers	Moderate	Weak	71–73
CO ₂ laser treated wounds	Moderate	Weak	74–76
Grafted wounds	Low	Weak	48
Chronic ulcers after burns	Low	Weak	48,53
Radiative dermatitis wounds	Low	Weak	77
Leg ulcers	Low	Weak	78

Table 4. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of granulocyte macrophage colony stimulating growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Deep partial-thickness burns	High	Strong	80–86
Diabetic foot ulcers	Low	Weak	87,88
Chronic refractory wounds	Low	Weak	89

Table 5. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of platelet-derived growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Diabetic foot ulcers	Moderate	Weak	90–92
Pressure ulcers	Moderate	Weak	93–95
Venous ulcers	Low	Weak	90

to promote wound [80–89] healing in different types of wounds are shown in Table 4.

PDGF PDGF possesses a wide range of biological activities. It acts on the membrane receptors of target cells, producing a series of biological effects that play an important role in the physiological and pathological processes of tissue repair. These include chemotaxis of inflammatory cells and repairing cells to the wound, promoting the mitosis of VECs, fibroblasts, SMCs and epithelial cells, promoting the formation and reconstruction of vascular regeneration of ECM, forming granulation tissue, and promoting re-epithelialization of the wound. The grades of evidence and expert recommendations for PDGF to promote wound healing in different types of wounds [90–95] are shown in Table 5.

Application of topical growth factors for skin wounds

As biological agents, eGFs are recommended to be applied to wounds according to the manufacturer's instructions. This is because there are stringent requirements for application environment and preservation conditions as well as various forms of different eGFs.

Experts especially stress that the application of eGFs must be based on the specific condition of the wound. The precondition for the effective application of eGFs on all kinds

of wounds is debridement. The necrotic tissue of the wound must be removed, and severe infections of the wounds should be effectively controlled before application of eGFs. The application methods of various growth factors are basically similar, and the forms of growth factors mainly include dry powder for the preparation of solutions and gels. The former can be dissolved in injection water or saline and applied directly or sprayed via a sprayer. Another way of application for eGFs is to drip the preparation solution evenly onto a suitably sized piece of gauze, which is then used to cover the wound. A gel, such as bFGF, can be evenly applied to the debrided wound or smeared evenly on a suitably sized piece of gauze, which is then used to cover the wound, with subsequently conventional bandaging (outer gauze) [4–6, 8,9,13,16,24,27] (GRADE recommendation: weak; quality of evidence: low). The doses and concentrations of various growth factors are determined mainly according to the manufacturer's instructions [4–6,8,9,13,14,16,21,24,27, 42,43,45,60,67,80–83,89–108], which are shown in Table 6. However, there is also literature supporting different methods of application, such as a combination of EGF and saline soaking or infrared ray therapy [101,104,109] (GRADE recommendation: weak; quality of evidence: low). As for the course of treatment, experts agree that one or more times a day is appropriate because growth factors exert their

Table 6. Application parameters of topical growth factors for skin wounds

Growth factor	Dosage form	Concentration	Common dose	Frequency	References
bFGF	Powder	Adjustable preparing solution	150 IU/cm ² or 1 µg/cm ²	Once or twice per day	4–6,8,9,13,14,16,24,27
	Gel	2100 IU/g	150 IU/cm ²	Once per day	96–99
aFGF	Powder	Adjustable preparing solution, e.g. 1000 IU/mL	100 IU/cm ²	Once per day	42–43,45
EGF	Powder or solution	Adjustable preparing solution, e.g. 2000 IU/mL or 2.5 to 5.0 µg/mL or 10.0 µg/g	400 IU/cm ² or 80 mg/cm ²	Once per day	21,100–103
	Gel or cream	10 µg/g or 20 to 40 µg/g	1 µg/cm ² or 50 000 IU/cm ² or 80 mg/cm ²	Once every 1–4 days	60,67,104–107
GM-CSF	Powder	Adjustable preparing solution	5 µg/cm ²	Once per day	108
	Gel	10 µg/g	1 µg/cm ² or 10 µg/cm ²	Once per day	80–83,89
PDGF	Powder	Adjustable preparing solution, e.g. 100 µg/mL	10 µg/cm ²	Once per day	93
	Gel	10 µg/g	10 µg/cm ²	Once per day	90–92,94–95

bFGF basic fibroblast growth factor, *aFGF* acidic fibroblast growth factor, *EGF* epidermal growth factor, *GM-CSF* granulocyte macrophage colony stimulating growth factor, *PDGF* platelet-derived growth factor

curative effects by rapid contact with receptors. Given the common frequency of clinical dressing changes, once a day is also reasonable. In addition, since application of eGFs is to promote wound healing, they can be used until the wound bed becomes appropriate for skin grafting or wound healing, as long as the patient has sufficient financial support.

Supplementary recommendations are as follows. (1) bFGF can effectively promote wound healing in a certain dose range (75–300 IU/cm²) while ensuring that the wound is clean. Increasing the number of applications or prolonging the moisturizing time can significantly shorten the wound healing time at a constant dosage of eGFs [15, 22–23] (GRADE recommendation: weak; quality of evidence: moderate). (2) The commonly used forms of topical rhEGF include solution, cream and hydrogel, of which hydrogel is the most effective in terms of wound healing [105] and can reduce the pain and the workload of dressing changes [60] (GRADE recommendation: weak; quality of evidence: moderate). (3) Literature on the application of growth factors for skin wounds in pediatric patients is insufficient at present. According to the existing scientific reports and expert opinions, bFGF [8, 14], aFGF [96, 97] and EGF [100] can be applied on superficial and deep second-degree burn wounds in children.

Adverse reactions and precautions for topical growth factors for skin wounds

So far, no toxic effects or adverse reactions have been reported to be caused directly by the application of eGFs onto human skin wounds [4, 42, 44, 45, 110–111] (GRADE recommendation: weak; quality of evidence: low). Possible adverse effects include local allergic reactions such as redness, swelling, pruritus, transient pain, etc. which will disappear after withdrawal of growth factors. Few reports have implicated eGFs in the promotion of scar development while one trial suggested that eGFs may reduce scar formation [61].

Precautions to be taken with the use of topical growth factors for skin wounds are as follows:

- (1) There is a lack of adequate evidence on the safety of topical eGFs for pregnant or lactating women, children and the elderly (>65 years old).
- (2) The premise of topical application of eGFs is thorough debridement which resulted in relatively clean wounds, and eGFs should not be used on contaminated or infected wounds.
- (3) It is not recommended to apply eGFs on wounds with severe peripheral inflammatory reaction and exudation.
- (4) Dose-effects of eGFs within a concentration range of 100–1000 IU/cm² have been supported by currently published data.
- (5) The frequency of application of eGFs is generally more than once a day when clinical condition permits.
- (6) The eGFs treatment can be maintained until the wound is healed or the wound bed is appropriate for skin grafting.
- (7) The effectiveness of combined use of multiple growth factors at different healing stages and different conditions needs to be confirmed by further high-quality evidence. The current literature suggests that the combined use of multiple growth factors may contribute to wound repair, but it is necessary to balance the benefits and costs for the patients.
- (8) Current data show that combined application of eGFs with other treatments, such as alginate dressing and vacuum sealing drainage (VSD), can accelerate wound healing, but the dose-effects of eGFs should be considered, and it still needs further substantial clinical observation and verification.
- (9) In order to prevent reduced effects of eGFs, combining topical eGFs with solvents attenuating protein activities (such as ethanol solution, hydrogen peroxide solution, etc.) or heavy-metal preparations (such as silver ion products) should be avoided.
- (10) Since growth factors can promote the proliferation and growth of tumor cells, they should not be used on cancerous wounds, skin wounds in patients with cachexia or malignant ulcer wounds.

The application of rhEGF is cost-effective for diabetic foot ulcer and Wagner's stage III or IV wounds while PDGF has been shown to be cost-effective for the treatment of pressure injuries [112, 113]. However, the decision should be made by patients and their family according to their preferences and values, economic and health insurance states.

Conclusions

Topical application of growth factors are promising in treating various kinds of skin wounds, and the effectiveness of several growth factors has been confirmed in certain conditions based on current scientific evidence. Their rational application leads to more reliable effects and fewer unexpected results. Recommendations concerning the effectiveness, standardized application and precautions are provided in this guideline based on the GRADE system and expert opinions. More clinical trials are expected to further determine the efficacy, optimization and cost-effectiveness of different growth factors and their combinations with other treatments in different conditions in the future.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CMH made major contributions to conception and design. CMH, BC and PW did the literature research for clinical data, most of the work in analysis, interpretation of data, and drafted the manuscript. All authors from writing group of growth factor guideline on behalf of Chinese Burn Association substantially contributed to the literature review, participating in meetings and formation of recommendations.

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