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ORIGINAL ARTICLE

Growth factor therapy in patients with partial-thickness burns: a systematic review and meta-analysis

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Key words
Growth factor; Partial-thickness burn; Wound healing

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Abstract

Growth factor (GF) therapy has shown promise in treating a variety of refractory wounds. However, evidence supporting its routine use in burn injury remains uncertain. We performed this systematic review and meta-analysis assessing randomised controlled trials (RCTs) to investigate efficacy and safety of GFs in the management of partial-thickness burns. Electronic searches were conducted in PubMed and the Cochrane databases. Endpoint results analysed included wound healing and scar formation. Thirteen studies comprising a total of 1924 participants with 2130 wounds (1131 GF receiving patients versus 999 controls) were identified and included, evaluating the effect of fibroblast growth factor (FGF), epidermal growth factor (EGF) and granulocyte macrophage-colony stimulating factor (GM-CSF) on partial-thickness burns. Topical application of these agents significantly reduced healing time by 5·02 (95% confidence interval, 2·62 to 7·42), 3·12 (95% CI, 1·11 to 5·13) and 5·1 (95% CI, 4·02 to 6·18) days, respectively, compared with standard wound care alone. In addition, scar improvement following therapy with FGF and EGF was evident in terms of pigmentation, pliability, height and vascularity. No significant increase in adverse events was observed in patients receiving GFs. These results suggested that GF therapy could be an effective and safe add-on to standard wound care for partial-thickness burns. High-quality, adequately powered trials are needed to further confirm the conclusion.

Introduction

Burn injuries are a global public health problem, accounting for an estimated 300 000 deaths throughout the world each year (1). Partial-thickness (grade II) burn is a common clinical burn, anatomically involving the epidermal layer as well as a varying thickness of the dermis, further subclassified into superficial (grade IIa) and deep (grade IIb) partial-thickness (2). Although a grade II burn is generally non-fatal and heals with standard wound care, the impaired wound healing and hypertrophic scar formation can severely undermine the quality of survival in patients (3).

Healing of a burn wound is a dynamic process, involving a series of complex cellular and molecular events with a great degree of overlap and interdependence (4). Polypeptide growth factors (GFs) are a cluster of multifunctional peptides, playing fundamental roles in this process: by stimulating cellular and chemotaxis proliferation, by providing signalling among cells of the same and different type, by controlling extracellular matrix formation and angiogenesis, by regulating the process of contraction and by reestablishing tissue integrity during tissue repair (5–7). However, the bioavailability of GFs is generally insufficient in the wound bed of burns because of diminished synthesis and/or excessive degradation (8).

Key Messages

- partial-thickness burn wound heals slowly with hypertrophic scar formation when standard wound care alone is performed
- growth factors serve in multiple capacities of wound healing, but their use in the treatment of burn injury is uncertain and is not routinely recommended
- the limited evidence suggests that add-on therapy with growth factors accelerates partial-thickness burn wound healing and lightens scar formation. Further large-scale studies are warranted to confirm its effect and safety

Table 1 Eligibility criteria for the inclusion in the meta-analysis

Inclusion criteria	1	Randomised controlled trial comparing growth factor (GF) therapy with standard wound care alone for partial-thickness burns
	2	Sufficient data reported for at least one clinical endpoint of interests
	3	Number of patients and wounds reported for each arms
Exclusion criteria	1	In vitro experiments or animal studies
	2	Articles from the same institution and/or author with patients duplicated
	3	Articles with less than 10 cases examined for each arm

Evidence from various in vivo studies supported that exogenous GFs serve in multiple capacities of burn wound healing (9). In 1986, Brown *et al.* (10) first demonstrated that biosynthetic human EGF accelerated epidermal regeneration in porcine models of partial-thickness burns. Study by Danilenko *et al.* (11) demonstrated that application of KGF-1 (also known as FGF-7) in the same model displayed a more significant increase in new epithelial area (KGF-treated versus control, $P < 0{\cdot}0001$) than EGF, and a modest increase in reepithelialisation (KGF-treated versus control, $P = 0{\cdot}09$), due to its marked stimulation of both epidermal and follicular proliferation. In a recent study by Galeano *et al.* (12), up-regulated expression of vascular EGF (VEGF) in deep partial-thickness burn wounds through a recombinant adeno-associated virus-mediated gene delivery system (vectors-VEGF165) was proved to increase wound content of nitrate, epithelial proliferation, angiogenesis, maturation of the extracellular matrix and activation of nitric oxide synthesis. In terms of scarring, Xie *et al.* (13) demonstrated that basic FGF (bFGF)-treated scars showed a better process of skin remodelling, which may avoid the subsequent development of fibro-proliferative disorders.

In the past 20 years, cloned recombinant form, commercially approved GF products have been used in the management of a variety of refractory wounds such as chronic venous ulcers (14–16), diabetic foot ulcers (17–20) and pressure ulcers (21,22), and have provided positive clinical benefit. A recently published review article presented a comprehensive discussion on the potential therapeutic applications of GFs on burn injuries (23). However, due to the limitation of narrative reviews, its conclusion was qualitative. Quantitative meta-analyses of randomised controlled trials (RCT) are recommended to substantiate knowledge about the effectiveness of a treatment by pooling data from smaller studies that do not always have enough power on their own to give clear statistical significance (24). We performed this systematic review and meta-analysis with RCT evidence of the effect of GF therapy on the management of partial-thickness burns. The outcomes were evaluated with emphasis on efficacy and safety of GF therapy in wound healing, scar formation and adverse reaction, compared with traditional standard wound care alone.

Methods

Search strategy and eligibility criteria

All prospective RCTs of GF therapy in the management of partial-thickness burns in patients treated for a minimum of 1 week were identified and selected. National Library of Medicine (PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library were searched for all publications up to January 2014 using Boolean expressions combining MeSH terms without language restriction: [Burns (Mesh) OR burn injury OR burn intervention OR burn scar] AND [Growth factor (Mesh) OR biologic agent OR biologic treatment OR biologic therapy OR cytokine therapy]. Study eligibility criteria are listed in Table 1. Titles and abstracts were first screened independently by two reviewers (YZ and JH), and discrepancies were resolved by consensus after consultation with the senior author (JD). Selected articles from this screening underwent subsequent independent full-text reviews. The references of all articles selected for full-text review were reviewed manually to identify other potentially appropriate publications that matched our criteria. Multiple articles from the same institution and/or author were analysed carefully to ensure that no patients were duplicated in the analysis, and only the most recent or most inclusive article was included.

Endpoint outcomes

Primary outcomes analysed included the average healing time in days or percentage reductions in the measured wound size. Secondary outcomes analysed were hypertrophic scars using the Vancouver Scar Scale (VSS) (25), and any potential adverse events (AEs) relative to wound therapy (i.e. toxic side effect, allergic reaction, wound infection and severe systemic reaction).

Data extraction

Data extraction was performed independently by two reviewers (YZ and TW), and discrepancies were resolved by consensus. Data extracted from each trial referred to the name of the first author, year of publication, location of the study, intention-to-treat (ITT) population, gender distribution, mean age (years), burn depth, wound numbers for each arms, total body surface area (TBSA) (%), intervention (agent type, dose, route, timing and duration of administration), data regarding the effectiveness and safety of compared treatments (time to healing, reduction in wound size, assessment of hypertrophic scars and any reporting AEs) and potential conflict of interests (COI) announced on the publication. The authors were contacted by phone or e-mail when information was inadequate in the articles.

Quality scoring and risk of bias assessment

Assessment of the methodological quality of the included trials was performed according to the Jadad scoring system by

methods of random allocation (up to 2 points), blinding (up to 2 points) and patient withdrawals (up to 1 point) (26). A study can obtain 0–5 points based on the criteria. A threshold of 3 points or above is considered as indicative for high quality. Risk of bias assessment in RCTs was performed according to the Cochrane Methodology under consideration of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential sources of bias (27). Each category was scored as low, unclear or high risk of bias and expressed in a summary table with a plus, question mark and minus, respectively. Publication bias was formally assessed with the Begg's test. All the scoring was performed independently by two reviewers (YZ and JH), and any disagreement was resolved by consensus.

Statistical methods

The statistical analysis was performed using STATA version 12 software (Stata Corp, College Station, TX). Continuous variables were reported as weighted mean difference (WMD) with 95% confidence intervals (CI), whereas dichotomous data were reported as odds ratios (OR) with 95% CI. The heterogeneity was tested with the chi-square-based Cochran's statistic and the inconsistency index (I^2) (28). Statistically significant heterogeneity was considered present with $P_{\text{heterogeneity}} < 0{\cdot}05$ or $I^2 > 50\%$. In the presence of substantial heterogeneity, a random effect model (REM) was adopted as the pooling method instead of a fixed effect model (FEM) (29). Subgroup analysis was performed when at least two studies included the considered outcome. Sensitivity analysis was performed by refitting the estimated OR omitting one study at a time. Statistical significance was indicated by P-value $< 0{\cdot}05$.

Results

Search and study selection

A flowchart of the selection process is shown in Figure 1. A total of 224 potentially eligible articles were identified in the literature search. After application of the inclusion and exclusion criteria described previously, 190 articles were initially excluded on the basis of the title and abstract. The remaining 34 publications underwent detailed evaluation of the full text, and 21 were proved not eligible: 5 for not reporting on outcomes of interests, 7 for data unavailable, 3 for having a small sample size (<10 participants per group) and 6 for reporting on burns of higher grade instead of partial-thickness. Thus, 13 trials were considered eligible for inclusion.

Characteristics of Included RCTs

The 13 RCTs included were published between 1998 and 2012, and comprised a total of 1924 participants with 2130 wounds (1131 GF receiving patients versus 999 controls). All patients in the clinical trials included were of Asian (China and Japan) origin. The efficacy and safety of the therapy with the following three agents were evaluated and compared with standard wound care (as control) in treating partial-thickness burn: fibroblast growth factor (FGF), epidermal growth factor (EGF) and granulocyte macrophage-colony stimulating factor (GM-CSF). The methodological features and outcomes measured in the studies are presented in Table 2. The evaluation of funnel plots did not suggest evidence for publication bias (Figure S1–S3, Supporting Information). Pooled analysis showed no statistically significant differences between GFs group and the control group in terms of TBSA (Figure S4). In the primary outcome, time to complete healing was investigated in 12 of the trials included, whereas in 4 trials [3 on EGF (30–32) and 1 on FGF (33)], outcomes from patients of subclassified burn depths (IIa and IIb) were further investigated. Scar formation was evaluated in four studies using VSS [three on FGF (34–36) and one on EGF (37)]. AEs were investigated in seven studies and reported in six [one on FGF (38), two on EGF (31,32) and three on GM-CSF (39–41)].

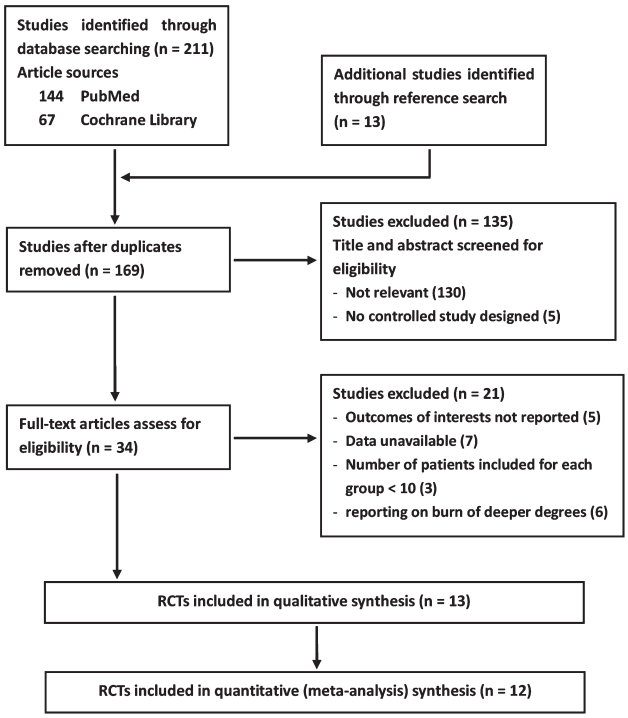

Figure 1 Study selection process.

Quality assessment

According to the Jadad Scoring System, the included RCTs were of moderate to high quality with a mean Jadad score of 3·0 (range, 2·0–5·0). Risk of attrition bias was not present across the studies included. Ten trials did not provide adequate description of allocation concealment, introducing an unclear risk of selection bias. Mild performance bias was present for inadequate description of double blinding in four trials. Unclear risk of detection bias was present for inadequate description of blinded outcome assessment in eight trials. Mild reporting bias was present for missing reporting on endpoint outcomes in three trials (Figure 2). In addition, age was introduced as a participant characteristic for the inclusion criteria of two trials (31,35), which might be a potential source of bias for the analysis.

Table 2 Details of the RCTs included in the meta-analysis

First author and year	Country	ITT (T/C)	Gender (M/F)	Mean age (years)	Wound number (T/C)	Burn depth (degree)	TBSA (percents)	Intervention	Outcome
FGF-treated versus control									
Akita 2008	Japan	51/51	57/45	57·2	119/122	II	T: 8·9 ± 4·3 C: 9·5 ± 5·0	Beginning: 2–4 days after burn injury Concentration: 1 μg (120 IU) per cm^2 area Frequency: daily Continuing until the wound had completely healed	WHT: 12·0 ± 2·2 versus 15·0 ± 2·7 days (bFGF versus control, $P < 0·01$) VSS scores showed significant differences between bFGF-treated and non-bFGF-treated scars ($P < 0·01$)
Nie 2010	China	44/41	60/25	32·7	59/58	IIb	Comparison I T: 12·2 ± 8·9 C: 10·8 ± 9·7 Comparison II T: 13·1 ± 9·9 C: 15·5 ± 10·1	Beginning: immediately after thorough debridement Concentration: 150 AU (262·5 IU) per cm^2 area Frequency: daily Continuing for 3 weeks	WHT: 18·2 ± 4·8 versus 24·2 ± 5·8 days (bFGF with oxygen therapy versus oxygen therapy, $P < 0·01$); 22·2 ± 6·8 versus 27·3 ± 6·6 days (bFGF versus control, $P < 0·01$) No statistical difference was found in clinical evaluation of VSS scores between bFGF-treated and non-bFGF-treated scars
Hayashida 2012	Japan	10/10	12/8	0·7	15/15	II	T: 7·7 ± 2·6 C: 8·3 ± 2·9	Beginning: immediately after thorough debridement Concentration: 1 μg (120 IU) per cm^2 area Frequency: daily Continuing until the wound had completely healed	WHT: 13·8 ± 2·4 versus 17·5 ± 3·1 days (bFGF versus control, $P < 0·01$) VSS scores showed significant differences between bFGF-treated and non-bFGF-treated scars ($P < 0·01$)
Fu 1998	China	300/300	312/282	34·2	300/294	IIa and IIb	<10	Beginning: within 2 days of burn injury Concentration: 150 AU (262·5 IU) per cm^2 area Frequency: daily Continuing until the burn wounds were closed	WHT: 9·9 ± 2·5 versus 12·4 ± 2·7 days (IIa burns, bFGF versus control, $P < 0·01$); 17·0 ± 4·6 versus 21·2 ± 4·9 days (IIb burns, bFGF versus control, $P < 0·01$) WHR on the 12th, 15th, 21st day: 56·0%, 78·4%, 95·6% versus 67·0%, 89·2%, 99·2%, respectively (IIb burns, aFGF versus control) No adverse effects were seen locally or systemically with bFGF
Ma 2007	China	39/39	NA	37	39/39	IIb	T: 3·81 ± 0·43 C: 3·73 ± 0·41	Beginning: within 5 days of burn injury Concentration: 100 AU (175 IU) per cm^2 area Frequency: daily Continuing until the burn wounds were closed	WHT: 17·23 ± 0·53 versus 18·92 ± 0·49 days (aFGF versus control, $P < 0·01$) No significant adverse drug events or adverse drug reactions in this study

Table 2 Continued

First author and year	Country	ITT (T/C)	Gender (M/F)	Mean age (years)	Wound number (T/C)	Burn depth (degree)	TBSA (percents)	Intervention	Outcome
EGF-treated versus control									
Guo 2010	China	40/40	42/38	70	38/34	IIa and IIb	Comparison I T: 13·9 ± 4·7 C: 12·3 ± 5·5 Comparison II T: 13·9 ± 5·74 C: 14 ± 6·36	Beginning: within 1 day of burn injury Concentration: 40 IU per cm^2 area Frequency: daily Continuing until complete wound healing occurred	WHT: 14·30 ± 1·26 versus 16·22 ± 1·40 days (IIa burns, EGF versus control, $P < 0·05$); 26·11 ± 2·97 versus 29·13 ± 4·99 days (IIb burns, EGF versus control, $P < 0·05$) No other side reactions were observed in treatment group except for flash stabbing pain (four cases) and pruritus (two cases)
Liao 2003	China	60/60*	41/19	32	60/60*	IIa and IIb	NA	Beginning: within 2 days of burn injury Concentration: 40 IU per cm^2 area Frequency: daily Continuing until complete wound healing occurred	WHT: 10·20 ± 2·20 versus 13·20 ± 2·40 days (IIa burns, EGF versus control, $P < 0·05$); 17·2 ± 3·12 versus 21·1 ± 3·40 days (IIb burns, EGF versus control, $P < 0·01$) Wound-edge inflammatory reaction was observed in nine control cases with second-degree burns
Wang 2002	China	105/105	NA	33·2	105/105	IIa and IIb	Comparison I T: 6·85 ± 3·19 C: 6·37 ± 2·92 Comparison II T: 7·66 ± 2·87 C: 7·34 ± 4·01	Beginning: immediately after thorough debridement Concentration: 0·8 μg (400 IU) per cm^2 area Frequency: daily Continuing until complete wound healing occurred	WHT: 8·39 ± 2·25 versus 9·52 ± 2·56 days (IIa burns, EGF versus control, $P < 0·05$); 16·80 ± 2·99 versus 18·27 ± 3·17 days (IIb burns, EGF versus control, $P < 0·01$) WHR on the 5th, 7th, 9th days: 46·0%, 76·1%, 94·2% versus 38·0%, 64·2%, 84·3%, respectively (IIa burns, EGF versus control) WHR on 12th, 15th, 18th days: 57·9%, 81·3%, 93·9% versus 43·4%, 69·7%, 88·1%, respectively (IIb burns, EGF versus control)
Wang 2003	China	37/37*	23/14	33	37/37*	IIb	9·33 ± 9·54	Beginning: within 1 day of burn injury Concentration: 600 IU per cm^2 area Frequency: daily Continuing until complete wound healing occurred	WHT: 7·19 ± 1·67 versus 8·92 ± 1·78 days (EGF versus control, $P < 0·01$) The VSS scores evaluated 1 year and 4 years after wound healing are significantly lower in EGF-treated group than that in the control group
GM-CSF-treated versus control									
Liu 2011	China	58/58*	36/22	32·4	58/58*	IIb	5·2 ± 2·1	Beginning: NA Concentration: NA Frequency: every other day Continuing until complete wound healing occurred	WHT: 18·41 ± 2·47 versus 23·58 ± 3·35 days (GM-CSF versus control, $P < 0·01$)

Table 2 Continued

First author and year	Country	ITT (T/C)	Gender (M/F)	Mean age (years)	Wound number (T/C)	Burn depth (degree)	TBSA (percents)	Intervention	Outcome
Wang 2008	China	214/107	NA	NA	200/102	IIb	<50	Beginning: immediately after thorough debridement Concentration: 1 μg per cm^2 area Frequency: every other day Continuing for 4 weeks	WHR on the 8th, 14th, 20th, 28th days: 24·5%, 70·5%, 95·3%, 99·6% versus 15·1%, 51·4%, 84·6%, 97·1%, respectively (GM-CSF versus control) No side effect was observed
Yan 2012	China	32/33	41/24	20·6	45/8	IIb	<5	Beginning: NA Concentration: NA Frequency: daily Continuing until complete wound healing occurred	WHT: 12·2 ± 5·0 versus 15·5 ± 4·7 days (rhGM-CSF versus control, $P < 0·01$) Transient wound pain was reported in three cases of the GM-CSF group and five cases of the control group WHR on the 7th, 14th day: 27·7%, 85·9% versus 31·8%, 97·5%, respectively (GM-CSF versus control) No other side reaction was observed during the study
Zhang 2009	China	60/30	75/15	33·7	56/27	IIb	T: 12·4 ± 10·7 C: 16·2 ± 12·2	Beginning: NA Concentration: 1 μg per cm^2 area Frequency: every other day Continuing for 4 weeks	WHT: 14·71 ± 0·48 versus 20·48 ± 1·09 days (GM-CSF versus control, $P < 0·01$) WHR on the 14th, 20th, 28th days: 84·6%, 97·6% 100·0%, versus 44·4%, 80·2%, 96·7%, respectively (GM-CSF versus control) There were no significant differences in adverse reactions found between the experimental and the control group

EGF, epidermal growth factor; FGF, fibroblast growth factor; GM-CSF, granulocyte macrophage-colony stimulating factor; ITT, intention-to-treat; NA, data not available; T, treated group; C, control group; M, male; F, female; TBSA, total body surface area; VSS, Vancouver scar scale; IU, international unit; WHT: wound healing time; WHR: wound healing rate.
*The reference studies are self-controlled trials.

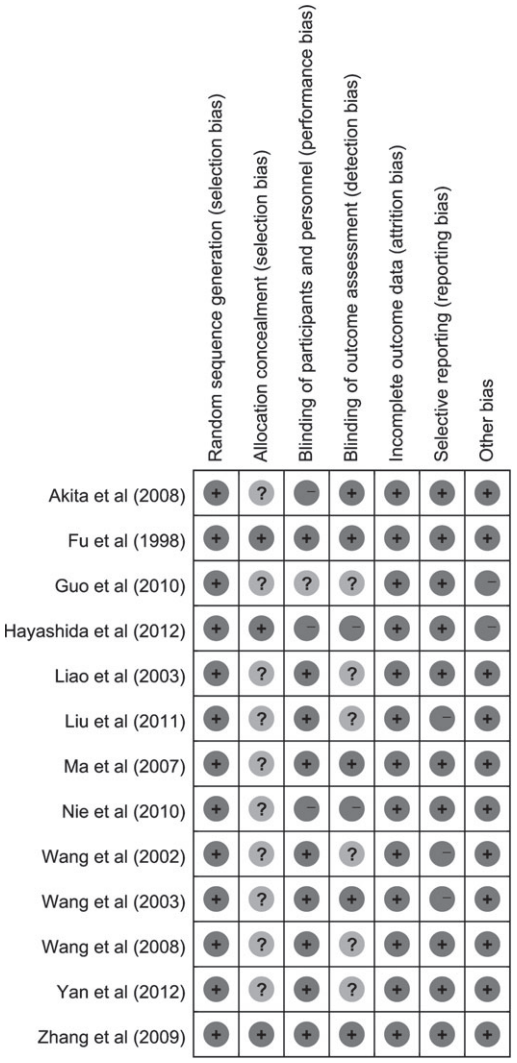

Figure 2 Overall risk of bias assessment.

Fibroblast growth factor

Add-on therapy with FGF has been examined by five RCTs comprising 885 participants with 1060 wounds (532 FGF versus 528 controls). All the five trials showed significant difference between the arms receiving FGF and control. The study by Fu *et al.* (33) further reported favourable effect of locally administered bFGF on both superficial and deep partial-thickness burns ($P = 0{\cdot}0008$ and $P = 0{\cdot}0003$, respectively). Three of the five trials documented the scarring at half to 1 year of follow-up using VSS. The studies by Akita *et al.* (34) and Hayashida *et al.* (35) favoured FGF therapy over standard wound care for less scarring ($P < 0{\cdot}01$ and $P < 0{\cdot}01$, respectively), whereas in the study by Nie *et al* (36), only a favourable trend with marginal statistical significance was presented.

A meta-analysis under the REM showed significantly shortened healing time for add-on therapy with FGF as compared with standard wound care used alone (1060 wounds, WMD = −5·02; 95% CI, −7·42 to −2·62, $P < 0{\cdot}01$) (Figure 3); significant improvement of scarring with FGF therapy was evident in terms of pigmentation (388 wounds, WMD = −0·85; 95% CI, −1·01 to −0·7, $P < 0{\cdot}01$), pliability (388 wounds, WMD = −1·09; 95% CI, −1·63 to −0·54, $P < 0{\cdot}01$), height (388 wounds, WMD = −0·83; 95% CI, −1·11 to −0·54, $P < 0{\cdot}01$) and vascularity (388 wounds, WMD = −1·01; 95% CI, −1·38 to −0·65, $P < 0{\cdot}01$) (Figure 4).

Epidermal growth factor

Add-on therapy with EGF has been examined by four RCTs comprising 387 participants with 476 wounds (240 EGF-treated versus 136 controls). Three of the four trials reported on the complete wound healing time, and all showed significant difference between the arms receiving EGF and control. Wang *et al.* (30) advocated that the healing acceleration following topical EGF use exhibited a dose-dependent manner (0·5 μg/g, 12·2 ± 1·5 days versus 10 μg/g, 9·6 ± 2·1 days versus 50 μg/g, 8·4 ± 2·3 days), and recommended 10 μg/g (400 IU/cm^2) as an optimal dose regimen with respect to cost-effectiveness and potential adverse reaction. Similar healing acceleration was achieved in the trials by Liao (32) and Guo (31) with EGF hydrogel of 40 IU/cm^2 for both superficial and deep partial-thickness burns. Study by Wang *et al.* (37) documented the scar appearance at 1 to 4 years of follow-up using VSS, and showed significant clinical benefit with the EGF treatment compared with standard wound care used alone ($P < 0{\cdot}01$).

A meta-analysis under the REM showed significantly shortened healing time for add-on therapy with EGF as compared with standard wound care used alone (402 wounds, WMD = −3·12; 95% CI, −5·13 to −1·11, $P < 0{\cdot}01$); Favourable effect of EGF was further observed in the subgroups of both superficial and deep partial-thickness burns (IIa: 238 wounds, WMD = −3·44; 95% CI, −6·59 to −0·3, $P = 0{\cdot}032$; IIb: 172 wounds, WMD = −2·61; 95% CI, −4·27 to −0·94, $P < 0{\cdot}01$) (Figure 3).

Granulocyte macrophage-colony stimulating factor

Add-on therapy with GM-CSF has been examined by four randomised, double-blind, controlled trials comprising 592 participants with 594 wounds (359 GM-CSF-treated versus 235 controls). Three of the four trials reported on the complete wound healing time, and all showed significant difference between the arms receiving GM-CSF and the control. Zhang *et al.* (41) found significantly higher reduction in wound size for GM-CSF group (94·64%) compared with that for the control group (51·85%) at the 20th day after therapy ($P < 0{\cdot}01$). Similarly, the study of Liu *et al.* (42) displayed higher reduction in wound size with GM-CSF treatment (98·36%) compared with standard wound care (68·88%) at the 10th day after therapy ($P < 0{\cdot}05$). Moreover, Liu *et al.* demonstrated that healing with GM-CSF was characterised by a more rapid growth of granulation tissue, generally observed in the wound bed at the 6th day, whereas in the control group that was not observed until day 10 (42).

A meta-analysis under the REM showed significantly shortened healing time for add-on therapy with GM-CSF as compared with standard wound care used alone (292 wounds, WMD = −5·1; 95% CI, −6·18 to −4·02, $P < 0{\cdot}01$) (Figure 3).

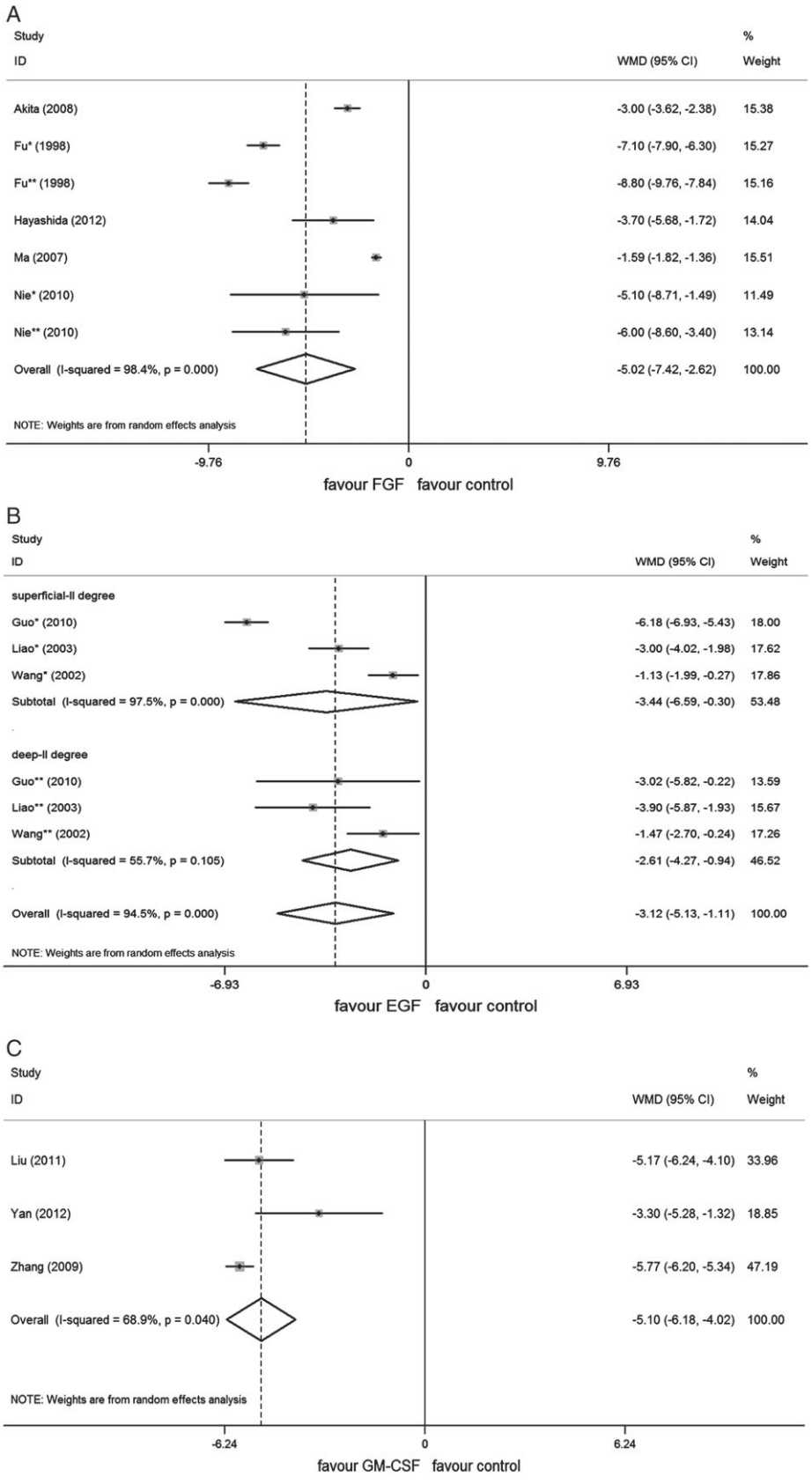

Figure 3 Forest plot depicting the meta-analysis of wound healing time between growth factors (GFs) versus control group. (A) Fibroblast growth factor (FGF), (B) epidermal growth factor (EGF), (C) granulocyte macrophage-colony stimulating factor (GM-CSF). CI, confidence interval; WMD, weighted mean difference; *, comparison of patients with IIa burns; **, comparison of patients with IIb burns.

Figure 4 Forest plot depicting the meta-analysis of Vancouver Scar Scale (VSS) scores between EGF versus control group. (A) Height, (B) pigmentation, (C) pliability, (D) vascularity. CI, confidence interval; WMD, weighted mean difference; *, comparisons of patients with IIa burns; **, comparison of patients with IIb burns.

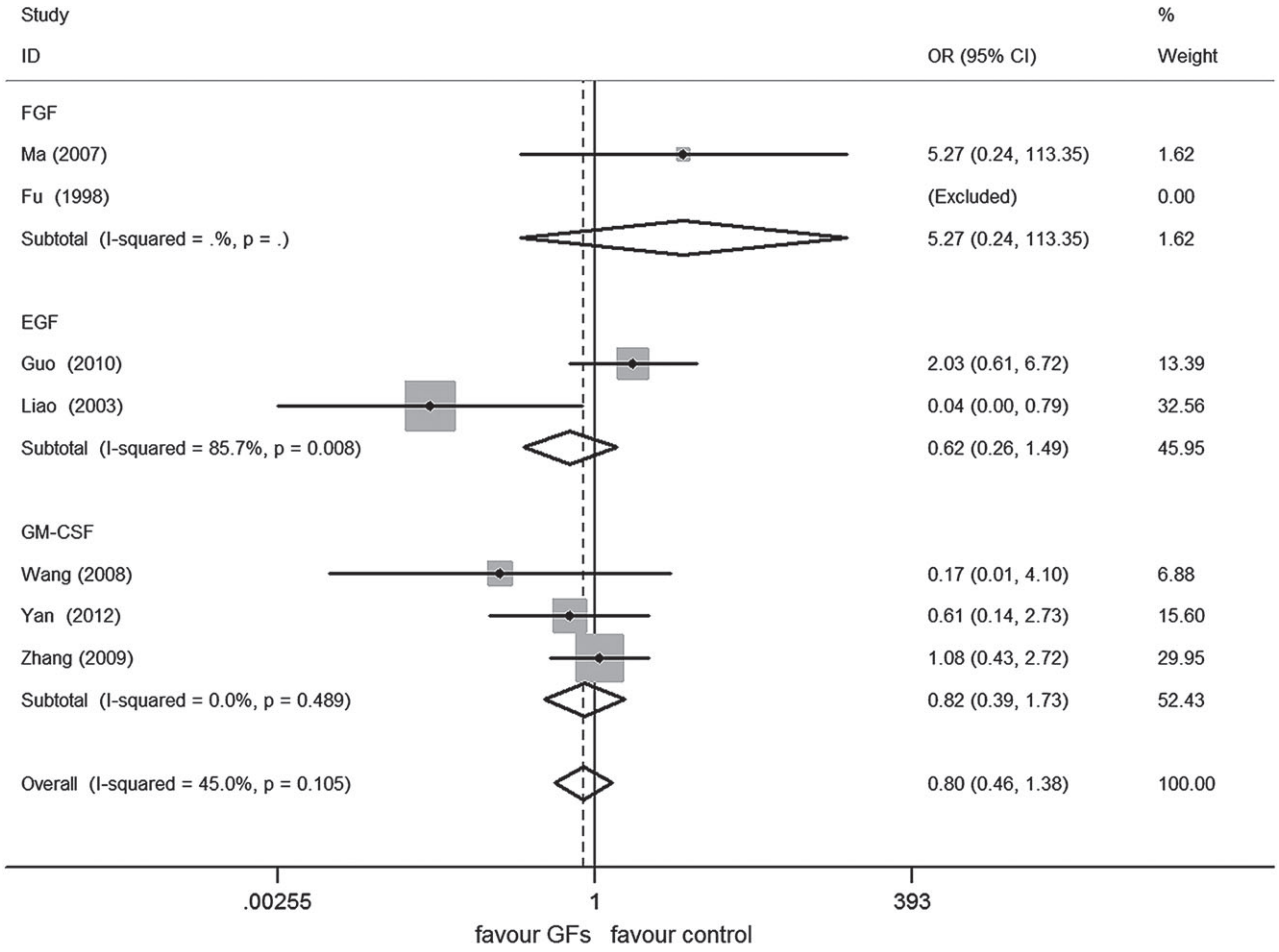

Figure 5 Forest plot depicting the meta-analysis of adverse events (AEs) between growth factors GFs versus control group. CI, confidence interval; OR, odds ratio.

Safety

AEs with GF use were evaluated in seven trials, generally, minor to mild. The incidence and profile of AEs were similar between the arm receiving GFs and control (4·6% GFs versus 4·8% Control). Non-infectious wound-edge reaction and transient local pain were the two most common AEs seen in both arms, the majority of which were relieved without further medical intervention. No severe allergic reaction, toxic side effect or systematic reaction was reported.

A meta-analysis under the FEM failed to show significant difference between the two arms on AEs (OR 0·80, 95% CI 0·46–1·38, $P = 0·427$) (Figure 5). Exclusion of any of the comparisons did not change the results.

Discussion

Analysis of the available data illustrates that GF therapy as an add-on to standard wound care is associated with consistent and significant clinical benefit for partial-thickness burn injuries. This association scarcely varied by study design, by year of publication or by subclassification of grade II burns. With respect to the primary outcome, add-on therapy with FGF, EGF and GM-CSF significantly enhances wound healing, reducing average healing time by 5·02 days ($N = 1060$, 95% CI, 2·62 to 7·42, $P < 0·01$), 3·12 days ($N = 402$, 95% CI, 1·11 to 5·13, $P < 0·01$) and 5·1 days ($N = 292$, 95% CI, 4·02 to 6·18, $P < 0·01$), respectively, as compared with standard treatment alone. With regard to the secondary outcomes, the result of the pooled analysis showed significant improvement of scarring with FGF therapy. Similar scar lightening effect was achieved in sporadic trials on EGF.

Previous reviews have demonstrated that the effect of GFs on tissue regeneration may vary by the mode of delivery. Fernandez (17) advocated that intralesional injection of EGF achieves faster wound healing and lower amputation rates than topical application in the management of severe chronic diabetic ulcer (Wagner grade III to IV), by providing better diffusion and bioavailability of the active agent to the deep layers of the wounds, and the related adverse reaction remains mild to moderate. Still, Lee (43) demonstrated that either local injection or topical application of GFs may lead to side effects owing to the extremely high initial concentration, and conversely may not allow a wide enough time-frame for sufficient levels of the factors to be sensed by the target tissue, owing to GF's rapid degradation and clearance. However, in this systematic review,

our finding suggests that FGF, EGF and GM-CSF are effective and safe for topical use.

The consistent clinical efficacy of GFs presented by this review may be explained by the biological characteristics of the GFs we assessed and the nature of the burn wound. Depth of partial-thickness burn is limited to the papillary dermis for grade IIa burns and to the reticular dermis for grade IIb burns, with the majority of hypodermal structures such as subcutaneous adipose tissue, connective tissue and blood vessels spared underneath the wound bed. FGF and EGF are direct mitogens for endothelial cells and dermal fibroblasts, and have been shown to accelerate reepithelialisation, increase proliferation and tensile strength of healed dermis (44–48). GM-CSF works directly on the keratinocyte and endothelial cell, and indirectly by mediating the production and release of other cytokines such as interleukin-6, interleukin-2 and interferon-γ (49,50). Wound bed of partial-thickness burns provides better nourishment and waste removal for the residual and regenerative cellular constituents of the skin than burns of higher grade or other deep wounds such as chronic diabetic ulcers and deep pressure ulcer, maintaining better cellular sensitivity to these GFs (51). Additionally, the high-frequency strategy for local GF application may likewise assist against the impairment of biological activity of the agents.

In the overview for safety, our findings failed to identify inferiority of GF therapy to the control arms. The results were identical with most previous studies (52–54). However, lack of long-term AEs is highlighted in most trials, that the maximum follow-up duration of 4 weeks falls short to achieve definitive safety conclusions for GFs use. Considering mechanisms whereby most GFs stimulate tissue repair are similar to ones involved in tumours development (55), further high-quality trials of large-scale and long-term follow-up would be important to confirm and strengthen our findings.

Our findings showed methodological flaws in study design of the current trials. As a common phenomenon, the efficacy of GFs was examined at various concentrations varying across the trials. A better understanding of dosage regimen for clinician is of great importance to achieve maximum patient's benefit, cost-effectiveness and minimum risk of adverse reaction. Regretfully, there were no studies specifically designed to address the issue of optimal dosage for GFs use, except for one study on EGF (30), which recommended that dosage regimen was nevertheless inadequately powered for lack of supporting evidence from other trials. There is methodological variation for other aspects of treatment that may influence wound healing. In terms of wound management, different types of wound dressing were alternately used among trials, antibiotics therapies are likewise inconsistently used (varying in administration route, timing and duration). In addition, the reporting of outcomes, especially AEs, has been variable in definition and surveillance. Although the treatment benefit seen is not in question with these variations, for the same criteria were applied to both arms of the trials, the variations may still be potential source of bias, posing challenges to drawing clear conclusions from the observations made here.

Of note, there are three RCTs (30,38,39) declaring conflict of interest due to affiliation with biologics manufacturers. Researches with such ties are more likely to contribute to conditions that are conducive to the relatively successful outcomes of patients receiving GFs products.

Conclusion

Results of the present systematic review and meta-analysis suggest that GF therapy could be an effective and safe add-on to standard wound care for partial-thickness burns. Noticing that current evidence is not powerful enough with limitations, future work should focus on well-designed prospective studies, consistent with therapeutic regimen and reporting outcomes. In addition, financial support from the medical industry should be avoided, and longer follow-up data should be presented before any definitive conclusions to be established.

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Supporting Information

The following supporting information is available for this article:

Figure S1. Begg's funnel plot of enrolled studies evaluating wound healing time with pseudo 95% confidence limits. (A) FGF, (B) EGF, (C) GM-CSF. WMD, weighted mean difference.
Figure S2. Begg's funnel plot of enrolled studies evaluating adverse events (AEs) (A) and total body surface area (TBSA) (B) with pseudo 95% confidence limits. WMD, weighted mean difference; OR, odds ratio.
Figure S3. Begg's funnel plot of enrolled studies evaluating Vancouver Scar Scale (VSS) scores with pseudo 95% confidence limits. (A) Height, (B) pigmentation, (C) pliability, (D) vascularity. WMD, weighted mean difference.
Figure S4. Forest plot depicting the meta-analysis of total body surface area (TBSA) between GF patients versus control group. CI, confidence interval; WMD, weighted mean difference; *, comparison of patients with IIa burns; **, comparison of patients with IIb burns.

Additional Supporting Information may be found in the online version of this article.

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