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Research Article

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The clinical effectiveness and safety of using epidermal growth factor, fibroblast growth factor and granulocyte-macrophage colony stimulating factor as therapeutics in acute skin wound healing: a systematic review and meta-analysis

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Abstract

Background: Promoting wound healing is crucial to restore the vital barrier function of injured skin. Growth factor products including epidermal growth factor (EGF), fibroblast growth factor (FGF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been used for decades although no systematic evaluation exists regarding their effectiveness and safety issues in treating acute skin wounds. This has resulted in a lack of guidelines and standards for proper application regimes. Therefore, this systematic review and meta-analysis was performed to critically evaluate the effectiveness and safety of these growth factors on skin acute wounds and provide guidelines for application regimes.

Methods: We searched PubMed/Medline (1980–2020), Cochrane Library (1980–2020), Cochrane CENTRAL (from establishment to 2020), ClinicalTrials.gov (from establishment to 2020), Chinese Journal Full-text Database (CNKI, 1994–2020), China Biology Medicine disc (CBM, 1978–2019), Chinese Scientific Journal Database (VIP, 1989–2020) and Wanfang Database (WFDATA, 1980–2019). Randomized controlled trials (RCTs), quasi-RCTs and controlled clinical trials treating patients with acute skin wounds from various causes and with those available growth factors were included.

Results: A total of 7573 papers were identified through database searching; 229 papers including 281 studies were kept after final screening. Administering growth factors significantly shortened the healing time of acute skin wounds, including superficial burn injuries [mean difference (MD) = −3.02; 95% confidence interval (CI):−3.31 ∼ −2.74; $p < 0.00001$], deep burn injuries (MD = −5.63; 95% CI:−7.10 ∼ −4.17; $p < 0.00001$), traumata and surgical wounds (MD = −4.50; 95%

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CI:−5.55 ∼ −3.44; $p < 0.00001$). Growth factors increased the healing rate of acute skin wounds and decreased scar scores. The incidence of adverse reactions was lower in the growth factor treatment group than in the non-growth factor group.
Conclusions: The studied growth factors not only are effective and safe for managing acute skin wounds, but also accelerate their healing with no severe adverse reactions.

Key words: Growth factors, Skin wounds, Meta-analysis, Wound healing

Highlights

- This study is the first to comprehensively evaluate the effectiveness and safety of using growth factors as therapeutics in acute skin wounds healing.
- Compared with non-growth factor treatment, administering growth factors significantly shortened the healing time while increasing the healing rate of acute skin wounds with lower scar scores and fewer adverse reactions.

Background

Skin maintains internal homeostasis and provides a barrier between our body and the outside environment [1]. Acute skin wounds break the barrier and expose the body to the risk of pathogen infections and fluid losses. Therefore, restoring skin integrity as soon as possible after wounding is the body's most effective way to restore the environment's balance, fight infections and prevent fluid and electrolyte disturbances from occurring. The speed of wound healing is of essential importance and can impact on the patient's prognosis [2].

Several factors can influence the speed of wound healing, such as the growth factors secreted by activated local cells. Numerous studies have recognized and elaborated upon growth factors' crucial roles in advancing angiogenesis, re-epithelialization, granulation tissue formation and inflammatory response regulation [3]. Until now, the growth factors reported to promote wound healing mainly include vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), transforming growth factor-β1(TGF-β1), epidermal growth factors (EGFs), granulocyte-macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), etc. [3–6].

In 1971, Frati and Scarpa reported the treatment of mouse burns with EGF [7]. The first human recombinant FGF-2 was reported in 1988 [8]. In 1989, Brown *et al*. reported in the *New England Journal of Medicine* that epidermal growth factor significantly accelerated the rate of healing of partial thickness skin wounds in a randomized clinical trial [9]. The development of growth factor products targeted at promoting wound healing has been thriving ever since and the clinical application of growth factors has become popular. In 1998, Fu *et al*. reported the result of a randomized placebo-controlled trial investigating the effect of recombinant bovine basic fibroblast growth factor (rbFGF) on burns healing. The study showed that rbFGF effectively decreased the time and improved the quality of healing. These favorable results started a wider trend of using growth factors in wound management [10]. In 2007, Ma *et al*. reported the use of recombinant human acidic FGF (rh-aFGF) for treating deep partial-thickness burns and skin graft donor site through a randomized, multicenter, double-blind and placebo-controlled trial. The study demonstrated that rh-aFGF can promote the healing of both burn wounds and skin graft donor sites [11], which further strengthened the evidence of applying growth factor products to promote acute wound healing, including both burns and surgical wounds.

Currently, EGF, bFGF, aFGF and GM-CSF are approved growth factor products for use on acute skin wounds. During the past decades, the therapeutic use of these growth factors in acute wounds management has gradually become a customary practice in China, however, controversies have raged about the benefits and safety of the clinical implementation of distinct kinds of growth factor products. It is known that acute wounds naturally hold plenty of growth factors, which can stimulate cell proliferation and matrix production at the wound bed. Whether the growth factor receptors are saturated prior to the application of more growth factors to acute wounds is unknown. Secondly, deep acute wounds usually heal with hypertrophic scars. It is still unclear whether deep acute wounds heal with more (or less) severe scars under the use of growth factors. Moreover, in light of the economic costs and possible side-effects (such as carcinogenesis) of high local/systemic growth factor levels, it is unclear whether the practice of using exogenous growth factors for the therapy of acute wounds is a real necessity. In addition, whether growth factor treatments provide true benefits remains uncertain given their instability and short *in vivo* half-life [4,12,13].

Notably, a systematic evaluation of the effectiveness and safety of the available growth factor products used for acute skin wound therapy is missing. There is still the need to investigate whether the routine administration strategies used in clinical treatments suffice to guarantee the growth factor products' benefits. To address these issues, we performed the present systematic review and meta-analysis to assess the clinical effectiveness and safety of all currently clinically available growth factor products in treating acute skin wounds as compared to non-growth factor treatments. The results of

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Table 1. Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Type of study	Randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials	Review; case study; mechanism study; research; development; preparation and storage of materials; animal experiment; marketing strategy; editorials; news; and newly registered clinical trials without any reported results
Participants	Patients with acute skin wounds from various causes (e.g. burns, trauma, surgery, etc.)	Patients with deep burns (third- and fourth-degree burns), bone wounds, mucosal wounds
Interventions	Treatment with growth factors (epidermal growth factor, basic fibroblast growth, acidic fibroblast growth factor. granulocyte-macrophage colony stimulating factor)	Growth factor not used for wound treatment
Controls	Any other non-growth factor treatment; placebo; blank control	Comparison before and after their administration of the clinical results among different growth factors
Outcomes	Effectiveness indicators including wound healing time; wound healing rate; infection rate; pain score; pain intensity level; etc. Safety indicators referring to the adverse reactions rate, including skin allergy and pruritus	Long-term follow-up results such as related to quality of life. The growth factor levels set as treatment outcomes

this study will supply the evidence to strengthen the future therapeutic use of growth factors in clinical settings.

Methods

This systematic review was conducted according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [14]. It was based on the planned Participants, Intervention, Control, Outcome and Study design (PICOS) elements.

Search strategy

The searched databases included: PubMed/Medline (1980–2020); Cochrane Library (1980–2020); Cochrane CENTRAL (from establishment to 2020); ClinicalTrials.gov (from establishment to 2020); Chinese Journal Full-text Database (CNKI, 1994–2020); China Biology Medicine disc (CBM, 1978–2019); Chinese Scientific Journal Database (VIP, 1989–2020); and Wanfang Database (WFDATA, 1980–2019). With the combination of subject words and free words, the search terms included two categories: (1) 'epidermal growth factor', 'basic fibroblast growth factor', 'acid fibroblast growth factor', and 'granulocyte-macrophage colony stimulating factor'; and (2) 'trauma', 'wound', 'burn', and 'surgery'. The logical relationship was created with 'OR' and 'AND'; and the search formula was thereafter developed according to the characteristics of the different databases. For example, the search strategy for PubMed was: ((epidermal growth factor OR EGF) OR (basic fibroblast growth factor OR bFGF) OR (acid fibroblast growth factor OR aFGF) OR (granulocyte-macrophage colony stimulating factor OR GM-CSF)) AND ((superficial OR surgical OR burn) AND wounds)). A pre-retrieval process improved the searches strategy. In addition, we conducted a manual search of unpublished studies and conference materials, tracking also the references of the included literature. For the analysis we included studies reported in both Chinese and English.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are listed in Table 1.

Study selection Two researchers independently read the titles and abstracts to exclude the literature that did not meet the inclusion criteria. As a further safeguard, the full texts of the literature that might have met the inclusion criteria were read and evaluated. At the same time, the following information was extracted: author, publication date, research type, characteristics of research objects, sample number, loss of or withdrawal from interview, intervention measures and measurement indicators, and more. For multiple studies published in the same literature, the required data were acquired according to their research contents. In the case of repetitive reports, the study included only the latest or the most comprehensive ones.

Quality evaluation The quality of the included research method was evaluated via Jadad's scale, which is an internationally recognized clinical trial scoring standard, as it includes data about random method, allocation concealment, blind use, loss of follow-up, withdrawal and outcome. The score range was 1–5 points, including 1–2 points for lower quality and 3–5 points for higher quality.

Meta-analysis The RevMan5.4 software recommended by Cochrane Collaboration served for meta-analysis. Subgroups considered types of wounds and outcome variables. The relative risk (RR) consisted of the joint effect size for the counting data, while the weighted mean difference (WMD) was used for the measurement data. All effects were conveyed with their 95% confidence interval (CI). Results heterogeneity

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was assessed by the chi square test. When the homogeneity of each study was statistically significant ($p > 0.1$, $I^2 < 50\%$), the fixed effect model was used; otherwise, the random effect model was used. Subgroup results from single studies were noted down.

Results

Study selection and characteristics

In total, our preliminary screening selected 7573 papers. After screening titles, abstracts and full-texts (Figure 1) we kept 229 papers including 281 studies, which consisted of 207 randomized controlled trials (RCTs) and 74 clinical controlled trials (CCTs) with a total of 30 562 patients. The basic characteristics of the included studies and the results of the methodological quality evaluations are shown in Table 2 [10,11,15–241]. All the growth factors in these studies were applied topically. In all studies, the patients' basic characteristics were comparable ($p > 0.05$) between intervention groups and control groups.

Healing time comparison of second-degree burn wounds

A total of 76 studies [10,15–25,27–55,57–86,144,230,234,236,237] enrolling 8915 cases compared the healing time of superficial second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the presence of statistical heterogeneity ($p < 0.00001$; $I^2 = 88\%$). Therefore, the random effect model was used for meta-analysis (Figure 2). The results showed that the

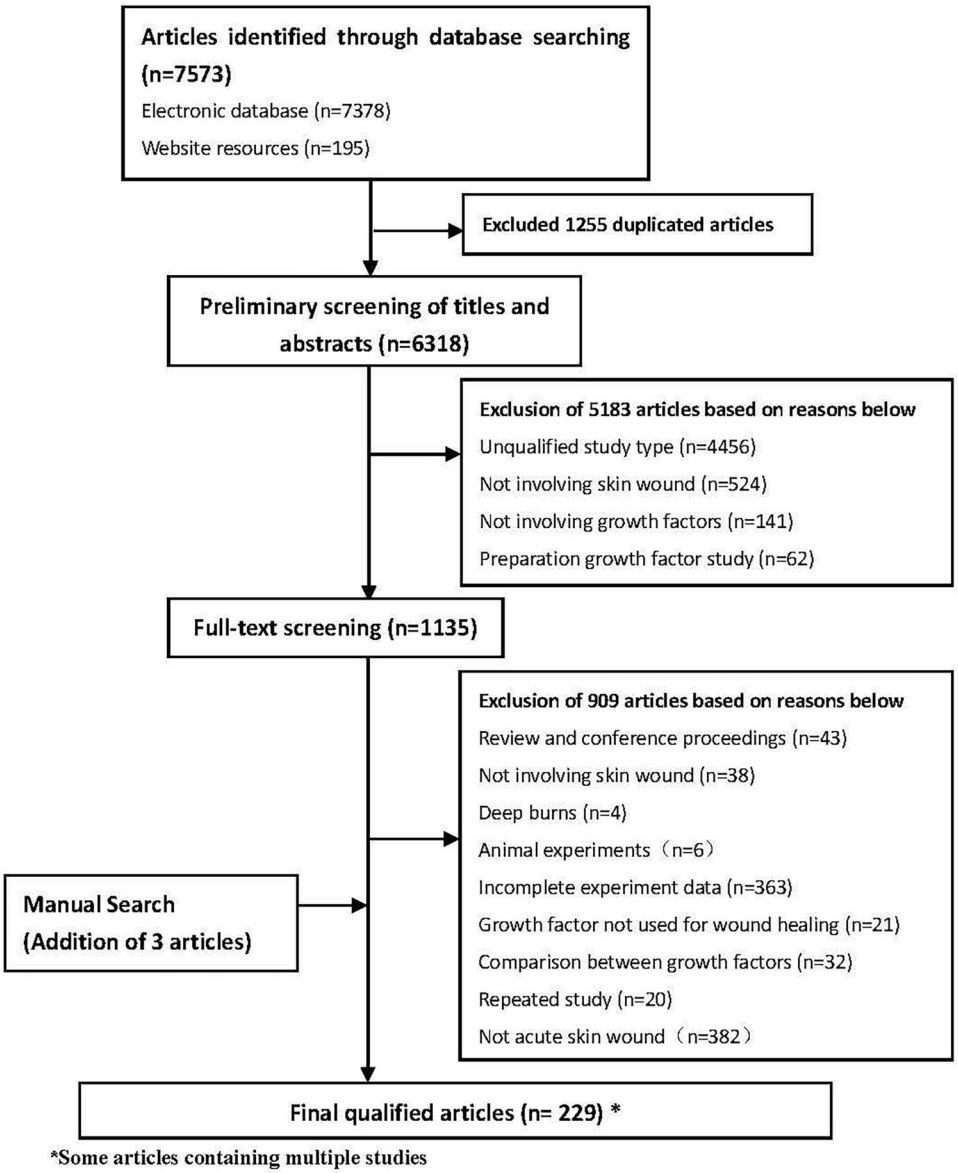


Figure 1. PRISMA flow diagram for inclusion or exclusion of studies used for this systematic review. *PRISMA* Preferred Reporting Items for Systematic Reviewsand Meta-analyses

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Table 2. Characteristics of included studies

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Pan *et al.* [15]	2009	CCT	China	Superficial Second-degree Burns	rhEGF+RI + 1%SD-Ag Cream(n = 64)	1%SD-Ag Cream(n = 64)	3
Wu *et al.* [16]	2013	CCT	China	Superficial Second-degree Burns	rhFGF+Zn-SD Gel(n = 19)	Zn-SD Gel(n = 19)	1
Guo *et al.* [17]	2017	RCT	China	Superficial Second-degree Burns	Er Huang Ointment +rhGM-CSF Gel(n = 49)	Ag-SD Cream(n = 49)	2
Ma *et al.* [18]	2014	CCT	China	Superficial Second-degree Burns	VSD + rb-bFGF(n = 9)	VSD(n = 9)	1
Huang *et al.* [19]	2004	RCT	China	Superficial Second-degree Burns	1% SD-Ag Cream+rhEGF(n = 30)	1% SD-Ag Cream(n = 26)	2
Li *et al.* [20]	2002	RCT	China	Superficial Second-degree Burns	rbFGF(n = 566)	0.9% NS(n = 167)	2
Chen *et al.* [21]	2001	RCT	China	Superficial Second-degree Burns	bFGF(n = 30)	SD-Ag Cream(n = 30)	2
Gao *et al.* [22]	2004	CCT	China	Superficial Second-degree Burns	bFGF(n = 15)	Blank(n = 15)	1
Huo *et al.* [23]	1996	CCT	China	Superficial Second-degree Burns	bFGF Spray(n = 29)	Blank(n = 29)	1
Li *et al.* [24]	2004	CCT	China	Superficial Second-degree Burns	bFGF(n = 191)	Blank(n = 191)	1
Hu *et al.* [25]	2012	RCT	China	Superficial Second-degree Burns	GM-CSF + AD-Ag Cream(n = 42)	SD-Ag Cream(n = 42)	2
Gong [26]	2007	RCT	China	Superficial Second-degree Burns	rhEGF Spray(n = 30)	Standard care(n = 30)	2
Luo [27]	2014	RCT	China	Superficial Second-degree Burns	1% Povidone iodine +rb-bFGF(n = 5)	1% Povidone iodine(n = 5)	2
Liao *et al.* [28]	1996	CCT	China	Superficial Second-degree Burns	EGF +1% SD-Ag(n = 48)	1% SD-Ag(n = 48)	2
Guo *et al.* [29]	2009	RCT	China	Superficial Second-degree Burns	rhEGF Hydrogel +Vaseline gauze(n = 32)	Vaseline gauze(n = 32)	2
Liu *et al.* [30]	2001	RCT	China	Superficial Second-degree Burns	rh-bFGF +1% SD-Ag(n = 23)	1% SD-Ag(n = 23)	1
Liu *et al.* [31]	2012	CCT	China	Superficial Second-degree Burns	rh-bFGF+1% SD-Ag(n = 12)	1% SD-Ag(n = 13)	1
Gao *et al.* [32]	2019	CCT	China	Superficial Second-degree Burns	rh-EGF Spray+Burn Cream(n = 90)	Povidone iodine(n = 60)	1
Li [33]	2003	RCT	China	Superficial Second-degree Burns	rhEGF+1% SD-Ag(n = 32)	1% SD-Ag(n = 32)	2
Liu *et al.* [34]	2005	CCT	China	Superficial Second-degree Burns	bFGF(n = 149)	Blank(n = 149)	1
Lin *et al.* [35]	2014	RCT	China	Superficial Second-degree Burns	rb-bFGF Gel(n = 37)	Blank(n = 36)	3
Guo *et al.* [36]	2002	CCT	China	Superficial Second-degree Burns	rb-bFGF Lyophilized powder(n = 566)	Standard Care(n = 167)	1
Fan *et al.* [37]	2018	RCT	China	Superficial Second-degree Burns	rb-bFGF Gel + Vaseline gauze(n = 45)	Vaseline gauze(n = 45)	2
Meng *et al.* [38]	2018	RCT	China	Superficial Second-degree Burns	rb-bFGF(n = 63)	Standard care(n = 63)	3
Guo *et al.* [39]	2010	RCT	China	Superficial Second-degree Burns	SD-Ag Cream+ rhEGF(n = 20)	SD-Ag cream(n = 19)	2
Fang *et al.* [40]	2014	RCT	China	Superficial Second-degree Burns	rhEGF(n = 35)	Blank(n = 37)	2
Liang *et al.* [41]	2007	CCT	China	Superficial Second-degree Burns	rhEGF(n = 60)	Normal saline(n = 60)	3
Liang *et al.* [42]	2006	CCT	China	Superficial Second-degree Burns	rhEGF(n = 60)	Normal saline(n = 60)	3
Huo *et al.* [43]	2001	CCT	China	Superficial Second-degree Burns	rhEGF+Topical antibiotics(n = 26)	Topical antibiotics(n = 26)	1

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Fu *et al.* [44]	2003	CCT	China	Superficial Second-degree Burns	rhEGF(n = 51)	Blank(n = 51)	1
Liao *et al.* [45]	2003	RCT	China	Superficial Second-degree Burns	rhEGF+SD-Ag(n = 39)	1%SD-Ag cream(n = 39)	2
Li *et al.* [46]	2004	RCT	China	Superficial Second-degree Burns	rhEGF+Wuhuang oil(n = 20)	Wuhuang oil(n = 25)	2
Liu *et al.* [47]	2005	RCT	China	Superficial Second-degree Burns	rh-bFGF Lyophilized powder +1% SD-Ag(n = 23)	1% SD-Ag(n = 23)	2
Chao *et al.* [48]	2003	RCT	China	Superficial Second-degree Burns	rh-bFGF+ Vaseline gauze(n = 30)	Vaseline gauze(n = 30)	2
Guo [49]	2006	RCT	China	Superficial Second-degree Burns	rh-bFGF+1% SD-A(n = 24)	1% SD-Ag(n = 25)	2
Liu [50]	2014	RCT	China	Superficial Second-degree Burns	rh-bFGF(n = 6)	Standard care(n = 6)	2
Chen [51]	2014	CCT	China	Superficial Second-degree Burns	rh-aFGF(n = 50)	Normal saline(n = 50)	1
Sun *et al.* [52]	2011	RCT	China	Superficial Second-degree Burns	rh-aFGF(n = 15)	Normal saline(n = 15)	1
Qiu *et al.* [53]	2010	RCT	China	Superficial Second-degree Burns	bFGF+Bashi Cream(n = 48)	Vaseline gauze(n = 45)	2
Sun *et al.* [54]	2018	RCT	China	Superficial Second-degree Burns	rh-bFGF+Chitosan(n = 40)	Chitosan(n = 40)	3
Tan *et al.* [55]	2000	CCT	China	Superficial Second-degree Burns	bFGF+Topical antibiotics(n = 46)	Topical antibiotics(n = 46)	1
Song *et al.* [56]	2003	CCT	China	Superficial Second-degree Burns	Topical antibiotics+bFGF(n = 16)	Topical antibiotics(n = 18)	1
Tong *et al.* [57]	2004	CCT	China	Superficial Second-degree Burns	rhEGF(n = 30)	0.5% Complex iodine(n = 41)	1
Shi [58]	2019	RCT	China	Superficial Second-degree Burns	Nano-Ag + rh-EGF(n = 25)	Nano-Ag(n = 26)	3
Sun *et al.* [59]	2015	RCT	China	Superficial Second-degree Burns	aFGF(n = 21)	SD-Ag(n = 25)	3
Tan *et al.* [60]	2001	RCT	China	Superficial Second-degree Burns	rhEGF+5%SD-Ag(n = 51)	5%SD-Ag(n = 51)	2
Wang *et al.* [61]	2004	RCT	China	Superficial Second-degree Burns	rhEGF(n = 30)	Normal saline(n = 30)	2
Yang *et al.* [62]	2000	CCT	China	Superficial Second-degree Burns	bFGF(n = 80)	Blank(n = 80)	1
Wang *et al.* [63]	2000	CCT	China	Superficial Second-degree Burns	bFGF(n = 14)	Blank(n = 14)	1
Ye *et al.* [64]	2008	RCT	China	Superficial Second-degree Burns	rh-EGF + SD-Ag(n = 30)	SD-Ag(n = 30)	2
Wang *et al.* [65]	2010	RCT	China	Superficial Second-degree Burns	rh-EGF + Nano-Ag(n = 40)	0.5% PVP-I(n = 38)	2
Xiong *et al.* [66]	2010	CCT	China	Superficial Second-degree Burns	rh-EGF + Amnion(n = 15)	Amnion(n = 15)	1
Wang *et al.* [67]	2009	CCT	China	Superficial Second-degree Burns	rh-bFGF +Vaseline gauze(n = 31)	Vaseline gauze(n = 31)	1
Xiong [68]	2019	RCT	China	Superficial Second-degree Burns	rb-bFGF +SD-Ag(n = 60)	SD-Ag(n = 60)	2
Wang *et al.* [69]	2002	RCT	China	Superficial Second-degree Burns	rh-EGF Spray + SD-Ag(n = 206)	SD-Ag(n = 206)	3
Xu *et al.* [70]	2016	RCT	China	Superficial Second-degree Burns	rb-bFGF Hydrogel(n = 49)	Standard care(n = 51)	2
Xiong [71]	2018	RCT	China	Superficial Second-degree Burns	rh-EGF Hydrogel(n = 46)	Zhenshi Burn cream(n = 46)	2
Yang *et al.* [72]	2002	RCT	China	Superficial Second-degree Burns	rh-bFGF+SD-Ag(n = 11)	SD-Ag(n = 11)	2

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Wang *et al.* [73]	2003	CCT	China	Superficial Second-degree Burns	rh-bFGF(n = 12)	Normal saline(n = 12)	1
Zhou *et al.* [74]	1999	RCT	China	Superficial Second-degree Burns	bFGF+Vaseline gauze(n = 20)	Vaseline gauze(n = 20)	2
Zhou *et al.* [75]	2005	RCT	China	Superficial Second-degree Burns	bFGF(n = 72)	Vaseline gauze(n = 80)	2
Zhan [76]	2015	RCT	China	Superficial Second-degree Burns	Nano-Ag + rh-EGF(n = 20)	Nano-Ag(n = 18)	2
Zhang *et al.* [77]	2014	RCT	China	Superficial Second-degree Burns	rb-bFGF Hydrogel(n = 37)	Topical antibiotics(n = 37)	2
Zhang *et al.* [78]	2001	CCT	China	Superficial Second-degree Burns	rb-bFGF(n = 31)	Blank(n = 31)	1
Zhao *et al.* [79]	2015	RCT	China	Superficial Second-degree Burns	rhEGF+Nano-Ag(n = 44)	Nano-Ag(n = 44)	3
Zou *et al.* [80]	2017	RCT	China	Superficial Second-degree Burns	rhEGF+Nano-Ag(n = 29)	Chlorhexidine(n = 27)	3
Zhou *et al.* [81]	2001	RCT	China	Superficial Second-degree Burns	rhEGF+SD-Ag Cream(n = 95)	SD-Ag Cream(n = 67)	3
Zhang [82]	2012	RCT	China	Superficial Second-degree Burns	rhEGF+ SD-Ag Cream(n = 30)	SD-Ag Cream(n = 30)	2
Zhen *et al.* [83]	2003	RCT	China	Superficial Second-degree Burns	rhEGF+ SD-Ag Cream(n = 100)	SD-Ag Cream(n = 100)	2
Zhou *et al.* [84]	2014	CCT	China	Superficial Second-degree Burns	rh-aFGF+ Hydrogen peroxide solution(n = 50)	Hydrogen peroxide solution(n = 50)	1
Wu *et al.* [85]	2015	RCT	China	Superficial Second-degree Burns	bFGF+ Hydrocolloid dressing(n = 45)	Vaseline gauze(n = 43)	3
Lu [86]	2002	CCT	China	Superficial Second-degree Burns	bFGF+1% SD-Ag Cream(n = 53)	1% SD-Ag Cream(n = 61)	1
Pan *et al.* [15]	2009	CCT	China	Deep Second-degree Burns	rhEGF+Insulin+1% SD-Ag(n = 56)	1% SD-Ag(n = 56)	3
Hu [87]	2013	RCT	China	Deep Second-degree Burns	bFGF Hydrogel+ Far infrared therapy(n = 22)	PVP-I Vaseline gauze + SD-Ag(n = 21)	3
Huang *et al.* [88]	2012	RCT	China	Deep Second-degree Burns	Local oxygen therapy +bFGF(n = 53)	Local oxygen therapy(n = 53)	2
Liu *et al.* [89]	2011	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 29)	Vaseline gauze(n = 29)	3
Hong *et al.* [16]	2013	CCT	China	Deep Second-degree Burns	bFGF+SD-Zn(n = 15)	SD-Zn(n = 15)	1
He *et al.* [90]	2018	RCT	China	Deep Second-degree Burns	Compound polymyxin B + EGF(n = 60)	Compound polymyxin B(n = 60)	3
Cheng *et al.* [91]	2011	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel+ Fulin honey(n = 56)	Placebo+SD-Ag Cream(n = 56)	4
Huang *et al.* [19]	2004	RCT	China	Deep Second-degree Burns	1% SD-Ag + rhEGF(n = 21)	1% SD-Ag (n = 20)	2
Li *et al.*n [20]	2002	RCT	China	Deep Second-degree Burns	rbFGF(n = 354)	Normal saline(n = 142)	2
Chen *et al.* [21]	2001	RCT	China	Deep Second-degree Burns	bFGF (n = 30)	SD-Ag Cream (n = 30)	2
Gao *et al.* [22]	2004	CCT	China	Deep Second-degree Burns	bFGF(n = 9)	Blank(n = 9)	1
Huo *et al.* [23]	1996	CCT	China	Deep Second-degree Burns	bFGF+1% SD-Ag Cream(n = 89)	1%1% SD-Ag Cream(n = 89)	1

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Li *et al.* [24]	2004	CCT	China	Deep Second-degree Burns	bFGF(n = 54)	Blank(n = 54)	1
Chen *et al.* [92]	2013	RCT	China	Deep Second-degree Burns	Collegen+rh-EGF Hydrogel(n = 44)	SD-Ag(n = 44)	2
Chen *et al.* [93]	2012	RCT	China	Deep Second-degree Burns	MEBO +bFGF(n = 66)	MEBO(n = 69)	2
Liao *et al.* [94]	2018	RCT	China	Deep Second-degree Burns	Nano-Ag + rb-bFGF(n = 48)	Nano-Ag(n = 48)	3
Li *et al.* [95]	2015	RCT	China	Deep Second-degree Burns	Nano-Ag + rhEGF Hydrogel(n = 48)	Nano-Ag(n = 48)	1
Liao *et al.* [28]	1996	CCT	China	Deep Second-degree Burns	EGF(n = 32)	Normal saline(n = 20)	2
Han [96]	2018	RCT	China	Deep Second-degree Burns	rh-bFGF(n = 35)	Antibacterial dressing(n = 35)	3
Lin *et al.* [97]	2017	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 50)	1%SD-Ag + Vaseline gauze(n = 50)	3
Zeng [98]	2012	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 50)	PVP-I(n = 50)	3
Li [99]	2014	RCT	China	Deep Second-degree Burns	Insulin+rh-aFGF(n = 29)	Insulin(n = 29)	2
Meng *et al.* [100]	2005	RCT	China	Deep Second-degree Burns	rh-EGF+ SD-Ag(n = 56)	SD-Ag(n = 42)	2
Liu *et al.* [30]	2001	RCT	China	Deep Second-degree Burns	rh-bFGF+1% SD-Ag(n = 39)	1% SD-Ag(n = 39)	1
Liu *et al.* [31]	2012	CCT	China	Deep Second-degree Burns	rh-bFGF(n = 32)	1% SD-Ag(n = 35)	1
Gao *et al.* [32]	2019	CCT	China	Deep Second-degree Burns	rh-EGF(n = 153)	PVD-I(n = 147)	1
Liu *et al.* [34]	2005	CCT	China	Deep Second-degree Burns	bFGF(n = 399)	Blank(n = 399)	1
Lin *et al.* [35]	2014	RCT	China	Deep Second-degree Burns	rb-bFGF(n = 23)	PVD-I(n = 24)	3
Guo *et al.* [36]	2002	CCT	China	Deep Second-degree Burns	rb-bFGF(n = 354)	Standard care(n = 142)	1
Meng *et al.* [38]	2018	RCT	China	Deep Second-degree Burns	rb-bFGF(n = 28)	PVD-I(n = 30)	3
Guo *et al.* [39]	2010	RCT	China	Deep Second-degree Burns	SD-Ag + rhEGF(n = 20)	SD-Ag(n = 21)	2
Fang *et al.* [40]	2014	RCT	China	Deep Second-degree Burns	rhEGF(n = 32)	Blank(n = 30)	2
Liang *et al.* [41]	2007	CCT	China	Deep Second-degree Burns	rh-EGF(n = 60)	Normal saline(n = 60)	3
Liang *et al.* [42]	2006	CCT	China	Deep Second-degree Burns	rhEGF(n = 60)	Normal saline(n = 60)	3
Huo *et al.* [43]	2001	CCT	China	Deep Second-degree Burns	rhEGF(n = 16)	Normal saline(n = 16)	1
Han *et al.* [101]	2017	RCT	China	Deep Second-degree Burns	rhEGF+SD-Zn Gel(n = 34)	SD-Zn Gel(n = 34)	3
Chen *et al.* [102]	2017	CCT	China	Deep Second-degree Burns	rhEGF+ Mupirocin ointment(n = 300)	MEBO(n = 300)	1
Li [103]	2016	RCT	China	Deep Second-degree Burns	rhEGF Hydrogel(n = 32)	SD-Ag(n = 32)	2
Hua [104]	2019	RCT	China	Deep Second-degree Burns	rhEGF(n = 50)	MEBO(n = 50)	3
Fu *et al.* [44]	2003	CCT	China	Deep Second-degree Burns	rhEGF(n = 28)	Blank(n = 28)	1
Liao *et al.* [45]	2003	RCT	China	Deep Second-degree Burns	rhEGF(n = 21)	1% SD-Ag Cream(n = 21)	2
Li *et al.* [46]	2004	RCT	China	Deep Second-degree Burns	rhEGF+Wuhuang oil(n = 20)	Wuhuang oil(n = 25)	2
Liu *et al.* [47]	2005	RCT	China	Deep Second-degree Burns	rh-bFGF(n = 39)	Normal saline(n = 39)	2
Jin *et al.* [105]	2014	CCT	China	Deep Second-degree Burns	rh-bFGF(n = 36)	SD-Ag(n = 37)	1
Chao *et al.* [48]	2003	RCT	China	Deep Second-degree Burns	rh-bFGF(n = 50)	Vaseline gauze(n = 50)	2

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Guo *et al.* [49]	2006	RCT	China	Deep Second-degree Burns	rh-bFGF(n = 16)	Normal saline(n = 15)	2
Liu *et al.* [50]	2014	RCT	China	Deep Second-degree Burns	Rh-bFGF(n = 4)	Standard care(n = 3)	2
Cai *et al.* [106]	2017	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 35)	Blank hydrogel(n = 35)	2
Lin [107]	2013	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 50)	Standard care(n = 40)	2
Chen *et al.* [51]	2014	CCT	China	Deep Second-degree Burns	rh-aFGF(n = 50)	PVD-I(n = 50)	1
Cai *et al.* [108]	2016	RCT	China	Deep Second-degree Burns	rh-aFGF+Vaseline gauze(n = 30)	Vaseline gauze(n = 30)	3
Sun *et al.* [52]	2011	RCT	China	Deep Second-degree Burns	rh-aFGF(n = 15)	Blank(n = 15)	1
Qiu *et al.* [53]	2010	RCT	China	Deep Second-degree Burns	rh-bFGF+Bashi cream(n = 38)	Vaseline gauze(n = 37)	2
Sui *et al.* [109]	2010	RCT	China	Deep Second-degree Burns	rb-bFGF+ Vaseline gauze(n = 132)	Vaseline gauze(n = 132)	2
Tong *et al.* [57]	2004	CCT	China	Deep Second-degree Burns	rhEGF(n = 32)	0.5% Complex iodine(n = 35)	1
Shi *et al.* [58]	2019	RCT	China	Deep Second-degree Burns	Nano-Ag + rh-EGF(n = 15)	Nano-Ag(n = 14)	3
Tong *et al.* [110]	2017	RCT	China	Deep Second-degree Burns	bFGF+SD-Zn(n = 53)	SD-Zn(n = 53)	2
Song *et al.* [111]	2018	RCT	China	Deep Second-degree Burns	rb-FGF Hydrogel(n = 37)	SD-Zn(n = 37)	3
Sun *et al.* [112]	2011	CCT	China	Deep Second-degree Burns	rh-aFGF(n = 24)	Normal saline(n = 22)	1
Sun *et al.* [112]	2011	CCT	China	Deep Second-degree Burns	bFGF(n = 20)	Normal saline (n = 22)	1
Qu [113]	2017	RCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel+Vaseline gauze(n = 48)	Vaseline gauze(n = 48)	3
Wang [114]	2014	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 15)	Placebo hydrogel(n = 15)	4
Xu [115]	2019	CCT	China	Deep Second-degree Burns	rh–bFGF(n = 15)	SD-Ag(n = 15)	1
Wang *et al.* [116]	2018	CCT	China	Deep Second-degree Burns	rhGM-CSF Hydrogel(n = 36)	Blank(n = 36)	1
Xu [117]	2017	RCT	China	Deep Second-degree Burns	EGF(n = 50)	Normal saline(n = 50)	3
Yan *et al.* [118]	2012	RCT	China	Deep Second-degree Burns	Silver ion dressing +rh-EGF hydrogel(n = 32)	Baikerui dressing(n = 32)	4
Wang *et al.* [61]	2004	RCT	China	Deep Second-degree Burns	rhEGF(n = 30)	Normal saline(n = 30)	2
Yang *et al.* [62]	2000	CCT	China	Deep Second-degree Burns	rh-bFGF(n = 37)	Blank(n = 37)	1
Xiong *et al.* [66]	2010	CCT	China	Deep Second-degree Burns	rh-EGF+ Amnion(n = 15)	Amnion(n = 15)	1
Yang *et al.* [119]	2018	RCT	China	Deep Second-degree Burns	Mupirocin ointment +GM-CSF hydrogel(n = 64)	Mupirocin ointment(n = 64)	3
Wang [67]	2009	CCT	China	Deep Second-degree Burns	rh-bFGF +Vaseline gauze(n = 31)	Vaseline gauze(n = 31)	1
Yang [120]	2014	RCT	China	Deep Second-degree Burns	GM-CSF Hydrogel(n = 38)	Vaseline gauze(n = 38)	3
Xiong *et al.* [68]	2019	RCT	China	Deep Second-degree Burns	rb-bFGF(n = 39)	SD-Ag(n = 41)	2

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Wang *et al.* [69]	2002	RCT	China	Deep Second-degree Burns	rh-EGF Derivative(n = 138)	SD-Ag(n = 138)	3
Wen *et al.* [121]	2016	RCT	China	Deep Second-degree Burns	GM-CSF Hydrogel+ Mupirocin ointment(n = 25)	Mupirocin ointment(n = 25)	3
Yang *et al.* [122]	2018	RCT	China	Deep Second-degree Burns	rh-aFGF(n = 49)	Standard care (n = 45)	2
Xie *et al.* [123]	2018	RCT	China	Deep Second-degree Burns	rh-aFGF(n = 43)	Standard care(n = 43)	2
Wang [124]	2015	RCT	China	Deep Second-degree Burns	rb-bFGF(n = 78)	Nano-Ag(n = 78)	3
Wang [125]	2015	RCT	China	Deep Second-degree Burns	rb-bFGF Hydrogel(n = 60)	Vaseline gauze(n = 60)	2
You *et al.* [126]	2010	RCT	China	Deep Second-degree Burns	rhEGF Hydrogel(n = 16)	Placebo(n = 16)	4
Yang [127]	2013	RCT	China	Deep Second-degree Burns	rhEGF(n = 30)	SD-Ag(n = 30)	4
Yang *et al.* [72]	2002	RCT	China	Deep Second-degree Burns	rh-bFGF(n = 8)	SD-Ag(n = 8)	2
Wang *et al.* [73]	2003	CCT-	China	Deep Second-degree Burns	rh-bFGF(n = 20)	Normal saline(n = 20)	1
Zhang *et al.* [128]	2014	RCT	China	Deep Second-degree Burns	rb-bFGF+Nano-Ag(n = 40)	SD-Ag(n = 40)	2
Zhou *et al.* [74]	1999	RCT	China	Deep Second-degree Burns	bFGF(n = 20)	Vaseline gauze(n = 20)	2
Zhou *et al.* [75]	2005	RCT	China	Deep Second-degree Burns	bFGF(n = 80)	Vaseline gauze(n = 62)	2
Zhou *et al.* [129]	2015	RCT	China	Deep Second-degree Burns	EGF(n = 30)	Normal saline(n = 30)	3
Zhang *et al.* [130]	2010	RCT	China	Deep Second-degree Burns	rhEGF + SD-Ag(n = 30)	SD-Ag (n = 30)	2
Zhang *et al.* [131]	2011	RCT	China	Deep Second-degree Burns	rhEGF + SD-Ag(n = 30)	SD-Ag(n = 30)	2
Zhan *et al.* [76]	2015	RCT	China	Deep Second-degree Burns	Nano-Ag + rh-EGF(n = 19)	Nano-Ag(n = 18)	2
Zhou *et al.* [132]	2016	RCT	China	Deep Second-degree Burns	Nano-Ag + rb-bFGF(n = 15)	Nano-Ag(n = 15)	2
Zhao *et al.* [133]	2001	RCT	China	Deep Second-degree Burns	rb-bFGF(n = 52)	Vaseline gauze(n = 52)	2
Zhang [134]	2019	RCT	China	Deep Second-degree Burns	GM-CSF Hydrogel(n = 80)	Vaseline gauze(n = 80)	2
Zhang *et al.* [78]	2001	CCT	China	Deep Second-degree Burns	rb-bFGF(n = 80)	Blank(n = 80)	1
Zou *et al.* [80]	2017	RCT	China	Deep Second-degree Burns	rh-EGF + Nano-Ag(n = 27)	Chlorhexidine(n = 28)	3
Zhou *et al.* [81]	2001	RCT	China	Deep Second-degree Burns	rhEGF(n = 109)	Placebo(n = 76)	3
Zhang *et al.* [82]	2012	RCT	China	Deep Second-degree Burns	rhEGF+SD-Ag Cream(n = 38)	SD-Ag Cream(n = 38)	3
Zhang *et al.* [135]	2010	RCT	China	Deep Second-degree Burns	rh-EGF(n = 21)	Ag-Zn Cream(n = 16)	2
Zhang *et al.* [136]	2016	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 20)	Rifampicin(n = 20)	3
Zhou *et al.* [84]	2014	CCT	China	Deep Second-degree Burns	rh-aFGF(n = 45)	Blank(n = 45)	1
Deng [137]	2017	CCT	China	Deep Second-degree Burns	rhGM-CSF + SD-Ag(n = 33)	SD-Ag(n = 33)	1
Chen *et al.* [138]	2009	RCT	China	Deep Second-degree Burns	Fulin honey+rh-EGF Hydrogel(n = 60)	Povidone iodine(n = 60)	3

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Liu *et al.* [139]	2016	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 177)	PVD-I(n = 181)	2
Yan *et al.* [140]	2016	RCT	China	Deep Second-degree Burns	rh-EGF Hydrogel + Nano-Ag(n = 40)	Nano-Ag(n = 40)	3
Jiao *et al.* [141]	2014	CCT	China	Deep Second-degree Burns	rhGM-CSF + SD-Ag(n = 15)	SD-Ag(n = 15)	1
Xia *et al.* [142]	2015	CCT	China	Deep Second-degree Burns	rhGM-CSF(n = 30)	Standard care(n = 28)	1
Ma *et al.* [143]	2008	RCT	China	Deep Second-degree Burns	rh-aFGF(n = 32)	Placebo(n = 32)	3
Shi *et al.* [144]	2018	RCT	China	Deep Second-degree Burns	Dragon blood powder +rb-bFGF Hydrogel(n = 100)	Jingwanhong ointment + Kangfuxin liquid(n = 100)	2
Wu *et al.* [145]	2012	RCT	China	Deep Second-degree Burns	Gentamicin + Heparin +bFGF Hydrogel(n = 63)	Gentamicin(n = 58)	2
Wu *et al.* [145]	2012	RCT	China	Deep Second-degree Burns	Gentamicin +Red light therapy+Heparin+bFGF Hydrogel(n = 60)	Gentamicin(n = 58)	2
Zhou *et al.* [146]	2016	RCT	China	Deep Second-degree Burns	rhGM-CSF+ Nano-Ag(n = 30)	Nano-Ag(n = 30)	3
Ge *et al.* [147]	2001	CCT	China	Trauma and Surgical Wound	bFGF(n = 53)	Furacilin + Vaseline gauze(n = 66)	1
Niu *et al.* [148]	2016	CCT	China	Trauma and Surgical Wound	rh-aFGF(n = 90)	Vaseline gauze(n = 90)	1
Dong [149]	2016	RCT	China	Trauma and Surgical Wound	bFGF + Mupifloxacin(n = 42)	Vaseline gauze(n = 42)	2
Chen *et al.* [150]	2017	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 143)	Infrared radiation(n = 143)	3
Hao *et al.* [151]	2015	RCT	China	Trauma and Surgical Wound	Compound schizonepeta fumigation lotion+rh-bFGF(n = 165)	Kangfuxin liquid(n = 144)	2
Liu *et al.* [152]	2004	CCT	China	Trauma and Surgical Wound	bFGF(n = 58)	Vaseline gauze(n = 48)	1
Li *et al.* [153]	2013	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 30)	40% Magnesium sulfate glycerin(n = 30)	3
Guo *et al.* [154]	2003	RCT	China	Trauma and Surgical Wound	bFGF(n = 68)	Furacilin + Vaseline gauze(n = 41)	2
Huang *et al.* [155]	2010	RCT	China	Trauma and Surgical Wound	bFGF(n = 30)	Standard care(n = 30)	2
Chen *et al.* [156]	2010	RCT	China	Trauma and Surgical Wound	bFGF(n = 20)	Gentamicin(n = 20)	3
Li *et al.* [157]	2015	RCT	China	Trauma and Surgical Wound	rb-FGF + ACRSC(n = 27)	ACRSC(n = 27)	2
Ge *et al.* [158]	2002	RCT	China	Trauma and Surgical Wound	bFGF(n = 87)	Furacilin + Vaseline gauze(n = 53)	2
Li *et al.* [159]	2002	CCT	China	Trauma and Surgical Wound	bFGF(n = 89)	Standard care(n = 84)	1
Li [160]	2016	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 120)	TCM lotions(n = 120)	2
Fu *et al.* [161]	2015	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 36)	Vaseline gauze(n = 36)	3
Qi *et al.* [162]	2009	CCT	China	Trauma and Surgical Wound	rh-EGF(n = 183)	0.1% Rivanol (n = 204)	1

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Li *et al.* [163]	2012	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 84)	Standard care(n = 83)	3
Li *et al.* [164]	2016	RCT	China	Trauma and Surgical Wound	Cosmetic suture + rh-EGF(n = 55)	Ordinary suture(n = 55)	2
Fan *et al.* [165]	2011	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 50)	TCM gauze(n = 50)	3
Deng [166]	2008	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 35)	TCM gauze(n = 35)	3
Liu *et al.* [167]	2019	RCT	China	Trauma and Surgical Wound	GM-CSF Hydrogel(n = 55)	Artificial dermis(n = 55)	3
Li *et al.* [168]	2015	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 25)	Sanqi Shengji ointment(n = 25)	3
Meng *et al.* [169]	2019	CCT	China	Trauma and Surgical Wound	rh-aFGF(n = 30)	Vaseline gauze(n = 30)	1
Huang *et al.* [170]	2018	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 29)	Fu Zhi Qing(n = 30)	3
He [171]	2015	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 40)	Vaseline gauze(n = 40)	2
Long *et al.* [172]	2014	RCT	China	Trauma and Surgical Wound	rb-bFGF +Arnebia oil guaze(n = 50)	Arnebia oil gauze(n = 50)	2
Guo *et al.* [173]	2018	RCT	China	Trauma and Surgical Wound	rb-bFGF(n = 40)	Standard care(n = 40)	2
Li *et al.* [174]	2018	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 30)	Standard care(n = 30)	2
Li *et al.* [174]	2018	RCT	China	Trauma and Surgical Wound	rh-EGF Solution(n = 30)	Standard care(n = 30)	2
Jiang *et al.* [175]	2018	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 24)	Standard care(n = 24)	2
Liu *et al.* [176]	2018	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 45)	Vaseline gauze(n = 45)	3
Liao *et al.* [177]	2008	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 60)	Vaseline gauze(n = 60)	2
Lu *et al.* [178]	2017	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 68)	Normal saline(n = 68)	2
Huang *et al.* [179]	2004	CCT	China	Trauma and Surgical Wound	rh-EGF(n = 30)	PVD-I gauze(n = 30)	1
Lin *et al.* [180]	2019	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 50)	Blank(n = 50)	2
Liu *et al.* [181]	2018	RCT	China	Trauma and Surgical Wound	rh-aFGF(n = 30)	Normal saline(n = 30)	3
Jiang [182]	2006	CCT	China	Trauma and Surgical Wound	bFGF(n = 91)	Normal saline(n = 85)	1
Sun *et al.* [183]	2017	RCT	China	Trauma and Surgical Wound	bFGF+ Mupirocin ointment(n = 44)	Mupirocin ointment(n = 32)	2
Sun *et al.* [184]	2011	RCT	China	Trauma and Surgical Wound	Rh-aFG F(n = 22)	Vaseline gauze(n = 18)	2
Sun *et al.* [185]	2014	RCT	China	Trauma and Surgical Wound	rh-aFGF(n = 22)	Vaseline gauze(n = 16)	2
Sun *et al.* [186]	2009	CCT	China	Trauma and Surgical Wound	bFGF(n = 50)	Shengji Yuhong ointment(n = 46)	1
Shi *et al.* [187]	2016	RCT	China	Trauma and Surgical Wound	Erythromycin ointment +rh-EGF Hydrogel(n = 65)	Erythromycin ointment(n = 65)	3
Shi *et al.* [188]	2012	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 53)	Vaseline gauze(n = 53)	2
Teng *et al.* [189]	2015	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 22)	Standard care(n = 22)	2
You [190]	2019	RCT	China	Trauma and Surgical Wound	bFGF(n = 30)	Chlorophyll derivative(n = 30)	3

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Wang [191]	2018	RCT	China	Trauma and Surgical Wound	rb-bFGF+Hydrosorb(n = 16)	Hydrosorb(n = 16)	2
Wang *et al.* [192]	2014	RCT	China	Trauma and Surgical Wound	rh-aFGF(n = 52)	Gelatin sponge(n = 52)	5
Wang *et al.* [193]	2008	RCT	China	Trauma and Surgical Wound	bFGF(n = 46)	Gentamicin(n = 50)	2
Wen *et al.* [194]	2005	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 86)	1%PVD-I(n = 73)	2
Wang [195]	2016	RCT	China	Trauma and Surgical Wound	rh-EGF+ 2%Iodine(n = 50)	Anisodamine + Gentamicin + Insulin + Normal saline(n = 50)	2
Xu [196]	2019	RCT	China	Trauma and Surgical Wound	Cosmetic suture + rh-EGF(n = 30)	Cosmetic suture(n = 30)	2
Yao *et al.* [197]	2014	RCT	China	Trauma and Surgical Wound	rh-aFGF(n = 81)	Normal saline(n = 86)	2
Wu *et al.* [198]	2016	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 37)	PVD-I(n = 39)	3
Wang *et al.* [199]	2018	RCT	China	Trauma and Surgical Wound	rb-bFGF Hydrogel(n = 30)	Jiyuhong ointment(n = 30)	2
Wu *et al.* [200]	2004	RCT	China	Trauma and Surgical Wound	rbFGF(n = 36)	Blank(n = 36)	2
Xu *et al.* [201]	2000	RCT	China	Trauma and Surgical Wound	rbFGF(n = 69)	Normal saline(n = 20)	2
Wei [202]	2017	RCT	China	Trauma and Surgical Wound	rh-EGF + bFGF(n = 80)	rh-EGF(n = 80)	3
Xie *et al.* [203]	2013	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 55)	Vaseline gauze(n = 55)	3
Wu *et al.* [204]	2004	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 31)	Mayinglong ointment(n = 35)	2
Wang *et al.* [205]	2014	CCT	China	Trauma and Surgical Wound	EGF(n = 30)	Normal saline(n = 30)	1
Wu *et al.* [206]	2013	RCT	China	Trauma and Surgical Wound	aFGF(n = 58)	Titanoreine(n = 58)	3
Zhi *et al.* [207]	2007	RCT	China	Trauma and Surgical Wound	EGF(n = 54)	Vaseline gauze(n = 53)	2
Zhu *et al.* [208]	2006	CCT	China	Trauma and Surgical Wound	rh-EGF(n = 24)	Blank(n = 26)	1
Zhang *et al.* [209]	2015	CCT	China	Trauma and Surgical Wound	rh-EGF(n = 148)	PVD-I(n = 148)	1
Zhong *et al.* [210]	2015	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 78)	Normal saline(n = 72)	2
Zhai *et al.* [211]	2010	RCT	China	Trauma and Surgical Wound	rb-bFGF(n = 23)	Vaseline gauze(n = 22)	2
Zhang *et al.* [212]	2007	RCT	China	Trauma and Surgical Wound	bFGF(n = 50)	Blank(n = 10)	2
Zhang *et al.* [213]	2001	CCT	China	Trauma and Surgical Wound	bFGF(n = 120)	Mupirocin ointment(n = 80)	1
Zhou *et al.* [214]	2011	RCT	China	Trauma and Surgical Wound	rb-bFGF(n = 64)	Longzhu ointment(n = 64)	2
Mei *et al.* [215]	2019	RCT	China	Trauma and Surgical Wound	rh-EGF + Cosmetic suture(n = 47)	Standard Care(n = 46)	2
Zhang *et al.* [216]	2012	RCT	China	Trauma and Surgical Wound	bFGF + Compound Sihuang liquid(n = 80)	Standard Care(n = 80)	3

(Continued)

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Table 2. Continued

Author	Year	Study Design	Country	Wound Type	Sample size (Treatment)	Sample size (Control)	Jadad's Score
Zhu *et al.* [217]	2012	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 24)	Vaseline gauze(n = 24)	2
Zhou *et al.* [218]	2015	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 56)	Metronidazole Ethacridine Lactate(n = 56)	2
Zhao *et al.* [219]	2019	RCT	China	Trauma and Surgical Wound	rh-EGF(n = 54)	Metronidazole(n = 54)	3
Zhu [220]	2007	CCT	China	Trauma and Surgical Wound	bFGF(n = 30)	5%PVD-I(n = 26)	1
Zhang [221]	2019	RCT	China	Trauma and Surgical Wound	rh-aFGF(n = 60)	Gelatin sponge(n = 60)	3
Zhang [222]	2004	RCT	China	Trauma and Surgical Wound	rb-bFGF(n = 65)	Shengji Yuhong ointment(n = 51)	2
Yun *et al.* [223]	2007	RCT	China	Trauma and Surgical Wound	bFGF(n = 61)	Standard care(n = 63)	2
Huang [224]	2017	RCT	China	Trauma and Surgical Wound	rh-EGF Hydrogel(n = 40)	Metronidazole(n = 40)	3
Xu [225]	2017	RCT	China	Trauma and Surgical Wound	EGF(n = 24)	PVD-I(n = 24)	3
Zhang *et al.* [226]	2017	RCT	China	Trauma and Surgical Wound	bFGF(n = 30)	Kangfuxin(n = 30)	2
Luo [227]	2018	RCT	China	Trauma and Surgical Wound	rh-bFGF(n = 30)	PVD-I(n = 30)	2
Wang [228]	2016	RCT	China	Trauma and Surgical Wound	GM-CSF Hydrogel(n = 30)	Metronidazole(n = 30)	2
Sun *et al.* [229]	2010	RCT	China	Trauma and Surgical Wound	rh-EGF Spray (n = 38)	Gentamicin(n = 20)	3
Fu *et al.* [230]	2000	CCT	China	Second Degree Burns	rb-FGF(n = 330)	Placebo(n = 324)	2
Ichiro *et al.* [231]	2007	CCT	Japan	Trauma and Surgical Wound	bFGF	Standard care	2
Yan *et al.* [232]	2017	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 95)	Placebo(n = 95)	3
Lin *et al.* [233]	2015	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 21)	Mupirocin ointment(n = 21)	2
Akita *et al.* [234]	2008	RCT	Japan	Superficial Second-degree Burns	bFGF(n = 51)	Vaseline gauze(n = 51)	2
Nie *et al.* [235]	2010	RCT	China	Deep Second-degree Burns	bFGF+Oxygen therapy(n = 44)	Oxygen therapy(n = 41)	2
Hayashida *et al.* [236]	2012	RCT	Japan	Superficial Second-degree Burns	bFGF(n = 10)	Placebo(n = 10)	2
Fu *et al.* [10]	1998	RCT	China	Second Degree Burns	bFGF(n = 300)	Placebo(n = 300)	2
Ma *et al.* [11]	2007	RCT	China	Deep Second-degree Burns	aFGF(n = 39)	Placebo(n = 39)	3
Wang *et al.* [237]	2002	RCT	China	Second Degree Burns	EGF(n = 105)	Placebo(n = 105)	2
Wang *et al.* [238]	2003	RCT	China	Deep Second-degree Burns	EGF(n = 37)	Placebo(n = 37)	2
Wang *et al.* [239]	2008	RCT	China	Deep Second-degree Burns	GM-CSF(n = 214)	Placebo(n = 107)	2
Yan Hong *et al.* [240]	2012	RCT	China	Deep Second-degree Burns	rhGM-CSF(n = 32)	Placebo(n = 33)	3
Zhang *et al.* [241]	2009	RCT	China	Deep Second-degree Burns	GM-CSF(n = 60)	Placebo(n = 30)	2

ACRSC avene cicalfate restorative skin cream, *CCT* controlled clinical trial, *EGF* epidermal growth factor, *FFG* fibroblast growth factor, *GM-CSF* granulocyte-macrophage colony stimulating factor, *MEBO* moist exposed burn ointment, *PVP-I* polyvinyl pyrrolidone, *PVD-I* povidone iodine, *rbFGF* recombinant bovine basic fibroblast growth factor; *rh-aFGF* recombinant human acidic fibroblast growth factor, *RCT* randomized controlled trial, *TCM* traditional chinese medicine

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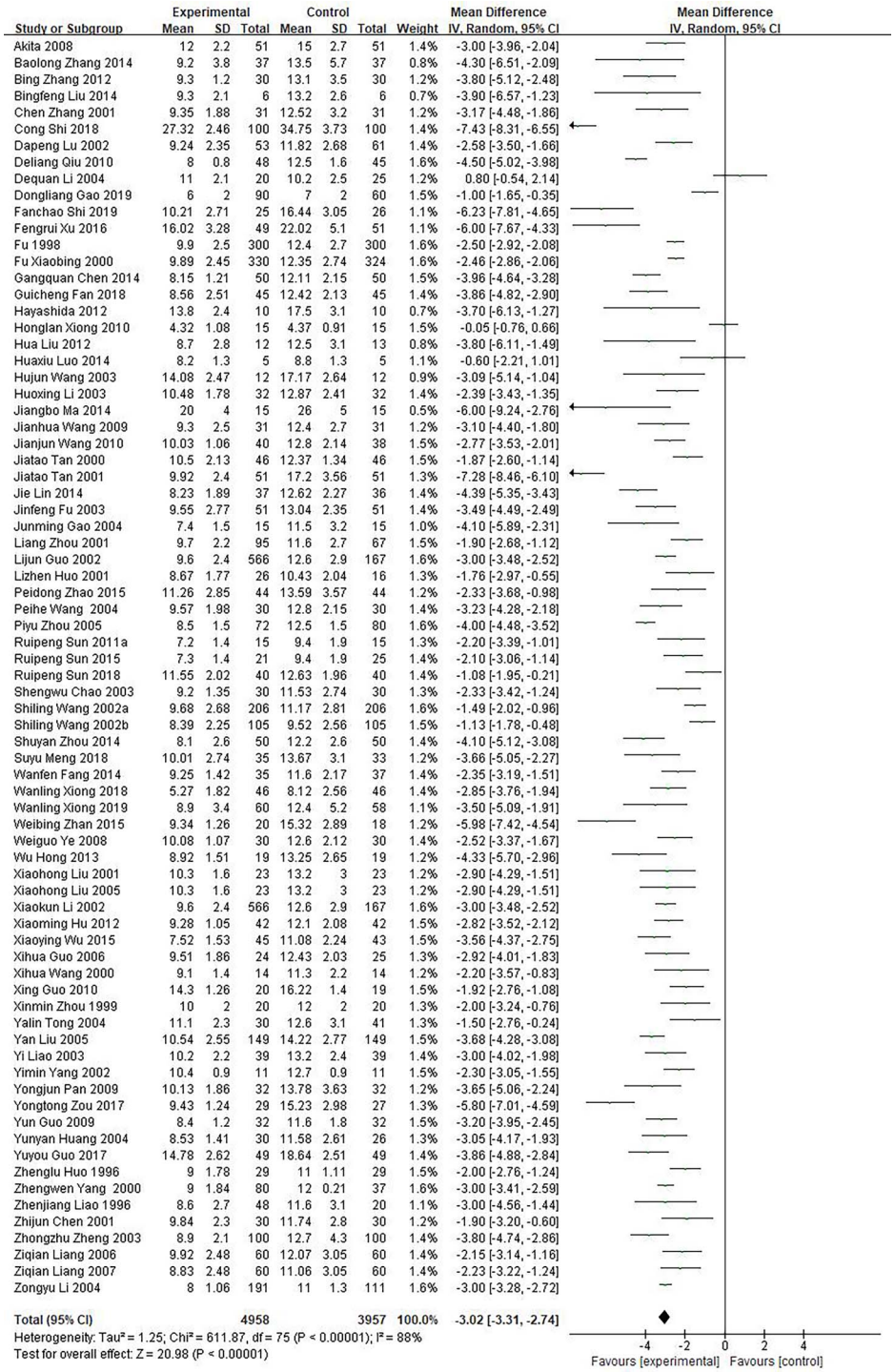


Figure 2. Comparative meta-analysis of the healing time of superficial second-degree burn wounds. *CI* confidence interval, *MD* mean difference

wound healing time was 3.02 days shorter in the growth factor group than in the control group (MD = −3.02; 95% CI:−3.31 ~ −2.74; $p < 0.00001$).

A total of 113 studies [10,11,15,16,19–24,28,30–32,34–36,38–53,57,58,61,62,66–69,72–76,78,80–82,84,87–97,100–110,112,115–120,122,123,125–134,136–143,145,146,230,232,233,235,237,238,240,241] enrolling 12 465 cases were conducted to compare the healing time of deep second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the occurrence of statistical heterogeneity ($p < 0.00001$; $I^2 = 100\%$). Therefore, the random effect model was used for meta-analysis (Figure 3). The results showed that the wound healing time was 5.63 days shorter in the growth factor group than in the control group (MD = −5.63; 95% CI:−7.10 ~ −4.17; $p < 0.00001$).

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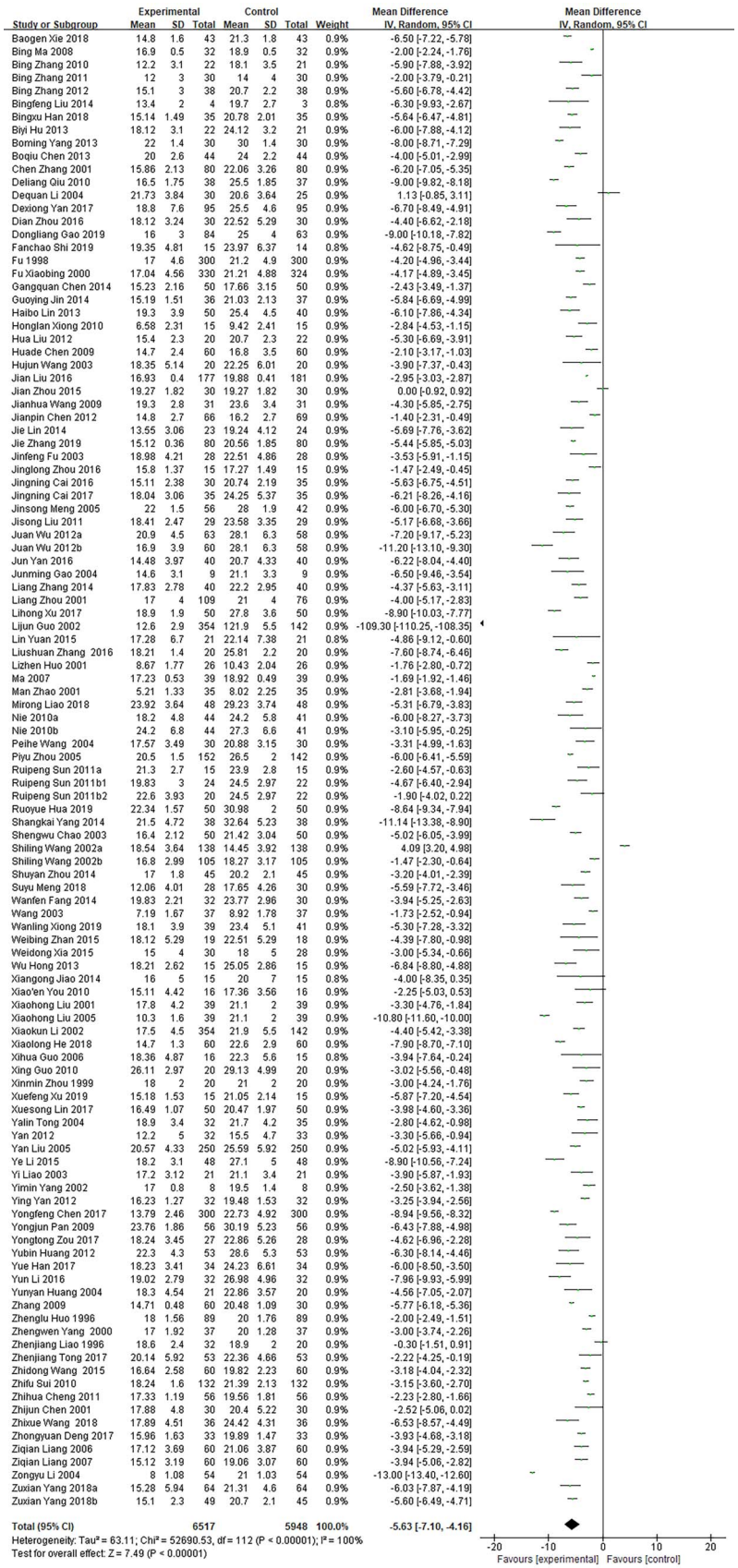


Figure 3. Comparative meta-analysis of the healing time of deep second-degree burn wounds. *CI* confidence interval, *MD* mean difference

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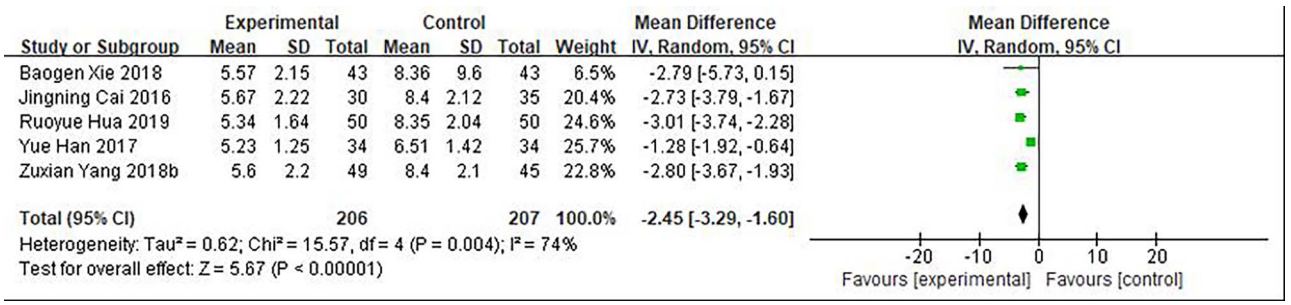


Figure 4. Comparative meta-analysis of the scar score of deep second-degree burn wounds. *CI* confidence interval, *MD* mean difference

Healing rate comparison of second-degree burn wounds

Healing rate was defined as the proportion of healed wound area compared with the total wound area. Seventeen studies [15,17,20,36,41,42,44,51,52,54,61,68,69,71,72,77,81] enrolling 3184 cases were conducted to compare the healing rate of superficial second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the presence of statistical heterogeneity ($p < 0.00001$; $I^2 = 99\%$). Therefore, the random effect model was used for meta-analysis (Figure S1, see online supplementary material). The results showed that the average wound healing rate was 15.60% higher in the growth factor group than in the control group (MD = 15.60; 95% CI: 10.51–20.68; $p < 0.00001$). A total of 43 studies [15,20,36,41,42,44,51,52,61,68,69,72,73,81,87,88,91,94,97,99,102,107,108,110,114,117–119,123,124,126,128,129,132,136,138,139,141,143,145,232,233] enrolling 5696 cases served to compare the healing rate of deep second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the occurrence of statistical heterogeneity ($p < 0.00001$; $I^2 = 98\%$). Hence, the random effect model was used for meta-analysis (Figure S2, see online supplementary material). The results showed that the wound healing rate was 10.84% higher in the growth factor group than in the control group (MD = 10.84; 95% CI: 8.31 ~ 13.37; $p < 0.00001$).

Infection rate of second-degree burn wounds

Seven studies [16,33,58,76,79,80,82] including 395 cases with superficial second-degree burn wounds compared the infection rate of growth factor and other non-growth factor treatment methods. There turned out to be no statistical heterogeneity between the results ($p = 0.24$; $I^2 = 25\%$). Therefore, the fixed effect model was used for meta-analysis (Figure S3, see online supplementary material). The results showed that the infection rate was lower in the growth factor treatment group than in the non-growth factor group, and the difference was statistically significant (RR = 0.52; 95% CI: 0.39–0.69; $p < 0.00001$). Seventeen studies [16,58,76,80,82,91,94,108,118,119,122,124,128,131,132,135,136] enrolling a total of 1389 patients were conducted to compare the infection rate of deep second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed no statistical heterogeneity ($p = 0.54$; $I^2 = 0\%$). Hence, the fixed effect model was used for meta-analysis (Figure S4, see online supplementary material). The results showed that the infection rate was lower in the growth factor group than in the non-growth factor treatment group (RR = 0.52: 95% CI: 0.42 ~ 0.64; $p < 0.00001$).

Vancouver scar scale score of deep second-degree burn wounds

Five studies [101,104,108,122,123] including 413 patients compared growth factor with other non-growth factor treatments concerning the deep second-degree burn scar score. The follow-up time was between 6 and 12 months. The results showed the presence of statistical heterogeneity ($p = 0.004$; $I^2 = 74\%$). Therefore, the random effect model was used for meta-analysis (Figure 4). The results showed that the Vancouver scar scale score of the growth factor treatment group was improved as compared with that of the non-growth factor group (5.23 ~ 5.67 *vs* 6.51 ~ 8.4, i.e. 2.45 lower than that of the non-growth factor treatment group) (MD = −2.45; 95% CI: −3.29 ~ −1.6; $p = 0.004$).

Adverse reactions of deep second-degree burn wounds

Three studies [95,96,124], including 522 patients with deep second-degree burn wounds, compared the incidence of adverse reactions after the treatment with growth factor vs. other non-growth factor treatments. The results showed that no statistical heterogeneity occurred ($p = 0.29$; $I^2 = 20\%$), so the fixed effect model was used for meta-analysis (Figure S5, see online supplementary material). The results showed that the incidence of adverse reactions was lower in the growth factor treatment group than in the non-growth factor group (RR = 0.35; 95% CI: 0.19–0.67; $p = 0.001$).

Healing time comparison between traumata and surgical wounds

A total of 67 studies [48,147–156,158–164,166–173,175–177,179,181,184–188,190,192–194,196–203,205,206,208–214,216,218–226] including 7106 cases with traumata or surgical wounds served to compare the wound healing time between growth factor and other non-growth factor treatments. The results showed that statistical heterogeneity occurred ($p < 0.00001$; $I^2 = 99\%$). Hence, the random effect model was used for meta-analysis (Figure 5). The results

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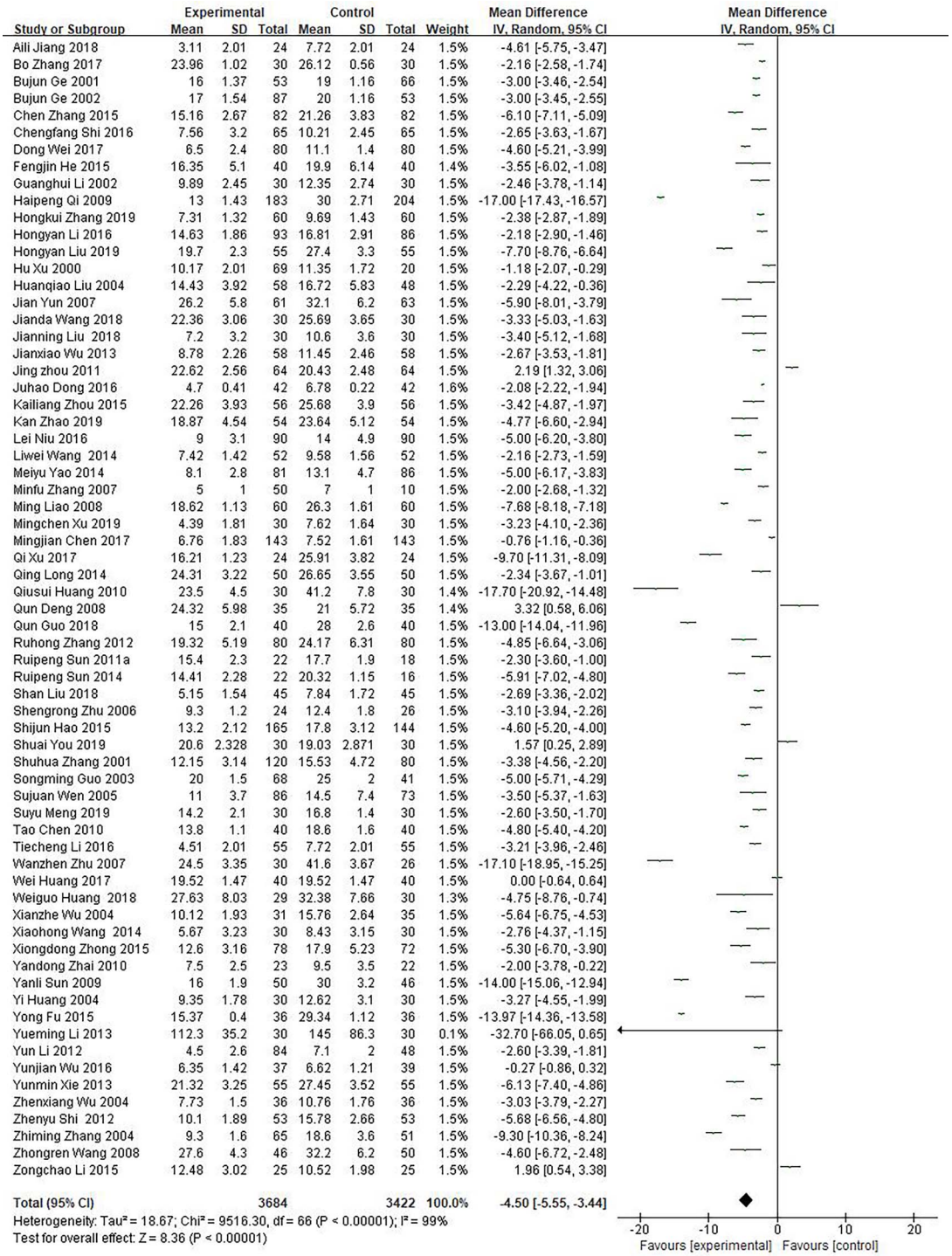


Figure 5. Comparative meta-analysis of the healing time of trauma and surgical wounds. *CI* confidence interval, *MD* mean difference

showed that the healing time was 4.50 days shorter in the growth factor group than in the control group (MD = −4.50; 95% CI: $-5.55 \sim -3.44$; $p < 0.00001$).

Healing rate comparison of traumata and surgical wounds

Thirteen studies [148,155,165–167,169,170,184,185,191,193,203,228] enrolling 1017 patients with traumata or surgical wounds allowed to compare the rate of wound healing between growth factor and other non-growth factor treatments. The results showed that statistical heterogeneity was present ($p < 0.00001$; $I^2 = 99\%$), so the random effect model was used for meta-analysis (Figure S6, see online supplementary material). The results showed that the wound healing rate in the growth factor group was 7.63% higher than in the control group (MD = 7.63; 95% CI: $4.44 \sim 10.82$; $p < 0.00001$).

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Adverse reaction of traumata and surgical wounds

Six studies [157,171,197,215,219,221] including 622 patients with traumata and surgical wounds compared the incidence of adverse reactions after growth factor treatment or other non-growth factor treatment methods. The results were statistically heterogeneous ($p < 0.0001$; $I^2 = 84\%$). Hence, the random effect model was used for meta-analysis (Figure S7, see online supplementary material). The results showed that the incidence of adverse reactions was lower in the growth factor group than in the control group (RR = 0.55; 95% CI: $0.46 \sim 0.65$; $p < 0.00001$).

Discussion

Growth factors are important biologically active molecules which can markedly impact on the wound environment, leading to rapid increases in cell migration, proliferation and differentiation, while regulating the cellular responses inherent to the wound healing process [14]. Recombinant growth factors have been used as adjunctive treatments for acute wounds to accelerate healing, however, the effectiveness and safety of administering these growth factor products under such conditions had not been systematically analyzed. In 2016, Zhang *et al*. [242] performed a meta-analysis concerning growth factor therapy in cases of partial thickness burns. Thirteen studies with a total of 1924 participants were included and the results showed that the topical application of growth factors including FGF, EGF and GM-CSF significantly reduced wound healing time as compared with standard wound care alone. Although these preliminary results seemed to be encouraging, the authors pointed out that high-quality and adequately powered trials were still needed to further confirm their conclusions. Another meta-analysis performed by Abdelhakim *et al*. included 9 clinical studies and has shown that local bFGF treatment accelerated wound healing and prevented pathological scarring. In a similar fashion, the author pointed out that further research was needed to indicate more clinical advantages [243].

In this systematic review, we performed a comprehensive search of relevant clinical studies published in either Chinese or English. We included many studies published in Chinese which had not been considered for evaluation before. Our data show that as compared to non-growth factor treatments, the therapeutic use of growth factor products including FGF, EGF and GM-CSF for acute wounds significantly changed the healing outcome in terms of lessening healing time, heightening healing rate and reducing incidence of infections and adverse reactions. Therefore, our study results positively support the therapeutic use of the current clinically available growth factor products for acute wounds, especially in the case of wounds that tend to have longer healing time.

However, one must point out that out of the 229 studies considered, only 3 were conducted outside China (i.e. in Japan) and reported in English, while the remaining 226 articles, including 7 reported in English and 219 in Chinese, were all carried out within China and reported by Chinese researchers. During the screening period, one randomized clinical trial conducted in the USA showed that epidermal growth factor accelerated skin-graft-donor sites wound healing significantly [9]. However, the types of outcome measurements in this study could not be combined with those from other included studies to conduct meta-analysis. Thus although it was eventually excluded, the results of this study did support our general conclusions. We have to admit that the lack of clinical data from other countries and areas has reduced the evidence's power level. This is especially true considering that most of the included studies are rated as low-quality ones (Jadad score: 1–2 for 202 papers, 4–5 for 6 papers only). The lack of sufficient clinical data from other countries and areas outside Asia is likely caused by the lack of available growth factor products for treating acute wounds in these places. Becaplermin in Regranex® is the only U.S. Food and Drug Administration (FDA) approved recombinant PDGF product and is only indicated for the treatment of neuropathic ulcers in diabetics. This product carried a boxed warning from the FDA and due to safety issues has been withdrawn in Europe [244]. We were only able to find one study using PDGF gel to treat acute full-thickness punch biopsy wounds on 7 healthy subjects [245]. The results of the study showed PDGF gel was effective in promoting wound healing, which was in accord with the general results of this meta-analysis. Since PDGF has not been officially approved for use on acute wounds, we did not include PDGF in this meta-analysis. However, we believe that when PDGF becomes more widely used for treating acute wounds in the future, it will be meaningful to conduct a more comprehensive evaluation regarding the efficacy and safety issues of all the important growth factor products that are still lacking evidence for clinical use today.

Although this meta-analysis has brought to light encouraging results, the collection of the latter from limited countries and areas (mainly in China) increases the bias of the study. From this standpoint, the evidence supporting the routine therapeutic use of growth factor products for acute wounds is still weak. More high-quality clinical studies and clinical studies from outside of China are needed to further confirm the efficacy, necessity and safety of their clinical application. Despite the possible bias of the conclusions drawn from clinical studies, the current data do show some potential merits of using growth factors to promote acute wound healing. It is interesting to note that several of the included studies focused on the healing of surgical wounds entailing high risks of contamination and infection, such as in the case of perianal surgery [154,214,218,219,223,224,226]. Growth factors were beneficial as they decreased the healing time of such wounds, and therefore decreased the chances of infection and of the development into chronic wounds. Thus, the therapeutic use of growth factors in cases with surgical wounds susceptible to contamination and infection could be a beneficial practice. Again, the need remains for more evidence reported by higher-quality studies.

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Moreover, we noted that therapeutically using growth factors for acute wounds not only increased the speed of healing, but also improved the quality of healing in the case of deep wounds. It is well worth pointing out that with growth factors treatments, deep second-degree burn wounds healed with lower scar scores [101,104,108,122,123], which is an important indicator for routine clinical use. It is well known that an increased wound healing time is an important risk factor for hypertrophic scarring in second-degree burns [246]. The current data showed that, instead of causing 'an overgrowth', growth factor treatments safely reduced wound healing time by 5.63 days while concurrently decreasing the degree of hypertrophic scarring. Similarly, in their study Abdelhakim *et al*. [243] also pointed out that bFGF might prevent pathological scarring through several cellular mechanisms, such as interfering with myofibroblasts formation and inducing apoptosis. However, longer follow-up times and large-scale clinical trials are still needed to confirm this scar-reducing effect and the causal relationship with reduced wound healing times.

Notably, most of the studies included in this systematic review used only a single growth factor either by itself or combined with other non-growth factor treatments and proved their effectiveness. However, it is yet to be proven that combining different growth factors achieves better clinical results, or whether the contrary is true. Since applying supra-physiological doses of growth factor(s) correlates with an increased risk of cancer, the importance of controlling the spatial–temporal release of growth factors at the wound site and of overcoming this challenge is probably crucial for any successful growth factor-based therapy [244]. Also, as different growth factors partake in the various stages of the wound healing process, using a single growth factor may not suffice for best wound healing. A sophisticated growth factor delivery system enabling a controlled spatial–temporal delivery [13], mimicking the synergistic wound healing activity of the combined release profiles of growth factors in real physiological situations, could be a promising direction for future research. Currently, the use of platelet rich plasma (PRP) to promote refractory wound healing has already supplied a hint for applying growth factor compounds in a more effective fashion. However, PRP has not been routinely used on acute wounds due to economic considerations. More in-depth study of the PRP's spatial–temporal working mechanism might provide stronger evidence to develop recombinant growth factor combination products for promoting acute wound healing in the future.

Conclusions

With the systematic review and evaluation of the currently available evidence, we conclude that the therapeutic use of growth factors including EGF, FGF and GM-CSF is effective and safe in the treatment of acute skin wounds, especially in the case of wounds entailing higher risks of infection. However, the need still remains for more higher-quality studies to further strengthen our conclusion.

Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

Acknowledgments

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Abbreviations

CI; Confidence interval; EGF; Epidermal growth factor; FGF, Fibroblast growth factor; GM-CSF: Granulocyte-macrophage colony stimulating factor; MD, Mean difference; PDGF: Platelet-derived growth factor; PRP: Platelet rich plasma; rbFGF: Recombinant bovine basic fibroblast growth factor; rh-aFGF: Recombinant human acidic fibroblast growth factor; RR: Relative risk.

Authors' contributions

YW and JL conducted the study, screened the included papers and wrote the manuscript. YH, XL, LZ, MY, JD and XW collected and extracted data from the included studies. XL performed primary data analysis. XF and JW designed the study and provided guidance for the manuscript preparation.

Conflicts of interests

None declared.

Data availability

Data are available from PubMed/Medline, Cochrane Library, Cochrane CENTRAL, ClinicalTrials.gov, Chinese Journal Full-text Database (CNKI), China Biomedy Medicine disc (CBM), Chinese Scientific Journal Database (VIP), and Wanfang Database (WFDATA).

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