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Review Article

The association between epidermal growth factor and the treatment of deep second degree burn wounds: a meta-analysis

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Abstract: *Objective*: The relationship between epidermal growth factor (EGF) therapy and the treatment of deep second degree burn wounds is still conflicting. We therefore conducted a meta-analysis to summarize the evidence from epidemiological studies. *Methods*: PubMed, Web of Science, Wanfang databases, Embase, and Cochrane library were used to search the relevant articles up to October 2015. We analyzed dichotomous variables by estimating odds ratios (OR) with their 95% confidence interval (CI) and continuous variables using the weighted mean difference (WMD) with the 95% CI. The random effect model (REM) was used to combine the results. The outcome measures included healing time (HT), wounds healing speed (WHS), and scar index (SI). *Result:* Nine articles were included in the meta-analysis. These studies involved a total of 441 patients. The results indicate that epidermal growth factor (EGF) therapy were significantly lower in epidermal growth factor (EGF) therapy than in other therapy (HT: WMD = -0.70, 95% CI = -0.87, -0.53), (WHS: WMD = 1.13, 95% CI = 0.94, 1.33), and (SI: WMD = -1.01, 95% CI = -1.21, -0.81). *Conclusion:* Compared with other therapy, epidermal growth factor therapy is generally safer and more reliable for patients with deep second degree burn wounds.

Keywords: Epidermal growth factor, deep second degree burn wounds, meta-analysis

Introduction

Burns are among the most common injuries in modern life [1]. Without proper treatment, burn surface area and depth may worsen and become life threatening over time [2]. So it is very important to focus on improving the overall survival rate and improving the quality of life [3]. Although many advances have been made to treat burn injuries, the consensus on the best treatment to hasten healing has not been reached [2].

Up to date, epidemiologic studies have reported the relationship between epidermal growth factor (EGF) therapy and the treatment of deep second degree burn wounds. However, due to small sample sizes, most studies were not adequately powered to detect the effect of EGF therapy on deep second degree burn wounds. Thus, in order to provide the latest and more convincing evidence, we systematically reviewed the current available epidemiologic studies to conduct the meta-analysis.

Methods

Literature search

The electronic databases of PubMed, Web of Science, Wanfang databases Embase and Co-chrane library were searched to identify eligible English and Chinese language publications (up to October, 2015). The following text and key words were used in the search: “epidermal growth factor therapy” or “therapy” in combination with “deep second degree burn wounds”. Logical combinations of these and related terms were used to maximize sensitivity. Additional relevant articles were identified by searching the references of eligible articles.

Inclusion criteria

The inclusion criteria for this meta-analysis were as follows: (1) reporting as a retrospective study or prospective study or randomized controlled trial; (2) comparison of epidermal growth factor (EGF) therapy with other therapy

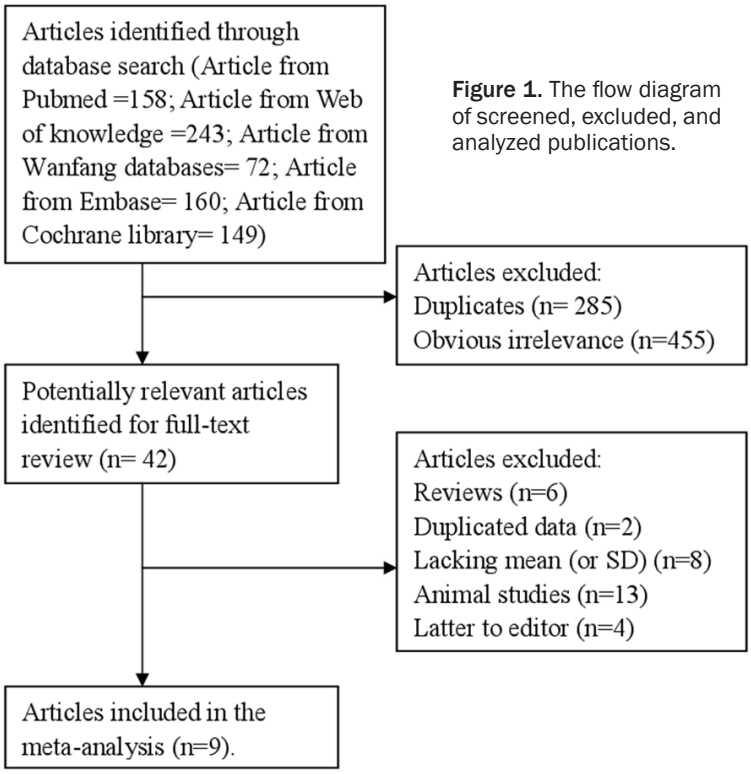

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

for treatment of deep second degree burn wounds; (3) available mean and standard deviation (SD) were provided for wounds healing speed (WHS), healing time (HT), and scar index (SI) (or data available to calculate them); (4) written in English or Chinese.

Exclusion criteria

The exclusion criteria for this meta-analysis were as follows: (1) reviews; (2) the above-mentioned outcomes of interest were not reported; (3) it was impossible to extract the appropriate data from the published results.

When the same institution reported more than once, the most recent publication was included. Two investigators carefully reviewed all identified studies independently to determine whether an individual study was eligible for inclusion criteria in this meta-analysis. Any disagreements were resolved by discussion between the two reviewers.

Quality assessment

The quality of studies was examined and controlled in accordance with checklists of Preferred Reporting Items for Systematic reviews and Meta-Analyses for randomized trials (PRISMA) [4]. To determine the quality score of included studies, two reviewers independently performed the quality assessment by using the Newcastle-Ottawa Scale, which is a validated scale for non-randomized studies in meta-analyses [5]. The Newcastle-Ottawa Scale is a nine-point scale that allocates points based on the selection process of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the identification of the exposure and the outcomes of study participants (0-3 points). We assigned scores of 0-3, 4-6, and 7-9 for low, moderate, and high quality of studies, respectively.

Statistical analysis

We analyzed dichotomous variables by estimating odds ratios (OR) with their 95% confidence interval (95% CI) and continuous variables using the weighted mean difference (WMD) with the 95% CI between EGF therapy and the treatment of deep second degree burn wounds. Random-effects model was used to combine the pooled effect, which considers both within-study and between-study variation [6]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [7], respectively. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [8]. Sensitivity analysis was conducted to describe how robust the pooled estimator is to removal of individual studies. Publication bias was evaluated using Egger regression asymmetry test [9]. All statistical analyses were conducted with STATA version 10.0 (StataCorp LP, College Station, Texas, USA). Two-tailed p-value ≤ 0.05 was accepted as statistically significant.

Results

Search results and study characteristics

In total, the electronic database searches identified 158 articles from PubMed and 243 arti-

Table 1. Characteristics of included studies

Study	Year	N1	N2	Quality score	Case		Control	
					Mean	SD	Mean	SD
Wounds healing speed (WHS)								
Li et al.	2004	30	30	7	62.31	3.46	52.08	2.7
Liang et al.	2006	60	60	7	75.93	22.02	62.26	19.25
Luo et al.	2007	28	28	6	79.93	21.02	60.26	18.25
Chen et al.	2009	60	60	7	88.93	20.06	66.25	19.78
Luo et al.	2013	30	30	8	83.78	9.05	62.24	7.97
Wang et al.	2002	44	44	7	81.36	2.71	69.66	25.18
Healing time (HT)								
Li et al.	2004	30	30	7	18.68	20.9	24.15	2.96
Liang et al.	2006	60	60	7	17.12	3.69	21.06	3.87
Luo et al.	2007	28	28	6	15.12	3.19	19.06	3.07
Chen et al.	2009	60	60	7	14.7	2.4	16.8	3.5
Luo et al.	2013	30	30	8	16.15	3.63	22.89	5.17
Guo et al.	2010	20	21	7	26.11	2.97	29.13	4.99
Liao et al.	2003	21	21	7	20.1	3.4	17.2	3.12
Wang et al.	2002	44	44	7	16.82	2.99	18.23	3.17
Scar index (SI)								
Liang et al.	2006	60	60	7	8.12	1.47	9.79	1.85
Luo et al.	2007	28	28	6	7.92	1.57	9.18	1.88
Chen et al.	2009	60	60	7	6.53	1.66	9.29	2.93
Luo et al.	2013	30	30	7	7.17	1.45	9.19	2.32
Wang et al.	2003	37	37	7	7.19	1.67	8.92	1.78

SD: Standard deviation; N1: Number for case; N2: Number for control.

cles from Web of Knowledge, 72 articles from Wanfang databases, 160 articles from Embase, 149 articles from Cochrane library. A total of 296 studies were excluded on abstract review. The remaining 32 studies were reviewed for further details. Additional 23 studies were excluded for various reasons as shown in **Figure 1**. Finally, 9 articles [10-18] involving a total of 441 patients were included in this meta-analysis. Characteristics of included studies are presented in **Table 1**. Three studies come from Italy, 2 from Japan, 2 from United Kingdom, 1 from United States and 1 from Netherlands. The quality of studies was generally good, with results of study quality assessment yielded a score of 6 or above for all included studies.

Comparison of the efficacy between EGF therapy with the other therapy

The healing time (HT) was significantly lower in epidermal growth factor (EGF) therapy group than in other therapy group (WMD = -0.70, 95% CI = -0.87, -0.53, I^2 = 83.0%) (**Figure 2**). The wounds healing speed (WHS) was significant in EGF therapy group compared with the other therapy group (WMD = 1.13, 95% CI = 0.94, 1.33, I^2 = 91.1%) (**Figure 3**). The scar index (SI) in EGF therapy group was also significant lower than the other therapy group (WMD = -1.01, 95% CI = -1.21, -0.81, I^2 = 0%) (**Figure 4**).

Meta-regression and sensitivity analyses

Significant heterogeneity existed, mainly in comparison of healing time and wounds healing speed. Univariate meta-regression with the covariates of publication year, location where the study conducted and number of participants was performed. However, no significant findings were found in the above-mentioned analysis. A sensitivity analysis was conducted to assess the influence of each study, by sequential omission of each eligible study. The results showed that the results were not affected by any single study.

Publication bias

Egger regression asymmetry test and funnel plot (**Figure 5**) showed that no evidence of significant publication bias between EGF therapy and the treatment of deep second degree burn wounds, when compared the HT, WHS, and SI.

Discussion

Unfortunately burns are a common occurrence, leading to scarring or death. Burns can be classified into first, second and third degrees, with first-degree burns being limited to the epidermis, second-degree burns involving the epidermis and part of the dermis, and third-degree burns destroying the epidermis and all dermis [19, 20]. Serious injuries to the skin such as burns require immediate treatment to rebuild the barrier function [21]. Therefore, accelera-

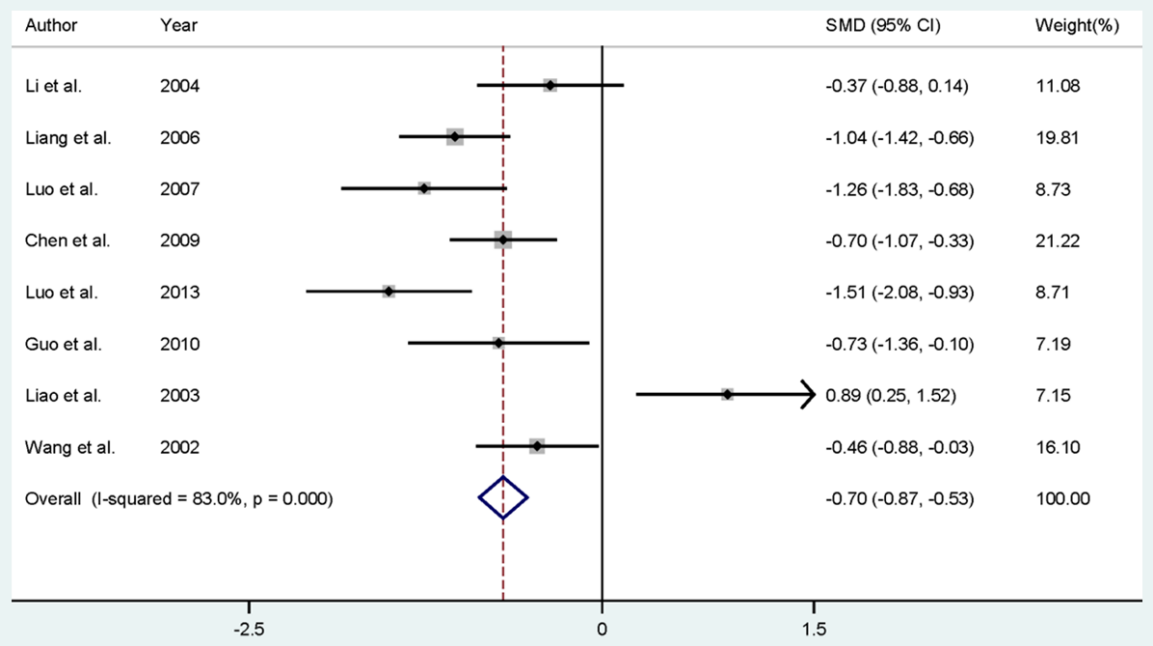

Figure 2. Comparison of epidermal growth factor therapy group and other therapy group with respect to healing time.

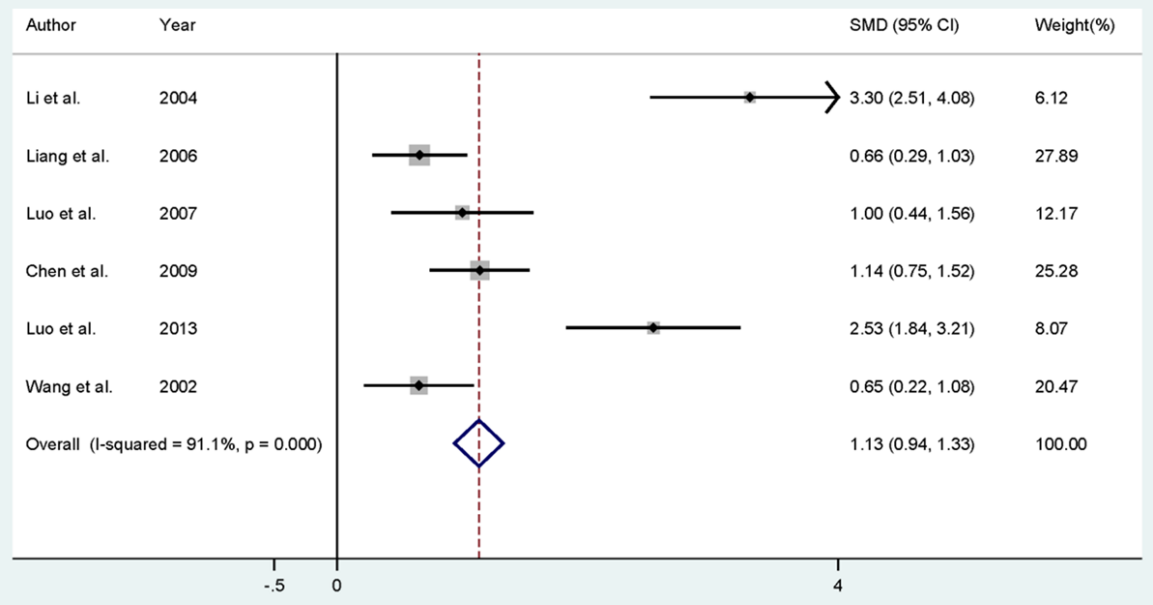

Figure 3. Comparison of epidermal growth factor therapy group and other therapy group with respect to wounds healing speed.

tion of the rate of tissue regeneration in wounds is a crucial procedure for burn treatment [22]. Although many advances have been made to treat burn injuries, the consensus on the best treatment to hasten healing has not been reached.

To the best of our knowledge, this is the first comprehensive meta-analysis to compare epidermal growth factor (EGF) therapy and other therapy for treatment of deep second degree burn wounds. The results of this study show that EGF therapy is superior to other therapy in

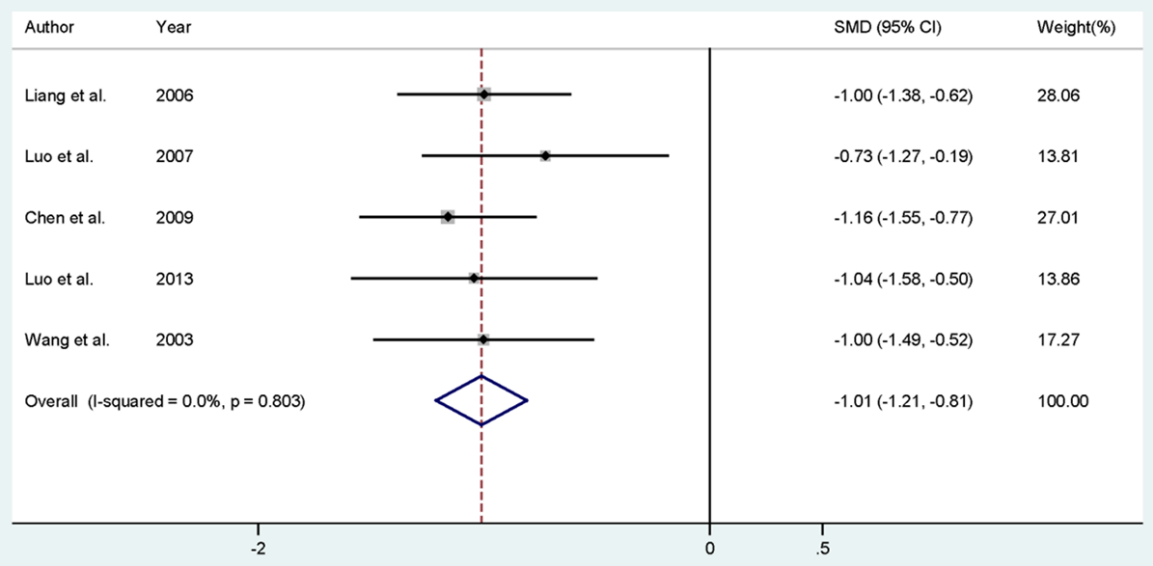

Figure 4. Comparison of epidermal growth factor therapy group and other therapy group with respect to scar index.

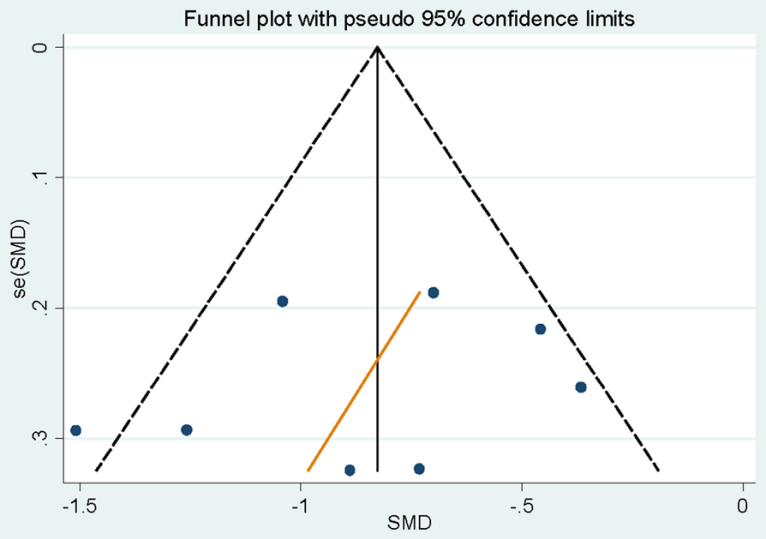

Figure 5. Funnel plot for the analysis of publication bias with respect to healing time.

terms of the healing time, wounds healing speed and the scar index.

More prospective studies are needed to fully compare the effectiveness of EGF therapy for treatment of deep second degree burn wounds. The results of this study should be interpreted while taking its limitations into account. First, some of the data used for the WMD statistical analysis were median and range rather than mean and SD, which may result in inaccuracy. Second, some original studies did not adjust for potentially relevant confounders. And these factors could lead to bias in the results. Finally, this meta-analysis was characterized by high heterogeneity in the HT and WHS, because it was impossible to match the patient characteristics among all studies.

In summary, this meta-analysis indicates that compared with other therapy, epidermal growth factor therapy is generally safer and more reliable for patients with deep second degree burn wounds.

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Disclosure of conflict of interest

None.

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