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The Safety and efficacy of botulinum toxin type A injection for postoperative scar prevention: A systematic review and meta-analysis

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Abstract

Background: Active prevention and treatment of scars are particularly important. Several studies have used botulinum toxin type A(BTXA) to prevent postoperative scarring. The aim of this systematic review and meta-analysis was to systematically evaluate the efficacy and safety of BTXA in preventing and treating postoperative scars.

Methods: A computer-based search was conducted for the five databases including PubMed, Cochrane Library, EMBASE, CNKI, and Wanfang up to May 22, 2019, to collect the relevant literatures on BTXA treatment of postoperative hypertrophic scars. A meta-analysis was made with the software of Revman 5.3 based on the study endpoint of scar width, Vancouver Scar Scale (VSS), Visual Analogue Scale (VAS) scores, and patient satisfaction as well.

Results: A total of 18 randomized controlled trials (RCTs) studies were included with 915 patients in all. The result showed that, compared with the control group, the scar width, VAS scores, and VSS scores of the BTXA group were significantly improved and higher patient satisfaction was achieved.

Conclusion: BTXA has a certain curative effect on postoperative scar prevention and treatment without obvious side effects.

KEYWORDS

BTXA, meta-analysis, scars

1 | INTRODUCTION

Scar is the natural product of wound healing, but pathological scar, including hypertrophic scar and keloid, may form when healing process is abnormal. When pathological scar occurs in the face, neck, or joints of limbs, it will not only affect the appearance, but also may be accompanied by itching, pain and other complications, and even cause functional disturbance, which will bring great harm to the physical and mental health of patients. Currently, the methods in common use for the treatment of pathological scars include silicone sheets and gel, pressure therapy, steroid injection, 5-fluorouracil, cryotherapy, and surgical resection.[1] Yet, the therapeutic effect is not ideal. Therefore, new and effective treatments are needed to address the patient's pain. BTXA is a neurotoxin secreted by Clostridium botulinum bacteria. It was first approved by the US Food and Drug Administration (FDA) for strabismus and blepharospasm.[2] In recent years, the application of BTXA in the treatment of hypertrophic scars and keloids has been reported from time to time, but its efficacy still needs further comprehensive evaluation. Therefore, this study will conduct a meta-analysis on existing

research evidences to systematically evaluate the efficacy of BTXA in the prevention and treatment of postoperative scars.

2 | MATERIALS AND METHODS

2.1 | Inclusion criteria and exclusion criteria

Inclusion criteria: (a) Study type and language: A randomized controlled trial (RCT) published in Chinese or English; (b) Subjects: The patients requiring surgical treatment; (c) Intervention measures: The treatment group was injected with BTXA before/after the operation, while the control group was injected with equal normal saline/did not receive injection. (d) Outcome indicators: including scar width, VSS score, VAS score, or patient satisfaction. Exclusion criteria: (a) Nonrandomized controlled trials, or studies of hormones, intense pulsed light treatment, and other treatments; (b) Correspondence, reviews, case reports, etc; (c) No relevant statistical data; (d) Redundant or duplicate publication.

2.2 | Search strategy

A computer-based search was conducted, including PubMed, Cochrane Library, EMBASE, CNKI, and Wanfang up to May 22, 2019, with the search terms of "BOTOX/Dysport/BoNT/botulin*/BTXA/botulinum/botulinum toxin type A" and "scar*/cicatrix." Based on the search results, relevant studies were further collected that meet the inclusion and exclusion criteria.

2.3 | Research data extraction and quality assessment

Two researchers conducted independent literature screening and data collection according to the inclusion and exclusion criteria, and conducted cross-checking. Any differences between the two opinions would be discussed and decided by a research group involving a third researcher. The quality of included studies would be assessed with the Cochrane assessment tool.

2.4 | Data analysis

The software of Revman5.3 provided by Cochrane Collaboration was applied for data analysis. First, the heterogeneity test was conducted. If the heterogeneity was small, that is, $I^2 \leq 50\%$ and $P \geq .1$, the fixed effect model was adopted; otherwise, if $I^2 > 50\%$ and $P < .1$, the random effect model was adopted. The continuous variables of weighted mean difference (WMD), standardized mean difference (SMD), and 95% confidence interval (CI) were used as statistics, the difference was statistically significant when $P < .05$.

3 | RESULTS

3.1 | Literature search result and included studies

Based on the preliminary identification of 787 Chinese and English records in all, removing 227 duplicates and conducting screening

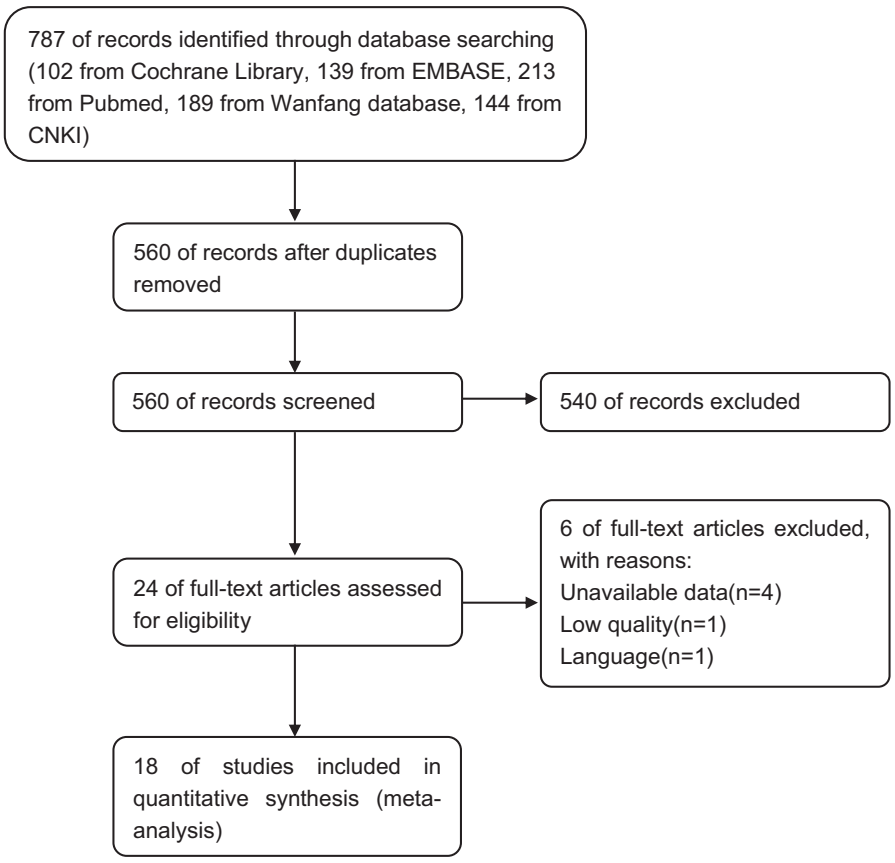

FIGURE 1 Flow chart of literature screening

FIGURE 2 Risk of bias summary

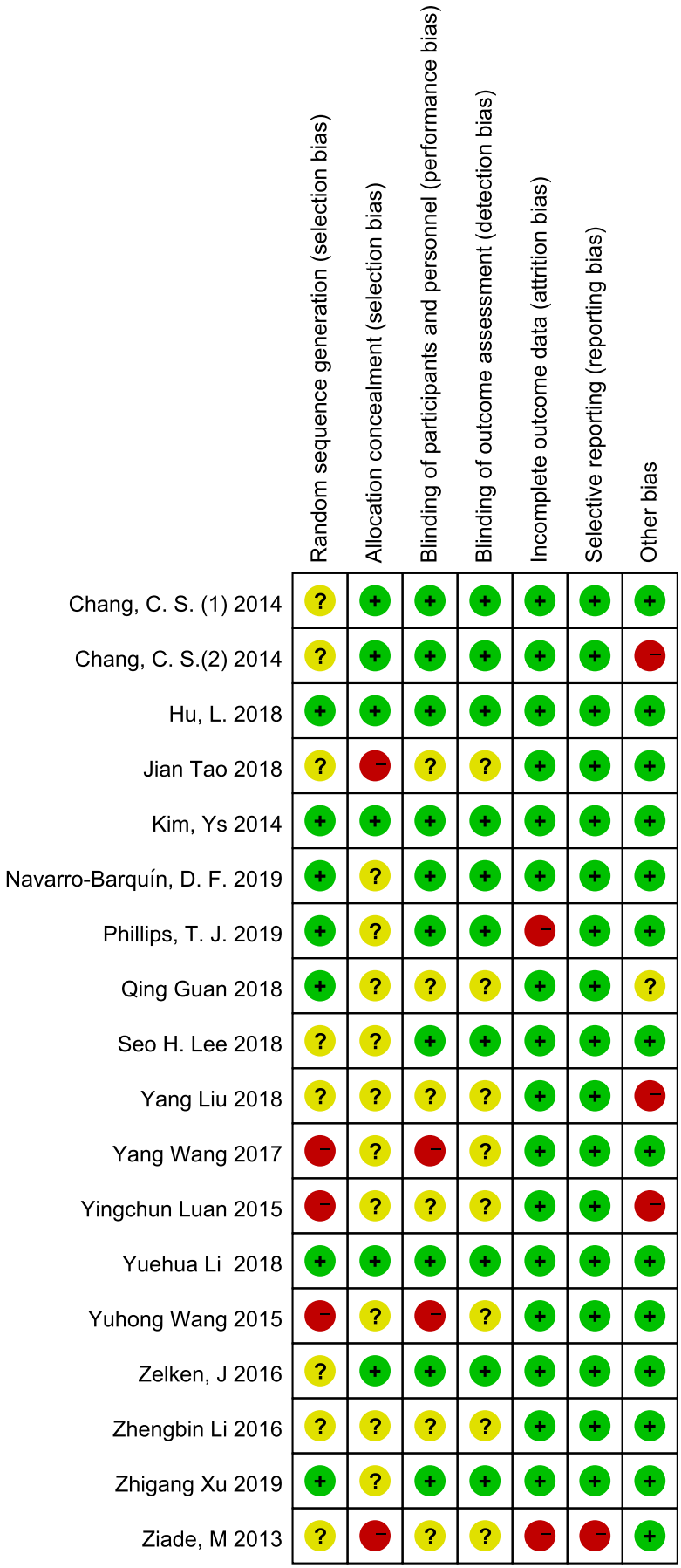

TABLE 1 Characteristics of included studies

Study	Country	Scar position	Relationship with tension line	Experimental				Control
				Number of patients	BTXA type	Concentration	Dose	Number of patients
Zhigang Xu 2019[3]	China	Face	Uncertain	32	HBTX-A	/	10 U/cm	32
Phillips 2019[4]	Canada	Neck	Parallel	40	Botox	100 U/mL	5 U/site	40
Navarro-Barquín 2019[5]	Mexico	Upper lip	Vertical	11	/	100 U/mL	total 8 U , <2 U/kg	11
Qing Guan 2018[6]	China	Face	Uncertain	57	HBTX-A	25 U/mL	/	58
Jian Tao 2018[7]	China	Forehead	Uncertain	20	HBTX-A	1 U/0.1 mL	1.5 U/cm	20
Yang Liu 2018[8]	China	Face	Uncertain	45	HBTX-A	/	5 U/site	45
YueHua Li 2018[9]	China	Chest	Vertical	19	BOTOX-A	50 U/mL	5 U/cm	19
Seo H. Lee 2018[10]	Korea	Forehead	Uncertain	18	NABTX-A	25 U/mL	/	18
Hu 2018[11]	China	Face	Uncertain	16	HBTX-A	50 U/mL	10 U/cm	16
Yang Wang 2017[12]	China	Forehead	Parallel	40	HBTX-A	/	0.5-2 U/site	40
Zelken 2016[13]	China	Forehead	Vertical	26	BOTOX-A	40 U/mL	2 U/site	26
Zhengbin Li 2016[14]	China	Face	Uncertain	49	HBTX-A	/	2-5 U/site	49
Yuhong Wang 2015[15]	China	Epicanthus	Parallel	39	BOTOX-A	/	1.7-3.3 U/cm	42
Yingchun Luan 2015[16]	China	Face	Uncertain	35	HBTX-A	/	/	35
Kim 2014[17]	Korea	Neck	Parallel	15	NEBTX-A	50 U/mL	/	15
Chang (1) 2014[18]	China	Upper lip	Vertical	30	BOTOX-A	25 U/mL	2.5 U/site	30
Chang (2) 2014[19]	China	Upper lip	Vertical	30	BOTOX-A	25 U/mL	1 U/kg	30
Ziade 2013[20]	France	Face	Uncertain	15	BOTOX-A	10 U/mL	/	15

Abbreviations: BOTOX-A, allergan botulinum toxin type A; BTXA, botulinum toxin type A; HBTX-A, hengli botulinum toxin type A; NABTX-A, nabota botulinum toxin type A; NEBTX-A, Neuronox botulinum toxin type A; OSAS, observer scar assessment scale; PSAS, Patient Scar Assessment Scale; SBSES, Stony Brook Scar Evaluation Scale; VAS, visual analogue scale; VSS, Vancouver Scar Scale.

and quality assessment by reading the title, abstract, and the full text when necessary and according to the above inclusion and exclusion criteria, finally 18 studies published from 2013 to 2019 (Figure 1) were included, including 8 Chinese articles and 10 English articles, involving 915 patients. The quality assessment results and basic information included in the studies are shown in Figure 2 and Table 1.

3.2 | Scar width comparison

A total of 10 studies were included in the comparison,[3,5,9-12,14,15,18,19] but two studies[18,19] measured the data from two points, so there were 12 data in total (Figure 3). The standardized mean difference (SMD) was chosen because of the large gap between the research results (0.32 ~ 3.25 mm). Heterogeneity test results suggested that

Intervention	Injection time	Injection site	Number of lost visits		Follow-up(month)	Outcome indicators
			Experimental	Control		
saline	Immediately after wound closure	5 mm from the scar's edge	0	0	6	Width of scar, VAS, VSS, patient satisfaction
saline	Immediately after wound closure	/	1 month-10 , 6 months-16 , 1 year-17		1/6/12	VSS, OSAS, PSAS
saline	At least 7 days before surgery	Oral sacral muscle injection	0	0	3/6	Width of scar, VSS
no treatment	Immediately after wound closure	/	0	0	1/3/6	Effectiveness, patient satisfaction
saline	Immediately after wound closure	3-4 mm from the scar's edge	2	2	12	VAS, VSS, PSAS
no treatment	Immediately after wound closure	1 cm from the scar's edge	0	0	3	VSS, SBSES, patient satisfaction
saline	Within 14 days after surgery	1 cm from the scar's edge	2	2	6	VSS, width of scar, patient satisfaction
no treatment	Within 5 days after surgery	/	3	3	6	VSS, width of scar, color difference
saline	Immediately after wound closure	5 mm from the scar's edge	2	2	6	VAS, VSS, width of scar
no treatment	7 days after surgery	1 cm from the scar's edge	0	0	6	Width of scar, OSAS, patient satisfaction
saline	10 days before surgery	/	0	0	27 in average	VAS
no treatment	Immediately after wound closure	1 cm from the scar's edge	0	0	12	width of scar, OSAS
no treatment	Immediately after wound closure	3 mm from the scar's edge	4	6	6	Width of scar, OSAS
no treatment	Immediately after wound closure	/	0	0	/	Effectiveness, patient satisfaction
saline	Within 10 days after surgery	/	2	2	6	SBSES, patient satisfaction
saline	Immediately after wound closure	5 mm from the scar's edge	0	2	6	VAS, VSS, width of scar
saline	Immediately after wound closure	5 mm from the scar's edge	0	1	6	VAS, VSS, width of scar
no treatment	Within 3 days after surgery	/	4	2	12	VAS, VSS, PSAS, OSAS

there was heterogeneity between studies (χ^2 = 29.26, P = .002, I^2 = 62%>50%), so the random effect model was adopted for the combination, SMD = −1.09[95%CI: (−1.36,-0.81), P < .00001]; The results suggested that the difference between the treatment group and the control group was statistically significant, and the combined results were located to the left of the invalid line, indicating that the patients in the BTXA group had narrower scar than those in the control group.

The subgroup analysis was performed according to the relationship between the scar direction and the skin tension line. The included studies were divided into three groups, namely vertical group, parallel group, and uncertain group. The heterogeneity test results showed that the homogeneity in the vertical group and the parallel group was good (χ^2 = 1.21, P = .94, I^2 = 0% and χ^2 = 0.28, P = .59, I^2 = 0%), and the effect of BTXA was obvious in the vertical group (P = .006) (Figure 4).

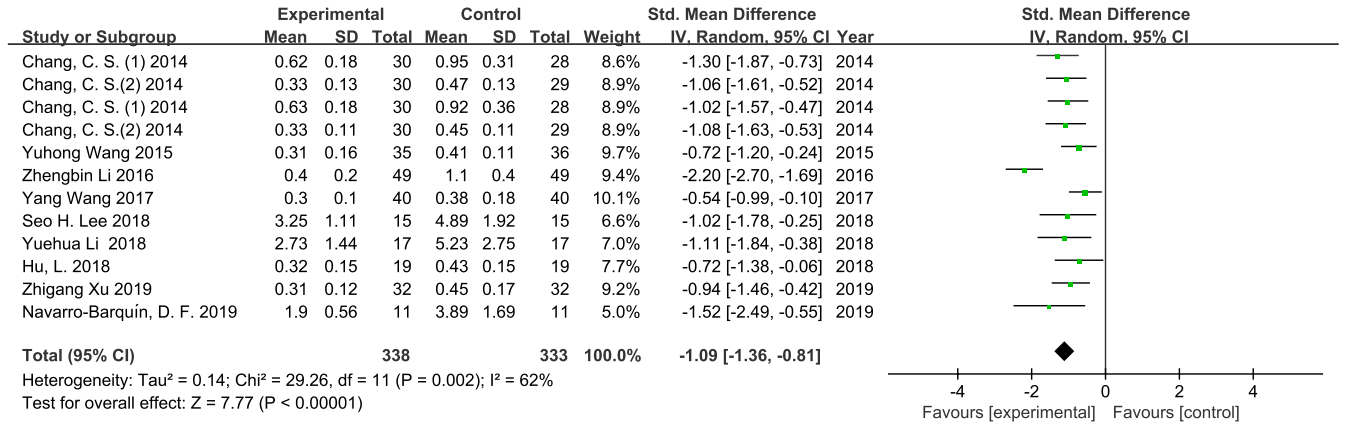

FIGURE 3 Forest map of scar width comparison

3.3 | VSS comparison

A total of 9 studies were included in the comparison (Figure 5).[3,5,7-11,18,19] The heterogeneity test suggested that there was heterogeneity between studies (χ^2 = 139.16, P < .00001, I^2 = 94%>50%), so the random effect model was adopted for the combination, WMD = −1.82[95%CI: (−2.54,-1.10), P < .00001]; The results suggested that the VSS scores were significantly different between the two groups, and the VSS score was lower in the BTXA group than in the control group.

3.4 | VAS comparison

A total of 7 studies were included in the comparison (Figure 6).[3,7,11,13,18-20] The heterogeneity test suggested that there was heterogeneity between studies (χ^2 = 332.73, P < .00001, I^2 = 98%>50%, so the random effect model was adopted for the combination, WMD = 1.69[95%CI: (0.38,3.01), P = .01]; The results suggested that the difference between the treatment group and the control group was statistically significant, and the combined results were located to the right of the invalid line, indicating that the VAS score was higher in the BTXA group.

3.5 | Patient satisfaction

A total of 7 studies reported patient satisfaction (Figure 7),[3,6,8,9,12,16,17] of which, the study of Wang Yang et al[12] used the questionnaire survey covering scar hypertrophy, recovery progress, discomfort, ecchymosis, and psychological impact; the study of Xu Zhigang et al[3] used a 10-point value to evaluate the scar of patients, which were not included in this comparison due to the lack of specific data; The remaining five studies used "very satisfied," "satisfied," "slightly satisfied" and "dissatisfied", or "satisfied," "average" and "dissatisfied" for rating. We defined the percentage of the sum of options other than the "dissatisfied" in the total number as patient satisfaction, and the heterogeneity test suggested limited heterogeneity between studies (χ^2 = 3.30, P = .51, I^2 = 0%<50%), so the fixed effect model was adopted, RR = 1.19[95%CI:(1.11,1.29), P < .00001]; The results showed that there was significant difference in patient satisfaction between the two groups, among which the patient satisfaction in the BTXA group was significantly higher than that in the control group.

3.6 | Adverse events

Ten of 18 studies reported adverse reactions.[3,5,7-10,12,14,15,20] Besides transient pain, pruritus, and mild headache at the injection point, there were 2 cases of ptosis, 1 case of philtrum fixation wound, 1 case of asymmetrical smile, 1 case of asymmetric oral commissure, 1 case of asymmetric eyebrow, 1 case of abscess, and 1 case of ischemia. The remaining 5 studies reported no adverse events,[4,11,13,18,19] and 3 studies did not report.[6,16,17]

4 | DISCUSSION

Botulinum toxin type A (BTXA) was first used to treat strabismus, eye muscle spasm, and other diseases, and has been widely used in plastic surgery. Recent studies have shown that BTXA has a positive effect on the prevention and treatment of postoperative hypertrophic scars and has some effect on keloids, contracture scars, etc,[21-23] but the mechanism of action is not clear yet, which may be related to the "chemo-denervation." Tension plays an important role in wound healing. The mechanical signals generated by tension on both sides of the wound can affect the movement and contraction of fibroblasts, the expression of Type I collagen, and the transformation from fibroblasts to myofibroblasts.[24] However, the N-terminal of BTXA light chain has the activity of zinc metalloproteinase, which can cut the synaptosomal-associated protein of 25 kDa (SNAP-25) and prevent the release of acetylcholine into the synaptic cleft, thus causing "chemo-denervation," reducing the tension on both sides of the wound and affecting the scar morphology.[25,26] In addition, some evidences suggest that BTXA may affect scar formation by reducing fibroblast proliferation, reducing TGF-β expression, and altering collagen deposition and remodeling processes.[27] Two experiments by Xiao, Z. et al indicated that BTXA can effectively inhibit

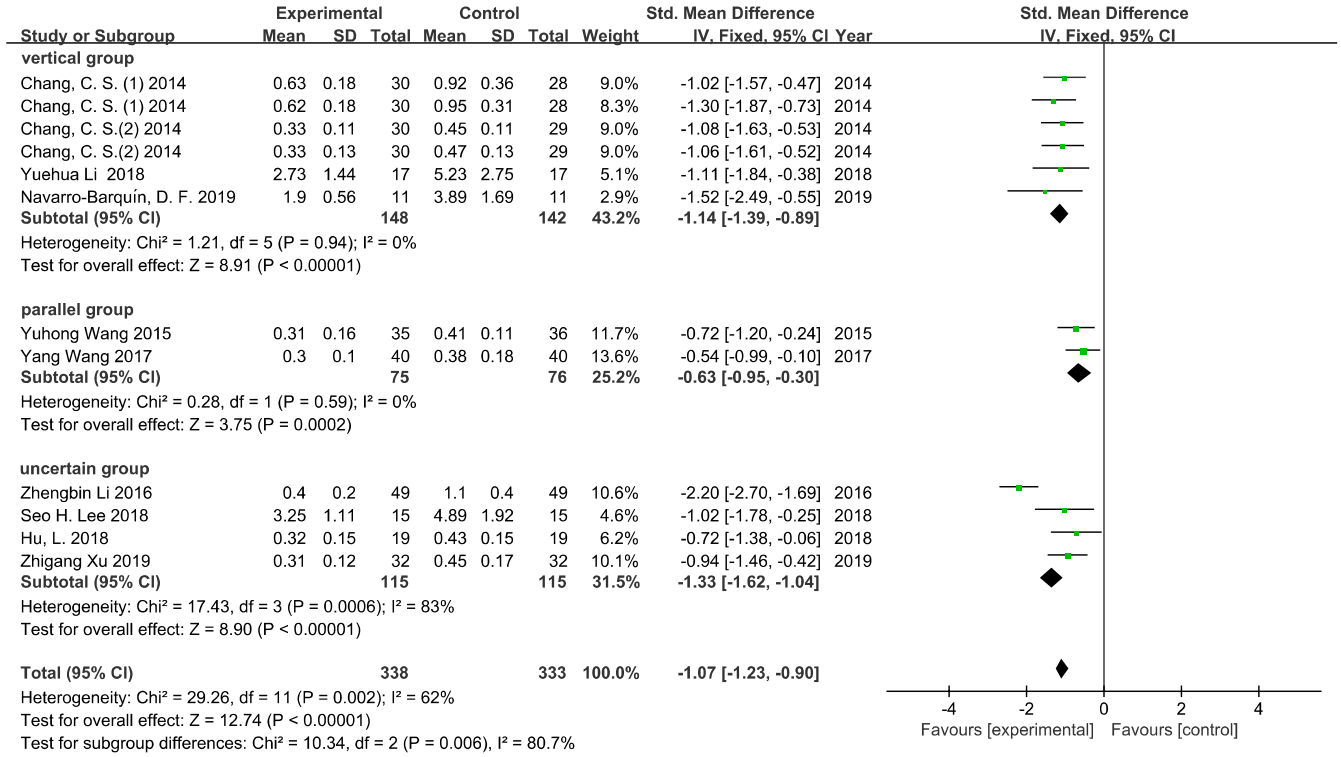

FIGURE 4 Forest map of scar width subgroup analysis

the proliferation of fibroblasts derived from hypertrophic scar and further reduce the content of TGF-β1[28] and its downstream regulator connective tissue growth factor (CTGF).[29] Jeong et al[30] found in the experiments that BTXA can reduce the expression of α-SMA and its mRNA in fibroblasts in hypertrophic scar and directly inhibit the differentiation of fibroblasts into myofibroblasts. However, Haubner et al[31] showed in the vitro experiments no significant effect of BTXA on the proliferation of fibroblasts in keloids and the expression of

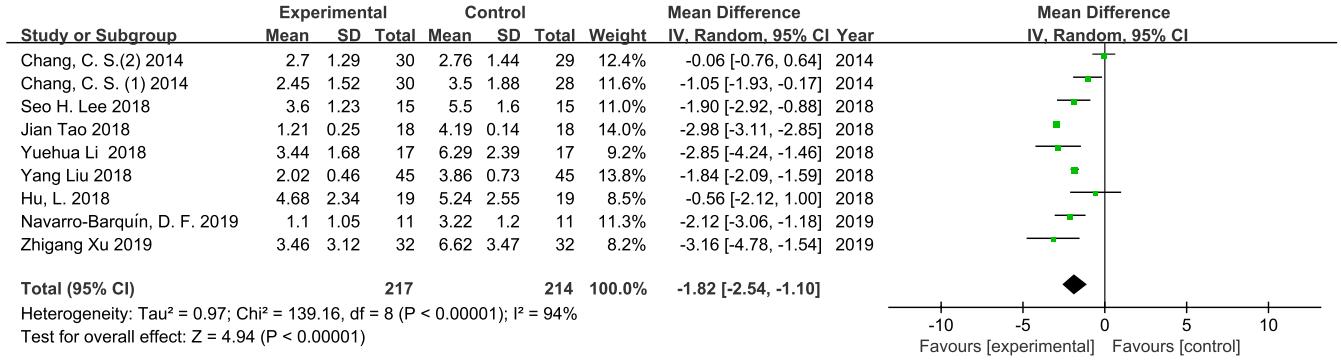

FIGURE 5 Forest map of Vancouver Scar Scale score comparison

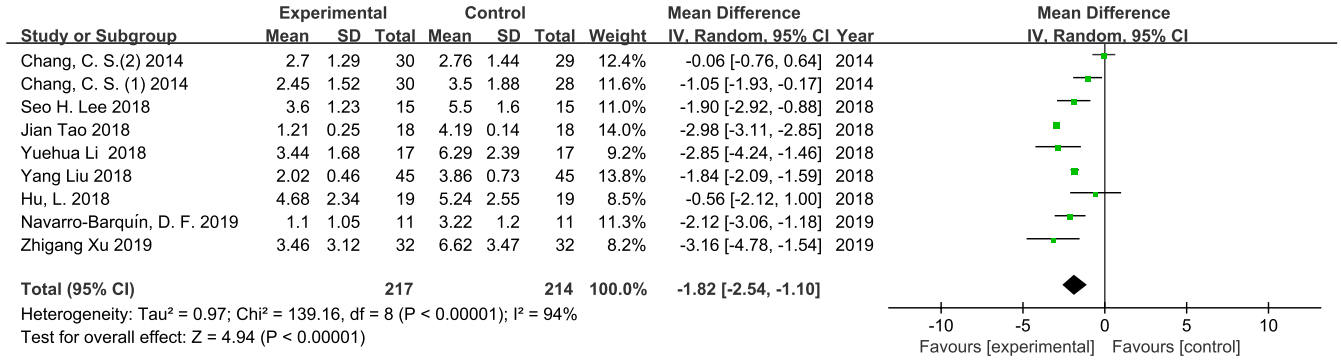

FIGURE 6 Forest map of visual analogue scale score comparison

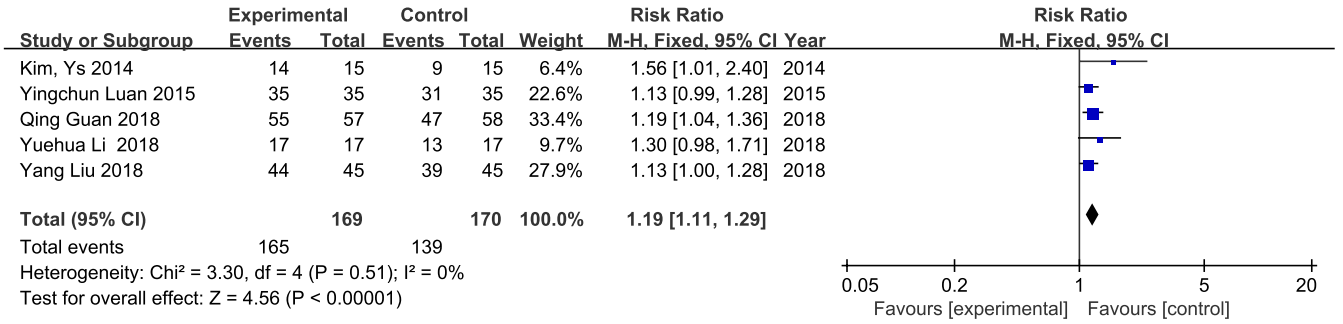

FIGURE 7 Forest map of patient satisfaction comparison

IL-6, VEGF, and TGF-β. The mechanism of BTXA and its effect on different types of scar still needs to be further clarified by follow-up studies.

Two meta-analysis results published by Wang[32] and Wang[33] before including 9 studies respectively have showed that BTXA injection is a safe and effective treatment for scar prevention, but some recent studies have reached negative conclusions.[4,7,10,11] Therefore, a larger range of meta-analysis is needed for evidence support. This paper counted the relevant studies published in English and Chinese, and finally included 18 studies with a total of 915 patients, all of which were randomized controlled trials. The results showed that the scar width (SMD = −1.09, $P < .00001$), VAS (WMD = 1.69, $P = .01$), VSS score (WMD = −1.82, $P < .00001$), and patient satisfaction (RR = 1.19, $P < .00001$) in the BTXA group were significantly improved compared with the control group. But the results of some experiments are inconsistent. In the 2 studies of Chang et al[19] and Hu et al,[11] there were significant differences in VAS score and scar width between the two groups, but no significant differences in VSS score. According to the authors, this may be because this scale is applicable to the evaluation of burn scars, but not highly sensitive to nonburn scars. In the study of Phillips et al,[4] there were no obvious difference in VSS, OSAS, and PSAS between the two groups; but the subgroup analysis found that BTXA in patients with a history of severe scars has a certain effect. The authors believe that it may be influenced by the origin of the wound and its relationship with tension lines, and speculate that the higher proportion of patients with a history of severe scars in other studies may lead to the inconsistent results.[4] However, no relevant analysis has been carried out in other included studies, and the number of cases in this study is small, with a large number of people lost to follow-up. Further study is needed for the details.

Many studies have included scar width as an evaluation index, but different measurement methods have been adopted, such as recording the average width of the widest and narrowest of the scar,[11] or measuring at two specified sites.[19] Considering that the width of the whole scar may not be consistent or even vary greatly in different parts, such measurement method may not reflect the level of the whole scar, so future research needs more objective and accurate measurement method. But overall, the average scar size in the BTXA group was significantly less than that in the control group.

Since the relationship between the wound direction and the skin tension line is an important factor affecting scar formation, the subgroup analysis of scar width results was conducted and found that the effect of BTXA was more obvious when the wound direction was perpendicular to skin tension line ($P = .006$). However, this result should be interpreted with caution because the site of scar is not completely consistent and the injection concentration, site and interval are not exactly the same in different studies. Subgroup analysis of VAS and VSS scores was not performed because the wound direction was either perpendicular to the tension line or not clear.

The time of BTXA injection varied from 10 days before surgery to 14 days after surgery, most of which were given immediately after wound closure. Since BTXA generally works within 3-14 days after injection, some scholars believe that preoperative injection of BTXA can provide more timely therapeutic effect, not only eliminating the influence of early exercise on the experimental area, but also reducing the influence of surgical operation (such as inflammation, intraoperative irrigation, local anesthesia, and the use of vasoconstrictor drugs) on the effect of BTXA.[13] Further research is needed on when BTXA injections are more reasonable. The drug concentration in each study varied from 10-100 U/mL. The total injection dose was generally less than 100 U. Five studies failed to state the dose of BTXA.[6,10,16,17,20] Two studies calculated the dose based on body weight (1-2 U/kg).[5,19] Others mainly determined the injection dose based on the length of the scar (1.5-10 U/cm)[3,7,9,11,15] or the number of injection point (0.5-5 U/site),[4,8,12-14,18] lacking of comparability. Considering the distribution of muscle tissue around the incision and the individual differences as well, it is difficult to determine the injection dose accurately. High concentrations of BTXA (>20 U/mL) have been shown to inhibit angiogenesis and thus affect wound healing,[34] but in all the included studies, only one patient developed ischemia.[20]

The follow-up time of each study was not exactly the same (3-27 months). In this article, we compare the data at the longest follow-up time. Considering that the effect of BTXA basically disappeared after 6-8 months, the follow-up time of most studies was 6 months. Some scholars believe that the follow-up time should be extended to at least 1 year to determine whether local injection of BTXA can improve scar, or only delay the production of scar.[4] The site of scar in each study was also not identical, most on the face and very few on the neck or chest. In addition to the site of scar,

the relationship between the scar and the tension line also has some influence on the results.

There are some limitations in this study: (a) Some included studies did not describe randomization, allocation concealment, or blinding methods, which resulted in a high risk of bias; (b) some studies did not describe the experimental process accurately, such as the distance between injection points, injection dose, concentration, etc, leading to a higher risk of bias; (c) there were certain differences in injection time, concentration, and dose of BTXA among various studies. Due to the small number of studies included, some subgroup analyses cannot be performed. (d) There may be publication bias.

In general, BTXA injection is a safe and effective method for the prevention and treatment of postoperative scar, but the operating standards of various clinical studies are not completely unified at present, and its exact efficacy still needs to be supported by more high-quality and large-scale RCT results. Follow-up studies need to clarify the most appropriate injection method for BTXA to prevent scar, including injection dose, spacing and injection timing, etc, as well as the effect differences of BTXA for different types of scars and for patients with a history of severe scar.

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