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Prospects for Use of Botulinum Toxin Type A for Prevention of Hypertrophic and Keloid Scars after Surgeries (Meta-analysis)

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Abstract

Objective To evaluate the possibility of improving and preventing the formation of postoperative hypertrophic and keloid scars using botulinum toxin type A (BTA).

Materials and Methods Scientific articles published in English have been systematically screened in PubMed/MEDLINE database over the entire period. The following information about the studies was analyzed: first author surname; year of publication; number of patients; average age; scar location; dosage of the drug administered; follow-up duration; scar assessment methods; results, incidence of hypertrophic and keloid scars formation. The odds ratio and 95% confidence interval were calculated for each of the estimated parameters. The statistical heterogeneity of publications assessed using the criteria of chi-square test and I^2. The differences were considered significant at $p < 0.05$.

Results A total of 18 prospective randomized studies were selected for evaluation, containing data on the use of BTA in 363 cases. Patients receiving botulinum toxin had a lower Vancouver scar scale index, higher visual analog scale index, and higher Stony Brook scar evaluation scale score. The use of BTA reduces the risk of perceptible scar formation, the incidence of hypertrophic and keloid scars.

Conclusion The use of BTA to obtain imperceptible scar and prevent hypertrophic and keloid postoperative scars demonstrates good prospects. However, there is no consensus regarding the pathophysiological mechanisms underlying the positive effect of BTA on the prevention of hypertrophic and keloid scars.

Keywords

- botulinum toxin type A
- scar
- hypertrophic scars
- keloid scars
- prevention of pathological scars

Introduction

One of the main functions of skin is to serve as a barrier. In the modern world, a person is exposed to the risk of skin injuries on a daily basis. As a rule, wound healing after surgical interventions occurs by primary tension with the formation of normotrophic scars, but in some cases, pathological (hypertrophic and keloid) scars are observed in patients after surgery. A special attention should be paid to situations when atypical scar changes occur after surgical interventions performed for esthetic reasons. Currently, there are many ways to prevent the formation of

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hypertrophic and keloid scars, but none of them is universal. In the last decade, researchers have published several scientific articles assessing the possibilities of using botulinum toxin type A (BTA) to prevent pathological scarring.[1–6] However, these data presented in a few clinical studies performed with insufficient power to form reasoned judgments. Therefore, to find an answer to the question about the possibility of using BTA to prevent hypertrophic and keloid scars, it is advisable to conduct a special study in the meta-analysis format.

Objective

To evaluate the possibility of improving and preventing the formation of postoperative hypertrophic and keloid scars using BTA.

Materials and Methods

Publications search for meta-analyses performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses statement recommendations.[7] A systematic selection of articles in the PubMed/MEDLINE database available for all years was performed, using the following search keywords: "Botulotoxin A," "Keloid scars," "Hypertrophic scars," "Treatment of hypertrophic scars," "Treatment of keloid scars." During the meta-analysis, we considered the data contained in the reports on randomized controlled trials (RCTs), the authors of which used BTA for the prevention of pathological scars.[8]

Selecting the scientific articles excluded articles not related to the scope of the study, conference materials, letters to the editor, comments, and literature reviews.

Two authors independently extracted data from all selected studies using the following selection criteria: first author surname; year of publication; number of patients; average age; scar location; dosage of the drug administered; follow-up duration; scar assessment methods; results, incidence of hypertrophic and keloid scars formation. Disagreements were resolved by other authors.

The odds ratio and 95% confidence interval (CI) were calculated for each of the estimated parameters. Statistical heterogeneity of publications assessed using the criteria of chi-square test and I^2. At values of $I^2 \geq 50\%$, heterogeneity regarded as significant. In these cases, the Mantel–Hensel model with random effects was used for data analysis. At $I^2 < 50\%$, the Mantel–Hensel model with fixed effects was applied. The differences were considered significant at $p < 0.05$. Egger's test was used to detect publication bias in the meta-analysis. Statistical analysis was performed using the Excel Spreadsheets (Microsoft Office 2019) and the Review Manager, Version 5.3 (Cochrane Collaboration).

Results

According to the initial search query, 2,498 potential studies were found in databases PubMed/MEDLINE (1,765 studies after exclusion of repeated publications). The data presented in the 261 scientific publications were analyzed; 96 publications were scrutinized, 18 of which met the criteria for inclusion in the study (►**Fig. 1**).

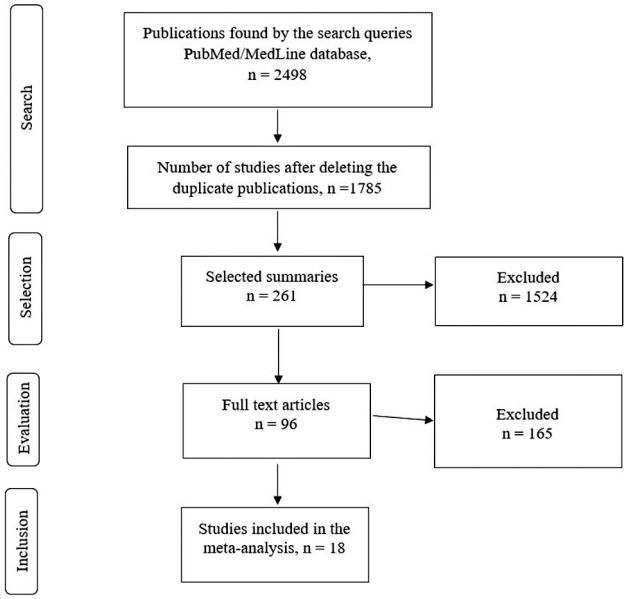

Fig. 1 Searching algorithm for scientific publications during the study.

For meta-analysis, selected data of 18 RCTs studies were of good quality (►**Table 1**) on the efficiency of the BTA use in pathologic scars treatment and prevention cases.[9–26]

In total, data on 363 cases of the BTA use for prevention of scars were analyzed. The age of the patients ranged from 6 to 68 years, average 37.3. In 15 of 18 analyzed studies, scars were located on face and neck. In 6 studies, researchers reported the BTA injections performed immediately after wound closure, in 10 articles, the BTA administered from 5 to 14 days after surgery. The amount of BTA IU injected during the procedure varied from 6 to 100. The duration of patient follow-up ranged from 6 to 24 months.

One of the most frequent scars assessment methods in the analyzed studies was visual analog scale (VAS). Obviously, this assessment method is subjective. VAS used to assess skin condition based on appearance. The rating scale includes 10 points from 0 (worst) to 10 (excellent).[27] RCTs containing data ~326 cases in BTA and control groups were included. During the meta-analysis, means and standard deviations were extracted and compared. The heterogeneity test revealed high heterogeneity in studies (chi-square test $= 23.02$, $p = 0.002$, $I^2 = 70\%$), and the Mantel–Hensel model with random effects was used for data analysis. The results showed that the VAS score in the BTA group was significantly higher than in the control group (mean difference [MD] $= 1.36$, 95% CI $= 1.12–1.59$, $p < 0.00001$) (►**Fig. 2**).

The Vancouver scar scale (VSS) was also used for assessment in the selected studies. It is the most common scar scoring system. The VSS includes following criteria: scar height (0–4 points), severity of blood vessels (0–3 points), degree of pigmentation (0–3 points), and scar elasticity (0–5 points). The higher the VSS score, the worse the

Table 1 Basic data on the analyzed publications of the study

Studies	Sample size		Average age (y)		Scar location	Study design	Assessment method
	BTA	Control	BTA	Control			
Winayanuwattikun et al (2023)	13	13	30.4	30.4	Breast	RCT	VSS, POSAS, standard measurement device
Tawfik and *Ali* (2023)	15	15	7.2	7.2	Head	RCT	VSS and by skin analysis camera system
Chen et al (2021)	22	22	37	37	Face, neck, trunk, upper extremity	RCT	SBSES, VAS
Huang et al (2021)	18	19	61.56	58.35	Eyelids	RCT	VSS, VAS
Abedini et al (2020)	19	19	37.84	37.84	Breast, abdomen	RCT	SBSES
Bae et al (2020)	20	20	50.20	50.50	Neck	RCT	SBSES, MSS
Elshahed et al (2020)	21	21	24.86	24.86	Face, neck, limbs,chest, abdomen	RCT	VSS, along with digital photograph standardization, patient self-assessment
An et al (2019)	30	30	50.53	50.53	Neck	RCT	Modified MSS, Minolta CR-400 chromometer
Huang et al (2019)	30	30	23.6	23.6	Medial canthal area	RCT	VSS, VAS
Kim et al (2019)	24	21	38.79	34.67	Forehead	RCT	VAS, SBSES
Phillips et al (2019)	23	23	54.0	54.0	Neck	RCT	VSS
Chen et al (2018)	21	17	27.19	26.41	Face	RCT	VAS
Hu et al (2018)	14	14	12.0	12.0	Face	RCT	VSS, VAS
Li et al (2018)	17	17	49.0	49.0	Sternum	RCT	VSS
Lee et al (2018)	15	15	34.33	30.27	Face	RCT	VSS
Kim et al (2014)	15	15	46.0	46.0	Neck	RCT	SBSES, patient self-assessment
Chang et al (2014)	30	28	24.7	21.87	Orbicularis oris muscle	RCT	VAS, VSS, scar width
Gassner et al (2006)	16	15	62	60.2	Forehead	RCT	VAS, complications

Abbreviations: BTA, botulinum toxin type A; MSS, Manchester scar scale; POSAS, patient and observer scar assessment scale; RCT, randomized controlled trial; SBSEC, Stony Brook scar evaluation scale; VAS, visual analog scale; VSS, Vancouver scar scale.

scar condition.[28] The VSS score was counted in cases of 391 scar assessment. There was significant heterogeneity of the studies (chi-square test = 108.72, $p < 0.00001$, $I^2 = 92\%$), and the Mantel–Hensel model with random effects was used for data analysis. The results revealed a lower score in the experimental group (MD = − 0.74, 95% CI = − 0.86 to −0.63, $p < 0.00001$). This means that patients injected with BTA had scars of better quality than patients treated with placebo (►**Fig. 3**).

The most objective noninstrumental method for scars assessment is the Stony Brook scar evaluation scale (SBSES). It evaluates the clinical results of scar treatment. The total SBSES score consists of the following criteria: scar height (2 = no raised scar, 1 = presence of raised scar, 0 = noticeable raised scar), visibility of the incision line (2 = no incision line, 1 = presence of incision line, 0 = prominent line incision), color (2 = scar the same color or lighter than the surrounding skin, 1 = redder than the surrounding skin, 0 = protruding above the surrounding skin), and width (2 = no scar widening, 1 = scar widening by 2 mm, 0 = scar widening by 2 mm).[29] The RCTs included in the study reported 197 cases of use of this scale for scars assessment. These studies showed high heterogeneity (chi-square test = 10.74, $p = 0.03$, $I^2 = 63\%$), and the Mantel–Hensel model with random effects was used for data analysis. The results showed significant difference between the experimental and control groups (MD = 1.53, 95% CI = 1.13–1.93, $p < 0.00001$), indicating that BTA injections can effectively improve the postoperative scars quality (►**Fig. 4**).

Analyzed data about the incidence of hypertrophic or keloid (pathological) scars in the experimental and control groups were reported in four studies. These RCTs included 178 cases, pathological scars developed in 4 cases in the control group, and 1 case in the experimental group (were considered an event). The heterogeneity test showed low heterogeneity between these studies (chi-square test = 1.79, $p = 0.62$, $I^2 = 0\%$), and the Mantel–Hensel model with fixed effects was applied. The differences between the two groups were significant (CI = 0.49, 95% CI = 0.12–1 0.99, $p = 0.32$) (►**Fig. 5**).

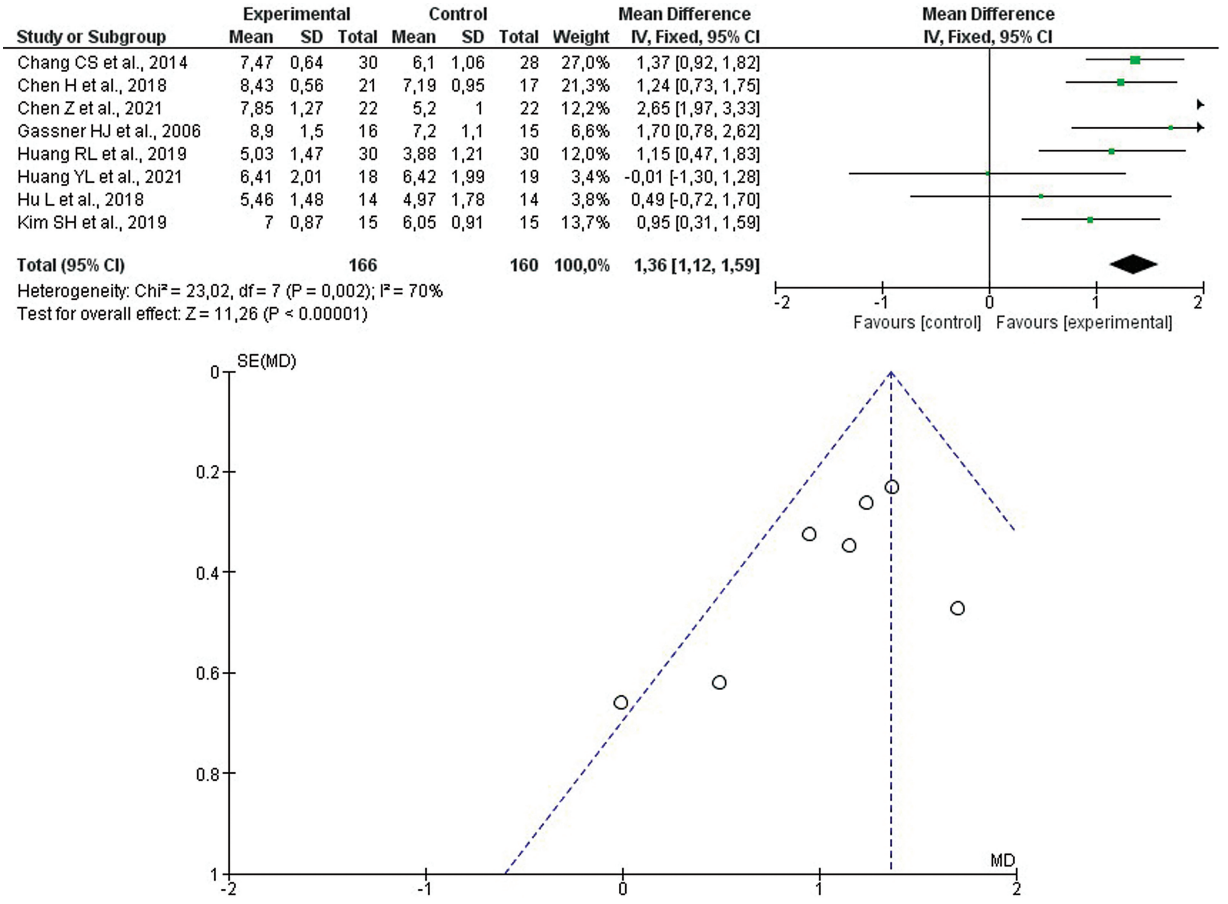

Fig. 2 Visual analog scale score forest and funnel plot. CI, confidence interval; SD, standard deviation.

The evaluation of adverse effects incidence after BTA injections for pathologic scars after surgeries prevention was performed on data extracted from four studies. The duration of scar follow-up was 6 months. During observation period, there was no serious side effects, such as suppuration, necrosis, dysfunction, or wound dehiscence. The main side effects were itching and moderate pain at the BTA injection site that resolved without treatment. Heterogeneity test showed low heterogeneity between these studies (chi-square test = 3.81, $p = 0.28$, $I^2 = 21\%$), and the Mantel–Hensel model with fixed effects was applied. There was no difference between the two groups (hazard ratio = 1.8, 95% CI = 0.51–6.28, $p = 0.36$). Taking into account that the listed symptoms were minor and possibly provoked by other factors, such as the use of antiseptic drugs or other physical impact on the wound, it can be considered that botulinum toxin, taking into account the positive effect on the developing scar tissue, can be safely used to prevent the development of hypertrophic and keloid scars (►**Fig. 6**).

Discussion

The results of treatment of patients with hypertrophic scars have always been controversial. Scars on visible parts of the body that cannot be hidden by clothing bring a lot of discomfort to patients. Hypertrophic and keloid scars are the result of excessive growth, lead to functional and cosmetic deformities, cause stress in the patient, which leads to psychological destabilization, and cause pain, itching, and other unpleasant symptoms. Such deformations significantly reduce the life quality and affect functional indicators. It was reported that the majority of recently examined patients are satisfied with even small improvements in the scars condition.[30–32] Over the years, a large number of methods have been proposed to improve the scars, such as rough excision of the scar, laser therapy, the use of vascular endothelial growth factor inhibitors, and other methods. However, there was no consensus on the best treatment option due to a lack of the evidence-based information. It is necessary to determine the optimal approach not only to the treatment of already developed but also to the prevention of pathologic scars development.[33–35]

In recent years, BTA has become increasingly popular, and it is used for various indications not only in esthetic cases. BTA is used to treat blepharospasm, spastic dysphonia, hemiparesis, and other diseases from related profiles.[36,37] BTA is a powerful neurotoxin produced by *Clostridium botulinum*. It causes paralysis of striated muscles lasting for about 6 months, suppressing the release of acetylcholine. Causing temporary denervation, BTA helps achieve the desired effect through decreasing muscle contractions.[38,39]

Hypertrophic scars are often formed as a result of excessive wound tension and stretching, as well as in persons prone to their development. Limiting facial expressions is quite a difficult task for a patient. When working with the upper

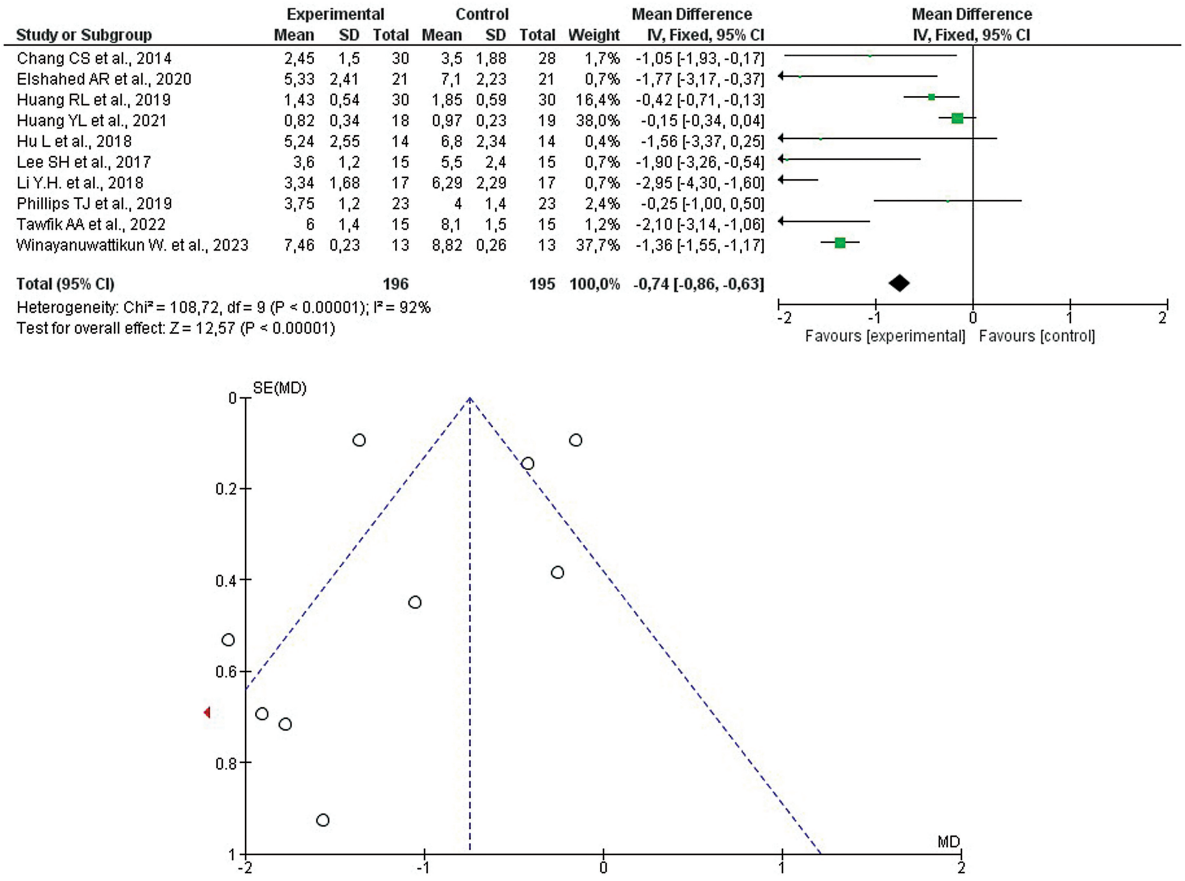

Fig. 3 Vancouver scar scale score forest and funnel plot. CI, confidence interval; SD, standard deviation.

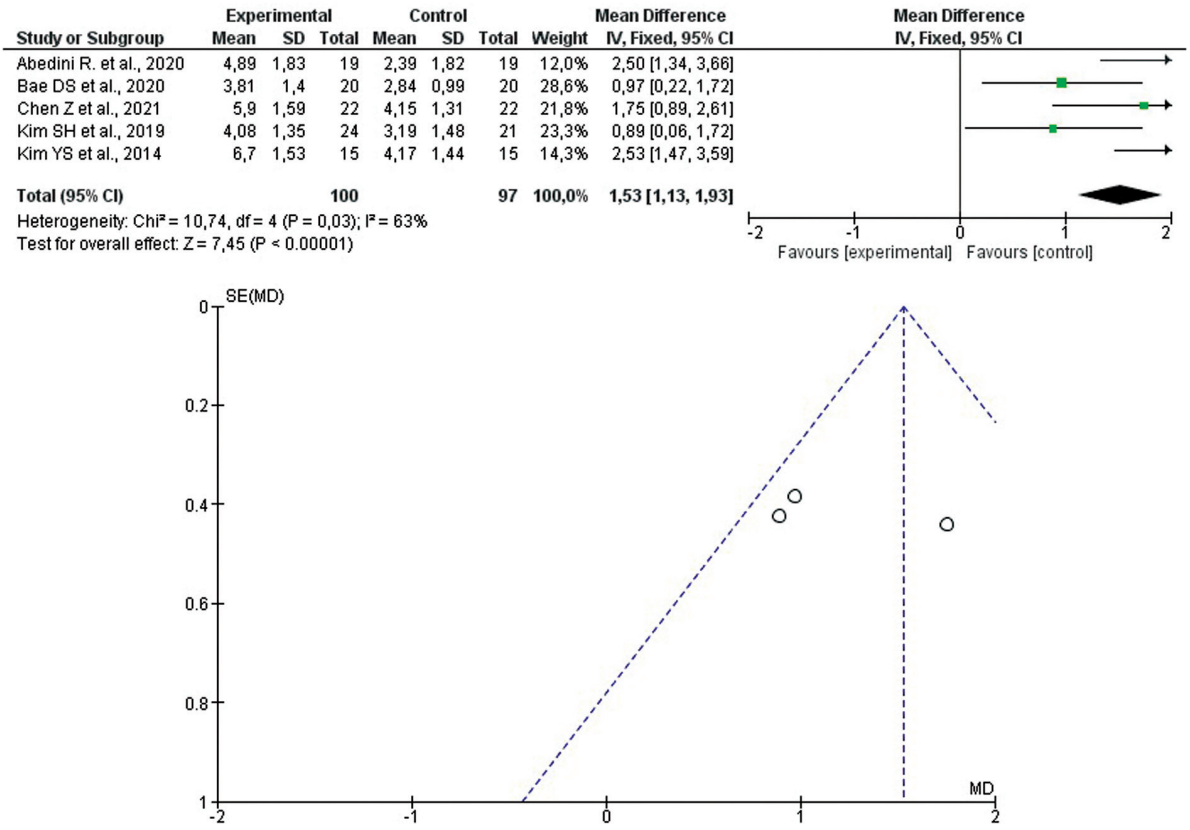

Fig. 4 Stony brook scar evaluation scales score forest and funnel plot. CI, confidence interval; SD, standard deviation.

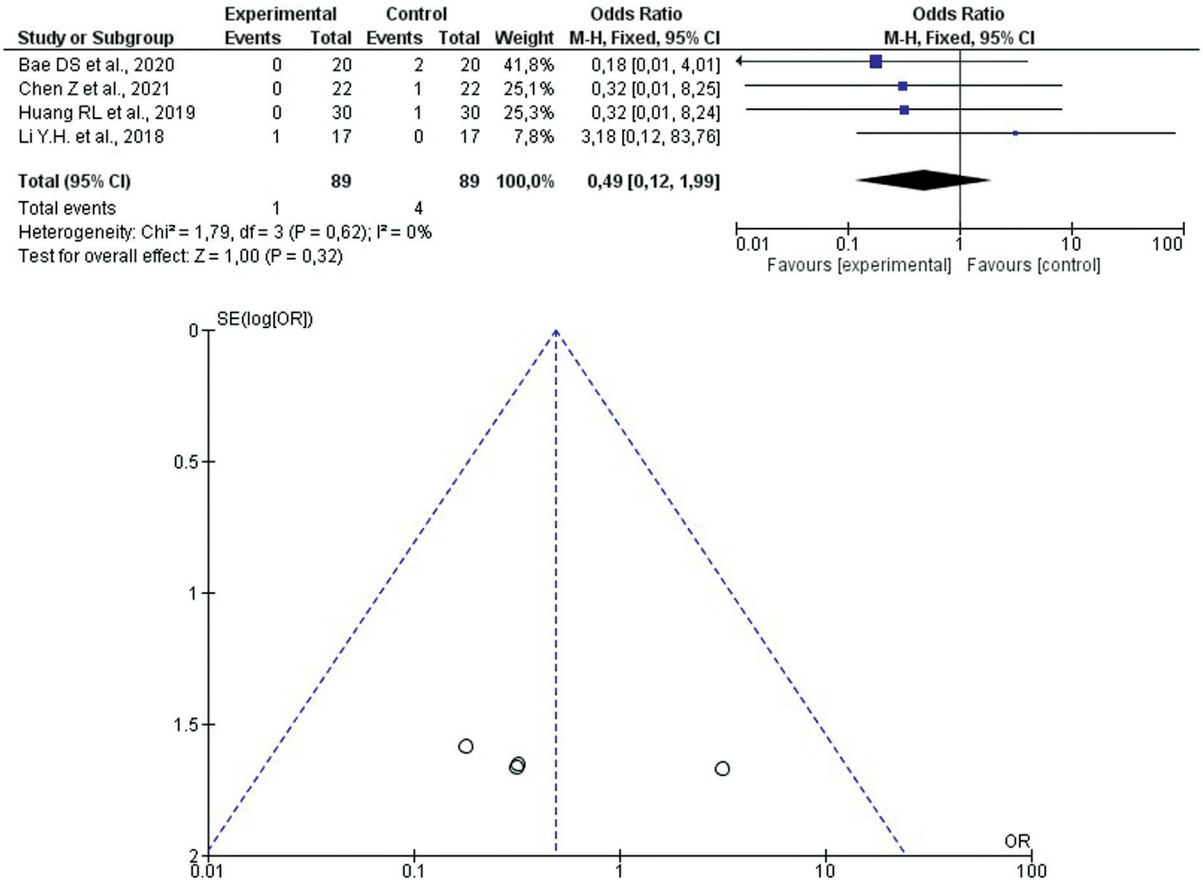

Fig. 5 Incidence of hypertrophic and keloid (pathological) scars forest and funnel plot. M-H, Mantel–Hensel; SD, standard deviation.

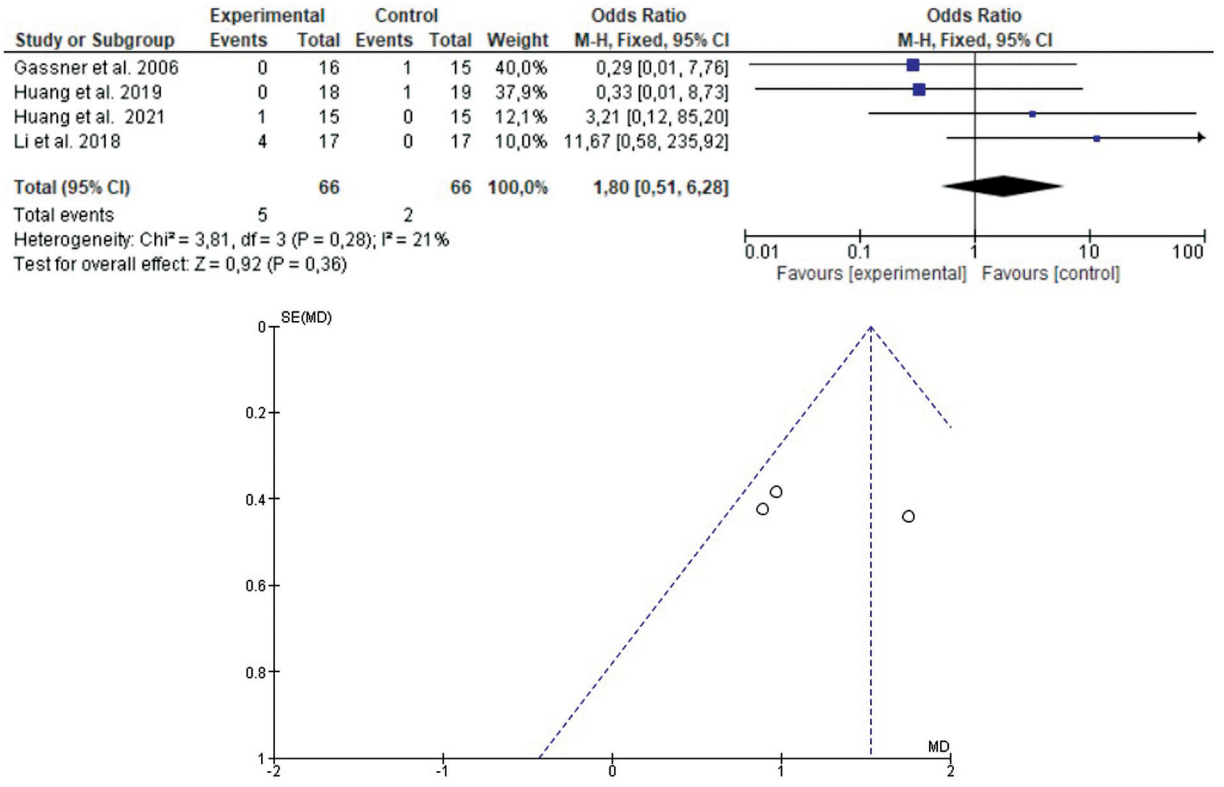

Fig. 6 Adverse events forest and funnel plot. M-H, Mantel–Hensel; SD, standard deviation.

or lower lip, cheeks, forehead, and neck, it is possible to stretch the edges of the wound. Normal wound healing process is divided into four stages: hemostasis, inflammation, proliferation, and remodeling.[40–42] It is believed that muscle stretching occurs during the phase of inflammation. The study of the effects of BTA and the development of a specific algorithm for its application, depending on the phase of the wound process, would make possible to reduce the incidence of hypertrophic scar development and improve the prognosis.[43,44]

Development of hypertrophic and keloid scars leads to negative consequences, that is, unsatisfactory appearance of the patients after surgery. To date, several studies have been conducted aimed at evaluating the effectiveness and safety of BTA for the prevention of pathological scars.[45,46]

The assumption that the use of BTA is effective in the treatment and prevention of keloid and hypertrophic scars is confirmed in the studies conducted in vitro and on experimental animals. Several authors[47,48] believe that BTA inhibits collagen production and limits wound hypertrophy in rabbit ear models, as well as inhibits the cell cycle of fibroblasts in vitro. Most fibroblasts that have not been treated with BTA are mainly in the G_2/M phase of the cell cycle compared with the treated ones that have been stopped during the G0/G1 phase.[49,50] BTA delays the growth of fibroblasts by inhibiting the cell cycle and thus reduces the development of hypertrophic scars. BTA reduces the expression of connective tissue growth factor, which regulates transforming growth factor-β_1 (TGF-β_1), and inhibits the growth of fibroblasts, which prevents scar expansion. BTA causes a decrease in the concentration of TGF-β_1 in fibroblasts.[51,52] It can be assumed that there is a direct proportional relationship between the number of the BTA units introduced and the concentration of TGF-β_1. An important property possessed by BTA is its ability to decrease cellular infiltration of tissues during wound healing, which leads to a decrease in the severity of fibrosis. One of the advantages of the BTA injections is leveling the tension of the wound edges during healing due to reversible paralysis of muscle fibers, which favorably affects the esthetic result.[53–56]

BTA was used to improve the esthetic indicators of forehead scars.[18,26] During the study, a significant improvement in the cosmetic appearance was found in the group of BTA injection compared with the control group. The analyzed studies demonstrate a positive effect of the use of BTA to prevent the development of hypertrophic and keloid scars and are consistent with studies on primates.

However, the present work has limitations that should be taken into account when interpreting the results. The studies included in the meta-analysis are subject to several limitations: a relatively small number of patients in the observation groups, as well as the subjective character of the results evaluation. The analysis performed here may not have taken into account differences in the age of patients. The characteristics of the patients included in the studies were not uniform. The keloid scars can form more than 2 years after skin injury. It is possible that some of the conducted studies have a higher risk of bias. All these facts demonstrate that further research in this area is necessary (►**Table 2**).

Table 2 Characteristics of included studies

Studies	*Intervention*		*BTA type*	*Injection time*	*Follow-up, mo*	*Injection site*
	BTA (IU)	Control				
Winayanuwattikun et al (2023)	50	0.9% saline	XEOMIN	14 d after surgery	6	Injection 1 cm away from the surgical scar. Each point of injection was 5 units for a total of 50 units
Tawfik and Ali (2023)	100	0.9% saline	Neuronox	5 IU/cm^2 every month for 6 mo	6	Postburn hypertrophic and keloid scars located on face, neck, chest, shoulders, abdomen, and extremities injected intradermally at the periphery then into the body of the scar
Chen et al (2021)	8	BTA 4 U	BTxA (Lanzhou Biochemical Company, People's Republic of China)	14 d after surgery	6	Injected intradermally from a site 5 mm away from the wound edges
Huang et al (2021)	7.5	0.9% saline	Botox; Allergan Inc., Ireland	14 d after surgery	6	Three injection points above and below the scar extending into the lower goose's foot

(*Continued*)

Table 2 (*Continued*)

Studies	*Intervention*		*BTA type*	*Injection time*	*Follow-up, mo*	*Injection site*
	BTA (IU)	Control				
Abedini et al (2020)	50	0.9% saline	XEOMIN	5–10 d after surgery	6	The entire scar in multiple points 1 cm apart. 5 IU BonT-A per 0.1 mL of the prepared solution in each point in the treatment side (5 IU/cm)
Bae et al (2020)	50	0.9% saline	BTA; Nabota; Daewoong Pharmaceutical, Korea	Immediately after surgery	6	Five injections were performed at 1 cm interval above the sutured platysma muscle (along the wound and below the incision)
Elshahed et al (2020)	2.5/cm^2	0.9% saline	Botox; Allergan Inc., Irvine, United States	1–10 y after trauma	6	Into the scar every month till 3 mo
An et al (2019)	60	0.9% saline	Parabotulinum toxin A, Nabota; Daewoong Pharmaceutical, Republic of Korea	Immediately after surgery, 14 d after surgery	6	Injections were delivered into the dermal layer 0.5 cm from the incision line in two rows (cephalad and caudad to the incision), 5 U at a time, at 1.5-cm intervals
Huang et al (2019)	5	0.9% saline	Botox; Allergan Inc., Irvine, United States	6–7 d after surgery	6	One injection was located 0.2 cm away from the medial surgical wound edge. Another injection was located 1 cm above and 0.2 cm away from the wound edge
Kim et al (2019)	25	0.9% saline	BoNTA Inj Hugel, Chuncheon, South Korea	5 d after surgery	6	The 5 IU/cm amount was injected into multiple sites that are symmetrical in the bottom side, centered on the suture line
Phillips et al (2019)	25	0.9% saline	BOTOX-A	Immediately after surgery	12	Closed wound after thyroid gland surgery, retreating 0.2 mm from the edge of the wound
Chen et al (2018)	6	0.9% saline	BOTOX-A	Immediately after surgery	Until the operation was finished, the A type of Botox was injected into the tissue closed to the incision with 1 cm interval. The dose for each injected pointed was administrated for 1–2 U Until the operation was finished, the A type of Botox was injected into the tissue	Closed wound after face scar removal and W-plasty with 1 cm interval. 1–2 IU for each injected pointed

Table 2 (*Continued*)

Studies	*Intervention*		*BTA type*	*Injection time*	*Follow-up, mo*	*Injection site*
	BTA (IU)	Control				
					closed to the incision with 1 cm interval. The dose for each injected pointed was administrated for 1–2 U Until the operation was finished, the A type of Botox was injected into the tissue closed to the incision with 1 cm interval. The dose for each injected pointed was administrated for 1–2 U 24	
Hu et al (2018)	50	0.9% saline	BOTOX-A	14 d after surgery	9	0.2 mL containing 10 U for each 1-cm scar were injected at a distance of 5 mm on either side of the wound
Li et al (2018)	58.2	0.9% saline	BOTOX-A	9.1 d after surgery	6	1 cm away from the wound edges, 5 IU in every point, with 1 cm interval
Lee et al (2018)	30	0.9% saline	BTA (Nabota; Daewoong Pharmaceutical, Seoul, Korea)	5 d after surgery	6	The entire forehead area, including the underlying musculature of the repaired wound, was injected
Kim et al (2014)	32.3	0.9% saline	NEBTX-A	10 d after surgery	6	The entre scar was treated, with sides randomized to receive treatment with BTA or 0.9% saline
Chang et al (2014)	15	0.9% saline	BOTOX-A	Immediately after surgery	6	0.6 mL (15 IU) were administered to the orbicularis oris muscle
Gassner et al (2006)	15–45	0.9% saline	Botox, Allergan, Irvine, United States	Immediately after wound closure	6	The injection was placed into the musculature adjacent to the wound in a diameter of ∼1–3 cm around the wound edges

Abbreviation: BTA, botulinum toxin type A.

Conclusion

Data analysis obtained during the study allows to state that there are prospects for the use of BTA in hypertrophic and keloid postoperative scars prevention. However, there is no consensus among the authors regarding the pathophysiological mechanisms underlying the positive effect of BTA in the prevention of hypertrophic and keloid scars. Therefore, to get more data about the prospects of BTA use to prevent the formation of pathological scars, it is necessary to conduct targeted prospective studies.

Conflict of Interest
None declared.

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