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Local injection of botulinum toxin for the prevention of hypertrophic scars and keloids: an overview of reviews

Inyección local de toxina botulínica para la prevención de cicatrices hipertróficas y queloides: una revisión panorámica

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Abstract

Introduction: Hypertrophic scars and keloids arise from an abnormal healing process in the skin, significantly affecting the quality of life. There is a wide array of treatment options available, but they often come with high costs and yield inconsistent results. Botulinum toxin is one such option that is thought to have a preventive effect, although evidence from multiple reviews have not provided a clear answer. Our objective is to compile evidence from systematic reviews of randomized controlled trials concerning the impact of local botulinum toxin injection on preventing hypertrophic scars and keloid formation following surgical skin trauma. **Methods:** We conducted an overview of reviews following the Preferred Reporting Items for Overviews of Reviews (PRIOR) reporting guidelines. We searched for the Epistemonikos Database up to January 2024. Quality was assessed using the AMSTAR-2 tool. We compared reviews addressing similar questions, calculated the covered area and corrected covered area to assess overlap, and explored reasons for differences between reviews. **Results:** Fifteen systematic reviews were included. All were classified as having low or critically low confidence according to AMSTAR-2. The covered area was 28.38%, and the corrected covered area was 23.26%, indicating very high overlap. Findings of the included reviews showed a beneficial effect on scar appearance and patient satisfaction, but in adverse events the direction of effect varied. **Conclusion:** Botulinum toxin could be an alternative for preventing hypertrophic scars and keloids after surgical skin trauma, but given the low confidence of the reviews, these results should be interpreted with caution.

Keywords: Hypertrophic scars; keloids; botulinum toxin; Epistemonikos

Resumen

Introducción: Las cicatrices hipertróficas y los queloides resultan de un proceso de cicatrización anómalo que puede afectar significativamente la calidad de vida. Existen diversas alternativas terapéuticas; sin embargo, suelen implicar altos costos y resultados poco predecibles. La toxina botulínica se ha propuesto como tratamiento preventivo, aunque la evidencia disponible no ha permitido establecer conclusiones definitivas. El objetivo de este estudio fue sintetizar la evidencia proveniente de revisiones sistemáticas de ensayos clínicos aleatorizados sobre el efecto de la inyección local de toxina botulínica en la prevención de cicatrices hipertróficas y queloides posteriores a trauma quirúrgico cutáneo. **Métodos:** Se realizó una revisión panorámica siguiendo las directrices PRIOR (*Preferred Reporting Items for Overviews of Reviews*). Se buscó en la base de datos Epistemonikos hasta enero de 2024. La calidad de las revisiones se evaluó mediante la herramienta AMSTAR-2. Se compararon revisiones con preguntas similares, se calcularon el área cubierta y el área cubierta corregida para determinar el grado de superposición, y se exploraron las causas de las diferencias entre las revisiones. **Resultados:** Se incluyeron quince revisiones, todas con nivel de confianza bajo o críticamente bajo según AMSTAR-2. El área cubierta fue de 28,38% y el área cubierta corregida del 23,26%, lo que indica una superposición elevada. Las revisiones reportaron un efecto beneficioso sobre la apariencia de las cicatrices y la satisfacción del paciente; no obstante, los resultados respecto a eventos adversos fueron variables. **Conclusión:** La toxina botulínica puede constituir una alternativa para prevenir cicatrices hipertróficas y queloides tras un trauma quirúrgico cutáneo; sin embargo, dado el bajo nivel de confianza de las revisiones, estos hallazgos deben interpretarse con cautela.

Palabras clave: Cicatrices hipertróficas; queloides; toxina botulínica; Epistemonikos

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Introduction

While all skin trauma, inflammation from surgery or burns leads to scarring, genetically predisposed individuals may experience the development of hypertrophic scars or keloids during the healing process. This involves excessive fibrosis that does not subside, along with an increased deposition of collagen and accelerated angiogenesis (Austin *et al.*, 2018). Keloids are characterized by continuous growth that exceeds the boundaries of the original wound, invading the adjacent healthy skin, while hypertrophic scars do not exceed the margins of the initial wound (Ogawa, 2024). In both cases, scar tissue results in changes in the histological configuration of the skin, making it different from the surrounding skin in terms of color, thickness, elasticity, texture, and degree of contraction. Such characteristics make these marks noticeable, aesthetically unappealing, and often disfiguring (Andrades *et al.*, 2006). They can also present symptoms such as itchiness, redness, pain, functional limitations, and dysesthesia (Austin *et al.*, 2018; Xu *et al.*, 2021). Moreover, people living with scars experience a negative impact on both physical and psychological aspects of their quality of life, potentially leading to severe emotional distress, lower self-esteem, and diminished self-confidence (Andrades *et al.*, 2006; Austin *et al.*, 2018; Bi *et al.*, 2019; Xu *et al.*, 2021).

The prevalence of keloids has no sex predilection, they develop more frequently between the first and third decades of life and are rare to see in older people (Hernández, 2011). Both hypertrophic scars and keloids can affect any skin type and its development has been observed in 30 to 91% of burn patients, and up to 75% of patients after surgical interventions experience signs indicative of hypertrophic scarring (Hernández, 2011; Austin *et al.*, 2018). These pathological healing conditions are reported in all ethnic groups; however, prevalence and incidence data are limited and show that they disproportionately affect individuals with genetic ancestry from Africa, Latin America, and Asia (Austin *et al.*, 2018; Ogawa, 2024). In these groups, keloids have a reported prevalence between 0.3% and 16% (Andrades *et al.*, 2006; Austin *et al.*, 2018).

The processes driving excessive scar formation remain incompletely understood (Hernández, 2011; Lee & Jang, 2018), leading to a lack of standardized treatment for hypertrophic scars and keloids. Many options exist, such as patches, topical and injectable medications, surgical interventions, laser therapy, and even radiation treatments. These interventions may lead to discomfort, pain, and high costs (Andrades *et al.*, 2006; Berman *et al.*, 2017; Bi *et al.*, 2019). Consequently, preventive and prophylactic approaches have gained popularity, particularly among patients undergoing elective surgeries (Berman *et al.*, 2017; Lee & Jang, 2018).

Botulinum toxin (BT) constitutes an alternative approach to managing hypertrophic scars and keloids. This substance acts altering the protein complex involved in acetylcholine release in the presynaptic space. Its mechanism of action involves cleaving the 25 kDa synaptosomal-associated protein (SNAP-25), thereby preventing synaptic vesicles from binding to the neuron's plasma membrane. This process induces muscle paralysis through chemoinactivation (Rizo & Südhof, 2002; Austin *et al.*, 2018), reducing tension at the wound edges, critical for the healing process (Austin *et al.*, 2018; Xu *et al.*, 2021). Additionally, BT may exert a prophylactic effect, as in vitro studies have shown its ability to suppress fibroblast differentiation into myofibroblasts and inhibit scar growth by modulating the cell cycle and collagen production in fibroblasts, mediated by TGF-β (Austin *et al.*, 2018; Xu *et al.*, 2021).

Research on BT has been promising, and its clinical utility has expanded in recent years, emerging as a potentially effective approach for scar treatment (Yue *et al.*, 2022). Existing systematic reviews (SRs) indicate a potential benefit of perioperative local BT injection in improving scar appearance and preventing keloids and hypertrophic scars (Prodromidou *et al.*, 2015; Zhang *et al.*, 2016; Bi *et al.*, 2019; Wang *et al.*, 2019*a*; Wang *et al.*, 2019b; Bartkowska *et al.*, 2020; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.*, 2020; Qiao *et al.*, 2021; Xu *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.*, 2022; Yue *et al.*, 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023). However, those reviews yield dissimilar conclusions, leading to uncertainty about the effects of BT use in this context. Therefore, it is imperative to collate and synthesize the body of evidence to inform clinical decision-making through a systematic analysis.

Objective

The objective of this overview of reviews is to synthesize the evidence from SRs of randomized controlled trials (RCTs) on the effects of local injection of BT in preventing hypertrophic and/or keloid scars in individuals who have undergone or will undergo surgical skin trauma.

Methods

This overview of reviews complies with the guidance for overviews in the Cochrane Handbook (Higgins *et al.*, 2023) and the PRIOR (Preferred Reporting Items for Overviews of Reviews) reporting guideline (Gates *et al.*, 2022). The checklist is reported in Appendix 1. The review was registered on PROSPERO with the number CRD42023431093, and a protocol was published (Silva-Ruz *et al.*, 2024).

Eligibility criteria

We included SRs of RCTs, defined as an article whose main objective is to synthesize primary studies, describes an explicit method to search in at least one electronic database, mentions at least one eligibility criterion, and searches for and includes RCTs.

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Additionally, SRs should fulfill the following criteria: a) include studies assessing participants of any age who have undergone or will undergo any surgical procedure without hypertrophic and/or keloid scars at the time of the intervention; b) assess studies evaluating the local injection of any type of BT administered preoperatively, intraoperatively (at closing), or postoperatively; c) local saline injection or no treatment as the comparison; and d) outcomes about the scar appearance, adverse events and/or patient satisfaction. We excluded reviews that used a combination of treatments as an intervention (e.g., BT + corticosteroids); comparisons where different from saline or no treatment (e.g., laser or triamcinolone); included primary studies conducted in vitro or in animals; narrative reviews and those that included more diverse populations (e.g., acne scars or wrinkles).

Search sources

We conducted searches in the Epistemonikos Database in January 2024. Epistemonikos is a comprehensive database maintained by regular searches in multiple databases and other sources (Rada *et al.*, 2013), and it has been validated as a comprehensive and reliable single source of SRs (Rada *et al.*, 2020). The search strategy is reported in Appendix 2. No restriction by language or publication status were applied. We complemented the electronic search through a manual review of references in the included reviews, relevant guidelines and narrative reviews for additional studies. We utilized Google Scholar to conduct cross-citation analysis. By inputting the most cited primary studies from the evidence matrix (as outlined in the synthesis methods, comparison between reviews), we employed the 'cited by' feature and refined our search using the terms "systematic review" or "meta-analysis" in the 'search within citing articles' tool.

Selection process

Two authors independently checked the titles and abstracts and evaluated the full texts of potentially eligible studies for final inclusion. To ensure consistency, we performed calibration exercises before beginning the screening. Disagreements were resolved by discussion or by a third reviewer. The reasons for exclusion after full text assessment were recorded and the study selection process was described in a PRISMA flowchart.

Data collection process

Two authors independently extracted data from each included review using standardized forms after calibration. Discrepancies were resolved by consensus or by a third experienced reviewer. Data extracted from the SRs were: list of trials included in the review that answer the question of interest, review objective and/or research question, inclusion/exclusion criteria, date of the last search, risk of bias assessment of the included trials, meta-analysis results of the included outcomes and other narrative outcomes. To characterize the intervention and population analyzed in the included reviews, we collected the following data items, as the SRs reported them: sample size, age of the included participants, anatomical segment operated on, treatment protocols for the intervention and control groups.

Quality assessment

We evaluated the quality of the included reviews using the "A Measurement Tool to Assess Systematic Reviews" (AMSTAR-2). This tool has been developed to evaluate SRs of observational and randomized studies. It contains 16 domains with three response options: "yes", "no" and "partial yes". Of the 16 domains, 7 are considered "critical" and determine the overall confidence (protocol registered before starting the review, proper literature search, list and reasons of excluded studies, risk of bias assessment of included studies, suitable methods to execute the meta-analysis, consideration of the risk of bias in the interpretation of the results, and evaluation of the existence of publication bias and its potential impact) (Shea *et al.*, 2017). Two authors independently evaluated the quality of the included SRs using AMSTAR-2. Discrepancies were resolved by discussion or arbitrated by a third experienced reviewer.

Synthesis methods

Comparison between reviews

We created an evidence matrix in the Epistemonikos Database to compare the included reviews. An evidence matrix is a tabular way of showing the group of SRs that address a similar question (i.e., share at least one included study) and all primary studies that address the question in those reviews (Rada *et al.*, 2014). The matrix was created independently by two reviewers and discrepancies were resolved by consensus. We presented the results of the evidence matrix through a table that also incorporates the results of the AMSTAR-2, and the reasons that explain the discrepancies between the studies included by the SRs.

Comparison of primary studies included in the reviews

We explored and documented the reasons why studies were not included in the individual reviews using the following categories:

- The study was published after the search date of the review.
- The study was mentioned as an excluded study in the review.
- The study was not mentioned as an excluded study, but this could be inferred from the review's inclusion criteria.
- The study was probably missed by the review.
- Other (for example, studies awaiting assessment).

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Management of primary studies overlapping

The overlap between the primary studies results included in the SRs was assessed through both graphical representation and a statistical approach. For this, we used the evidence matrix developed with the Groove tool, complemented by estimations of the covered area (CA) and corrected covered area (CCA) (Bracchiglione *et al.*, 2022). We determined the degree of overlap, considering a CCA ≥ 15% as very high overlap, 10% to < 15% as a high overlap, 5% to < 10% as a moderate overlap and, <5% as a slight overlap.

Results

Search results

Our search retrieved 96 potentially eligible SRs which were subsequently evaluated based on their title and abstract. Thirty-four were considered as potentially eligible and were reviewed in full text. Finally, we included 15 SRs (Zhang *et al.*, 2016; Wang *et al.*, 2019*a*, Wang *et al.*, 2019b; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al.*, 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023). The selection process is summarized in figure 1. The list of excluded SRs, and the reasons, is available in Appendix 3.

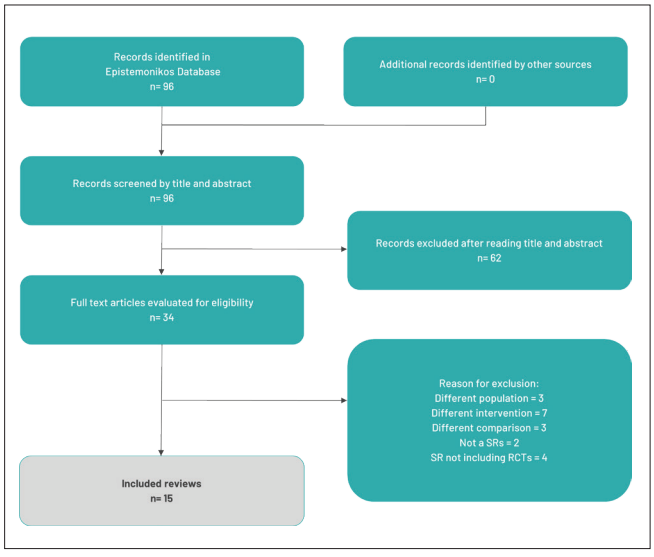

Figure 1: PRISMA flowchart, summarized selection process. SRs: Systematic reviews; RCTs: Randomized controlled trials. (Author's own elaboration).

Review characteristics

The characteristics of the participants to be eligible for the reviews are found in Table 1. All reviews included BT as an intervention, but 86.7% (Zhang *et al.*, 2016, Wang *et al.*, 2019b; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.*, 2020; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.* 2022; Yue *et al.*, 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) specified BT type A as an inclusion criteria. Only 20% of the reviews (Wang *et al.*, 2019*a*; Yang & Li, 2020; Qiao *et al.*, 2021) mentioned that the application could be pre- or post-surgical. None of the reviews specified the maximum or minimum time to carry out infiltration in the inclusion criteria. In all SRs (Zhang *et al.*, 2016; Wang *et al.*, 2019*a*, Wang *et al.*, 2019b; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al.*, 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) saline or no treatment served as control across all the studies. 86.7% of the reviews (Zhang *et al.*, 2016; Wang *et al.*, 2019*a*, Wang *et al.*, 2019b; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al.*, 2022) included only RCTs, while 13.3% (Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) included both observational studies and RCTs, with results presented separately according to study design. 40% of the reviews (Wang *et al.*, 2019b; Zhang *et al.*, 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Wang *et al.*, 2022; Rammal & Mogharbel, 2023) included only studies published in English, 6.7% (Yang & Li, 2020) included only studies in English or Chinese, and 6.7% (Martinez *et al.*, 2023) included only studies in English or Portuguese or Spanish. A quantitative synthesis of the results through a meta-analysis was performed on 93.3% of the reviews (Zhang *et al.*, 2016; Wang *et al.*, 2019*a*, Wang *et al.*, 2019b; Chen *et al.*, 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al.*, 2022; Rammal & Mogharbel, 2023). All the reviews assessed the risk of bias of the included primary studies, with the tools reported for these purposes being RoB1 (Zhang *et al.*, 2016; Wang *et al.*, 2019*a*, Wang *et al.*, 2019b; Song *et al.*, 2020; Yang & Li, 2020; Guo *et al.*, 2020; Zhang *et al.*, 2020; Qiao *et al.*, 2021; Ji *et al.*, 2022; Wang *et al.*, 2022; Yue *et al.*, 2022; Rammal & Mogharbel, 2023), RoB2 (Fu *et al.*, 2022; Martinez *et al.*, 2023), MINORS criteria (Martinez *et al.*, 2023), and a 3-question instrument (Chen *et al.*, 2020). Only 20% of the included SRs (Wang *et al.*, 2019b; Qiao *et al.*, 2021; Yue *et al.*, 2022) had a registry or protocol published in a repository. Finally, 13.3% (Chen *et al.*, 2020; Guo *et al.*, 2020) of the reviews assessed the certainty of the evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

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Table 1: General characteristics of the reviews (author's own elaboration).

General characteristics of the reviews									
Study/Year	**Population**	**Intervention**	**Comparison**	**Exclusion criteria**	**Included designs studies**	**Last search**	**Meta-analysis**	**Risk of bias tool**	**Registered protocol**
Zhang *et al.*, 2016	Patients who had been diagnosed with hypertrophic scarring, including babies born with cleft lips who were slated for primary cheiloplasty, individuals (16 years or older) slated for revisional surgery due to unsightly outcomes of primary cheiloplasty, and individuals with facial wounds from injuries and other causes.	The studies evaluated the effects of BTX-A on the oral, maxillofacial, or neck scars, injected alone and not combined with any other treatments.	Normal saline as a control treatment, injected alone and not combined with any other treatments.	The study covered keloids or burn scars.	RCT only	August 2015	Yes	RoB 1	No
Wang *et al.*, 2019a	Individuals of any age with scars, potential scars after surgery or facial and/or neck injury.	Injections of BT, pre-surgery or post-surgery injections for prevention or cure of scars.	Placebo (saline) or no treatment.	Patients with keloids were excluded. Cortico-therapy as placebo and combined therapy were excluded. Studies that did not distinguish prevention and remodeling using BT were not considered for inclusion.	RCT only	June 2018	Yes	RoB 1	No
Wang *et al.*, 2019b	Patients with postoperative scars.	BTXA for preventing postoperative scars.	Saline or no treatment as a control treatment.	Studies evaluating the use of BTXA in the treatment of hypertrophic scars and keloids. Studies in a language other than English were excluded.	RCT only	November 2018	Yes	RoB 1	Yes (CRD42018118640)
Song *et al.*, 2020	Patients with facial trauma or surgery, preoperative, trauma or immediately after surgery, when there is no obvious scar formation on the wound, the patient has no age or gender limit.	BTXA (alone) to prevent facial trauma or postoperative scarring.	Blank control or saline.	Combined application of BTXA and other methods used (including local injection of other drugs, laser, and other photoelectric treatment methods): 1. Laser or other photoelectric treatment; 2. Silicone gel membranes or other silicone products; 3 pressure therapy; 4 radiation therapy; 5 other single or comprehensive treatments.	RCT only	2019 (month not reported)	Yes	RoB 1	No
Guo *et al.*, 2020	Patient with scars.	BTXA without any additional treatment.	Control or placebo (saline or blank control).	Articles were excluded if they evaluated burn scars, acne scars, or keloids.	RCT only	February 2019	Yes	RoB 1	No
Chen *et al.*, 2020	Patients with age below 90 years old; both female and male patients; and with postoperative scars (face or neck).	BTXA.	Placebo or no treatment.	We did not include cluster and crossover trials.	RCT only	March 2019	Yes	3-question instrument	No
Zhang *et al.*, 2020	Patients with postoperative scars.	BTXA in preventing the generation of hypertrophic scars or keloids.	Normal saline or a blank control.	Studies were excluded in the analysis if other treatments were provided simultaneously. Studies in a language other than English were excluded.	RCT only	February 2020	Yes	RoB 1	No
Yang & Li, 2020	Patients requiring surgical treatment.	BTXA before/after the operation.	Normal saline or did not receive injection.	Studies of hormones, intense pulsed light treatment, and other treatments. Studies in a language other than English or Chinese were excluded.	RCT only	May 2022	Yes	RoB 1	No
Fu *et al.*, 2022	Patients with postoperative scars.	BTXA for pathological scars formation.	Normal saline or nothing.	Studies were then excluded if they were treating keloids, hypertrophic scars, or other non-postoperative wounds. Studies in a language other than English were excluded.	RCT only	December 2020	Yes	RoB 2	No
Qiao *et al.*, 2021	Participants that required surgical treatment.	BT, either pre or postoperatively.	Normal saline or not treated.	Studies in a language other than English were excluded.	RCT only	December 2020	Yes	RoB 1	Yes (CRD42020214958)
Ji *et al.*, 2022	Patients with postoperative scars (cleft lip or palate).	BTXA.	Placebo.	Patients had a history of chemical peeling and other previous laser or resurfacing procedures to the scar.	RCT only	January 2022	Yes	RoB 1	No
Wang *et al.*, 2022	Participants with facial scars.	BTXA.	Placebo (saline or blank control)	Studies in a language other than English were excluded.	RCT only	April 2021	Yes	RoB 1	No
Yue *et al.*, 2022	Patients with postoperative facial scars.	BTXA in preventing postoperative facial scars.	Saline or not treatment.	Studies with full text or date not available were excluded.	RCT only	May 2021	Yes	RoB 1	Yes (INPLASY202170077)
Rammal & Mogharbel, 2023	Patients who have any scar on the face, head, or neck.	BTXA.	Placebo or control.	Studies comparing BTXA by any intervention other than placebo. Studies in a language other than English were excluded.	RCT and non-RCT	May 2023	Yes	RoB 1	No
Martinez *et al.*, 2023	Patients who underwent cleft lip repair.	BTXA.	Placebo (normal saline).	Studies in a language other than English, Spanish or Portuguese were excluded.	RCT and non-RCT	February 2022	No	RoB 2 and MINORS	No

Notes
BT: Botulinum toxin
BTX-A: Botulinum toxin type A
RCT: Randomized controlled trial
Guo *et al.*, 2019 and Chen *et al.*, 2020 report having used Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Primary studies characteristics

All studies included in the SRs (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) utilized BT type A as the intervention, with 26.7% of the reviews (Guo *et al*., 2020; Yang & Li, 2020; Zhang *et al*., 2020; Qiao *et al*., 2021) reporting the specific brand used in the primary studies. The number of participants included ranged from 161 to 915, with ages between 3 months and 88 years. Regarding the longest follow-up reported, it varied from 3 months to 27 months. The dose used during the intervention in the studies was reported by 66.7% of the included SRs (Wang *et al*., 2019b; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al*., 2020; Fu *et al*., 2022; Ji *et al*., 2022; Wang *et al.,* 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) and ranged from 1U/kg to 80U/total (see in detail in Appendix 4). In terms of scar location, 93.3% (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Yue *et al*., 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) of the SRs included studies with participants who had scars on the lips, 86.7% (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) on the forehead and face, 73.3% SRs (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) on the neck, 40% (Wang *et al.,* 2019b; Guo *et al*., 2020; Yang & Li, 2020; Zhang *et al*., 2020; Qiao *et al*., 2021; Fu *et al*., 2022) on the thorax and breast, and 13.3% (Qiao *et al*., 2021; Fu *et al*., 2022) on the abdomen. Regarding scar type, all SRs (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) included studies with patients who had primary surgical wounds, 46.7% (Wang *et al.,* 2019b; Chen *et al.,* 2020; Guo *et al*., 2020; Ji *et al*., 2022; Wang *et al.,* 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) secondary surgical wounds, 26.7% (Wang *et al*., 2022; Wang *et al.,* 2019b; Song *et al*., 2020; Rammal & Mogharbel, 2023) traumatic wounds, and 93.3 (Zhang *et al*., 2016; Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Yue *et al*., 2022; Martinez *et al*., 2023; Rammal & Mogharbel, 2023) included patients who had cleft lip wounds. Finally, concerning the timing of the intervention, 73.3% of the included reviews included studies that specified when the intervention occurred, either pre-surgery (Wang *et al*., 2019*a*, Wang *et al*., 2019b; Guo *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al*., 2023) (between 9 to 10 days), at wound closure (Wang *et al*., 2019b; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Ji *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al*., 2023), or post-surgery (Wang *et al*., 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al*., 2020; Song *et al*., 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al*., 2022; Wang *et al.,* 2022; Yue *et al*., 2022) (see Table 2).

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Table 2: Characteristics of the studies interventions, reported by the reviews (author's own elaboration).

Study	Scar location						Type of wound				Time of injection		
	Lip	Forehead	Face	Neck	Chest/Breast	Abdomen	Primary surgical	Secondary surgical	Traumatic	Cleft lip	Pre-surgery	Intraoperative or immediately after wound closure	Post-surgery
Zhang *et al.*, 2016	■	■	■	■			■			■	Not reported	Not reported	Not reported
Wang *et al.*, 2019*a*	■	■	■	■			■			■	(-)		(-)
Wang *et al.*, 2019b	■	■	■	■	■	Not reported	■	■	■	■	■	■	■
Song *et al.*, 2020	■	■	■				■	Not reported	■	■		■	■
Guo *et al.*, 2020	■	■	■	■	■	Not reported	■	■		■	(-)	■	■
Chen *et al.*, 2020	■	■	■	■			■	■	Not reported	■	Not reported	Not reported	(-)
Zhang *et al.*, 2020	■	■	■	■	■	Not reported	■			■	■	■	■
Yang & Li, 2020	■	■	■	■	■	Not reported	■			■	■	■	■
Fu *et al.*, 2022	■	■	■	■	■	■	■			■	■	■	■
Qiao *et al.*, 2021	■	■	■	■	■	■	■			■	■	■	■
Ji *et al.*, 2022	■						■	■		■	(-)	■	
Wang *et al.*, 2022		■	■				■	■	■		■	■	■
Yue *et al.*, 2022	■	■	■	■			■	Not reported		■	■	■	■
Rammal & Mogharbel, 2023	■	■	■	■			■	■	■	■	Not reported	Not reported	Not reported
Martinez *et al.*, 2023	■						■	■		■	■	■	Not reported

Notes

■ = Reported in the systematic review

■ = Not included in the systematic review

Face includes: epicanthus, medial canthus, cheek, jowl, eyebrow, glabella, nasolabial fold or chin

Time reported in presurgical injection ranged from 9 to 10 days

Time reported in post-surgical injection ranged from 1 to 14 days

(-) time in days or hours not reported

The distance between wound edge and injection site varied from 3mm up to 3 cm.

Quality assessment

All of the included SRs were classified as having low or critically low overall confidence, according to the AMSTAR-2 assessment (see Appendix 5). Regarding the critical domains: the 80% of the included SRs (Zhang *et al*., 2016; Wang *et al.*, 2019*a*; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) did not register a protocol before commencement of the review (D2), 66.7% (Wang *et al.,* 2019b; Chen *et al.,* 2020; Yang & Li, 2020; Zhang *et al*., 2020; Qiao *et al*., 2021; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) did not provide the list of excluded studies and the reasons for exclusion (D7), 80% (Zhang *et al*., 2016; Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022 ; Wang *et al.,* 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) did not consider the of risk of bias when interpreting the results of the review (D13), and 40% (Wang *et al.,* 2019b; Chen *et al.,* 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Wang *et al., 2022*) of them did not assess the presence and likely impact of publication bias (D15). Relating to the non-critical domains: none of the included SRs (Zhang *et al*., 2016; Wang *et al.*, 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) explained the reasons for the selection of study designs to be included in the review (D3) or the funding sources of the primary studies included in the review (D10), and the 73.3% (Zhang *et al*., 2016; Wang *et al.*, 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Wang *et al.,* 2022; Martinez *et al.*, 2023; Rammal & Mogharbel, 2023) did not consider the RoB results of the primary studies in the results of the meta-analysis (D12).

Evidence matrix

The evidence matrix is presented below (see Table 3, also available online) (Epistemonikos, 2023) showing the 15 SRs included (first column) and their 39 primary studies included, of which 92.3% correspond to RCTs (see Appendix 6, list of studies). The number of primary studies identified by each review ranged from 4 to 20. After identifying the most reported primary studies in the evidence matrix and checking if they had been cited by other SRs using Google Scholar, we did not identify additional SRs.

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Table 3: Matrix of evidence. The rows represent the SRs included, and the columns represent the primary studies included. Each colored cell indicates that the study was included in the corresponding review (author's own elaboration).

			Matrix of evidence																																										
	PRIMARY STUDIES →		**Wilson *et al***	**Gassner *et al***	**Xiao *et al***	**Wang Xiaoyu *et al***	**Ziade *et al***	**Li *et al***	**Kim *et al***	**Chang *et al***	**Chang *et al****	**Luan *et al***	**Icahn School of...**	**Wang *et al***	**Li *et al***	**Zelken *et al***	**Wang *et al***	**Koonce *et al***	**Chen**	**Guan *et al***	**Liu *et al***	**Tao *et al***	**Li *et al***	**Lee *et al***	**Hu *et al***	**Xu *et al***	**Huang *et al***	**Navarro-Barquín *et al***	**Phillips *et al***	**Kim *et al***	**Elshahed *et al***	**Bae *et al***	**Abedini *et al***	**Huang *et al***	**Ebrahim *et al***	**Samarth *et al***	**Patil *et al***	**Sonane *et al***	**Lin *et al***	**Lu *et al***	**Uyar *et al***	
SRs ↓	Search date	Publication date	2006	2006	2009	2013	2013	2014	2014	2014	2014	2015	2015	2015	2016	2016	2017	2017	2018	2018	2018	2018	2018	2018	2018	2018	2019	2019	2019	2019	2020	2020	2020	2021	2022	2022	2022	2022	2022	2022	2023	**AMSTAR-2** Overall Confidence
Zhang *et al.*, 2016	Aug, 2015	Mar, 2016																																									Critically low
Wang *et al.*, 2019*a*	Jun, 2018	Aug, 2019																																									Low
Wang *et al.*, 2019b	Nov, 2018	Mar, 2019																																									Critically low
Song *et al.*, 2020	Nov, 2019	May, 2020																																									Critically low
Guo *et al.*, 2020	Feb, 2019	May, 2020																																									Critically low
Chen *et al.*, 2020	Mar, 2019	Apr, 2020																																									Critically low
Zhang *et al.*, 2020	Feb, 2020	Dec, 2020																																									Critically low
Yang & Li, 2020	May, 2019	Apr, 2020																																									Critically low
Fu *et al.*, 2022	Dec, 2020	Jun, 2022																																									Critically low
Qiao *et al.*, 2021	Dec, 2020	Oct, 2021																																									Critically low
Ji *et al.*, 2022	Jan, 2022	Jun, 2022																																									Critically low
Wang *et al.*, 2022	April, 2021	Mar, 2022																																									Critically low
Yue *et al.*, 2022	May, 2021	Feb, 2022																																									Low
Rammal & Mogharbel, 2023	May, 2023	Nov, 2023																																									Critically low
Martinez et al., 2023	Feb, 2022	Aug, 2023																																									Critically low

Notes:

SRs: Systematic Reviews

AMSTAR-2: A Measurement Tool to Assess Systematic Reviews

= The study is included in the specific review

= Trial registry

= Write in chinese

= The study was published after the search conducted by the review

= The study was probably missed by the review

= The study is mentioned as an excluded study in the review

= The study is not mentioned as an excluded study, but this can be inferred from the review's inclusion criteria (only studies in English, other study design, scars located in anatomical segments outside the face, presence of co-interventions or lack of data)

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Primary study overlap

The overlap assessment reveals that, out of the 39 primary studies included in SRs, 17 exhibited no overlap, 8 were included in 2 SRs, and 14 appeared in 3 or more SRs. This analysis demonstrates a significant overlap for both CA and CCA, with rates of 28.38% and 23.26%, respectively. Notably, when accounting for structural missingness, the overlap increases, resulting in a corrected covered area—adjusted for structural zeros—of 54.27%. Furthermore, 89.5% of the nodes (representing pairs of SRs) exhibited a very high degree of overlap, with 94 out of 105 total nodes affected. The reasons why primary studies were not included in the individual SRs are available in Table 3 notes.

Prioritized outcomes

The results from the meta-analysis conducted in the SRs are presented in Table 4. Scar appearance was reported using six different scales, resulting in the following ranges when using BT: the 93.3% of the included SRs (Zhang *et al*., 2016; Wang *et al.*, 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) reported the Visual Analogue Scale (VAS) with a score that ranged from 1.10 to 1.70 points higher (more is better, favors intervention); 86.7% (Wang *et al.*, 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al*., 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) reported the Vancouver Scar Scale (VSS) for which the score ranged from -0.64 to -1.82 points lower (less is better, favors intervention); 93.3% (Zhang *et al*., 2016; Wang *et al.*, 2019*a*, Wang *et al*., 2019b; Chen *et al*., 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) reported the scar width, which ranged from -0.18 to -1.09 mm less (less is better, favors intervention); 20% (Wang *et al.*, 2022; Yue *et al*., 2022; Rammal & Mogharbel, 2023) reported the Observer Scar Assessment Scale (OSAS) and the score ranged from -0.83 to -1.30 points less (less is better, favors intervention); 20% (Song *et al.*, 2020; Wang *et al.*, 2022; Rammal & Mogharbel, 2023) reported the Patient Scar Assessment Scale (PSAS) and the score ranged from 0.06 to 0.32 points higher (less is better, favors control); 20% (Qiao *et al.*, 2021; Fu *et al.*, 2022; Rammal & Mogharbel, 2023) reported the Stony Brook Scar Evaluation Scale (SBSES) and the score ranged from 1.23 to 1.63 points higher (more is better, favors intervention).

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Table 4: Prioritized outcomes reported in the meta-analysis of the included systematic reviews (author's own elaboration).

Prioritized outcomes reported in the meta-analysis of the included systematic reviews									
Outcome/Study	**Scar appearance**						**Patient satisfaction**		**Adverse events**
	VAS (more is better) Pooled median/mean 95% CI	**VSS (less is better) Pooled median/mean 95% CI**	**Scar width (less is better) Pooled median/mean 95% CI**	**OSAS (less is better) Pooled median/mean 95% CI**	**PSAS (less is better) Pooled median/mean 95% CI**	**SBSES (more is better) Pooled median/mean 95% CI**	**Dichotomous**	**Continuous (more is better) Pooled median/mean 95% CI**	**Dichotomous**
Zhang *et al.*, 2016	MD: 1.30 (1.00 to 1.60) 2 RCTs, n=117	Not reported	MD: -0.41 (-0.68 to -0.14) 6 RCTs, n=373	Not reported	Not reported	Not reported	OR: 25.76 (2.58 to 256.67) 4 RCTs, n=344	-	Not reported
Wang *et al.*, 2019*a*	MD: 1.30 (1.05 to 1.54) 5 RCTs, n=231	MD: -0.87 (-1.73 to -0.02) 4 RCTs, n=185	SMD: -1.05 (-1.29 to -0.81) 6 RCTs, n=302	Not reported	Not reported	Not reported	Not reported	Not reported	RR: 0.36 (0.09 to 1.45) 9 RCTs, n=395
Wang et al., 2019b	MD: 1.32 (1.06 to 1.58) 5 RCTs, n=193	MD: -1.25 (-2.23 to -0.26) 5 RCTs, n=207	MD: -0.18 (-0.24 to -0.12) 7 RCTs, n=324	Not reported	Not reported	Not reported	RR: 1.38 (1.09 to 1.74) 2 RCTs, n=65	-	Reported as narrative
Song *et al.*, 2020	MD: 1.70 (0.38 to 3.02) 7 RCTs, n=293	MD: -1.61 (-2.96 to -0.26) 7 RCTs, n=287	MD: -0.17 (-0.22 to -0.12) 7 RCTs, n=360	Not reported	MD: 0.32 (0.22 to 0.42) 1 RCT, n=36	Not reported	-	MD: 1.84 (1.01 to 2.67) 1 RCT, n=64	Reported as narrative
Guo *et al.*, 2020	MD: 1.30 (1.05 to 1.55) 5 RCTs, N=225	MD: -1.24 (−2.22 to −0.26) 5 RCTs, n=209	MD: -0.18 (−0.29 to −0.08) 5 RCTs, n=209	Not reported	Not reported	Not reported	RR: 1.40 (0.96 to 2.05) 4 RCTs, n=292	MD: 1.51 (1.13 to 1.89) 2 RCTs, n=64	Reported as narrative
Chen *et al.*, 2020	SMD: 1.17 (0.85 to 1.50) 4 RCTs, n=174	SMD: -0.64 (-1.00 to -0.28) 3 RCTs, n=128	SMD: -1.04 (-1.30 to -0.77) 5 RCTs, n=248	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Zhang *et al.*, 2020	MD: 1.31 (1.06 to 1.55) 6 RCTs, n=285	MD: -1.02 (-1.72 to -0.32) 6 RCTs, n=269	MD: -0.18 (-0.29 to -0.08) 5 RCTs, n=209	Not reported	Not reported	Not reported	RR: 1.25 (1.06 to 1.49) 3 RCTs, n=88	-	Reported as narrative
Yang & Li, 2020	MD: 1.69 (0.38 to 3.01) 9 RCTs, n=431	MD: -1.82 (-2.54 to -1.10) 9 RCTs, n=431	SMD: -1.09 (-1.36 to -0.81) 12 RCTs, n=671	Not reported	Not reported	Not reported	RR: 1.19 (1.11 to 1.29) 5 RCTs, n=339	-	Reported as narrative
Fu *et al.*, 2022	MD: 1.29 (1.05 to 1.52) 6 RCTs, n=281	MD: -1.32 (-2.00 to -0.65) 7 RCTs, n=291	MD: -0.18 (-0.27 to -0.10) 6 RCTs, n=231	Not reported	Not reported	SMD: 1.23 (0.82 to 1.65) 3 RCTs, n=108	RR: 1.46 (0.64 to 3.33) 8 RCTs, n=285	-	RR: 1.25 (1.06 to 1.49) 3 RCTs, n=88
Qiao *et al.*, 2021	MD: 1.26 (1.04 to 1.47) 8 RCTs, n=337	MD: -0.97 (-1.56 to -0.39) 7 RCTs, n=309	MD: -0.25 (-0.37 to -0.12 8 RCTs, n=348	Not reported	Not reported	MD: 1.63 (0.77 to 2.49) 4 RCTs, n=153	RR: 3.38 (1.45 to 7.89) 5 RCTs, n=102	-	RR: 2.49 (0.54 to 11.47) 4 RCTs, n=149
Ji *et al.*, 2022	MD: 1.30 (1.06 to 1.55) 3 RCTs, n=139	MD: -0.75 (-1.68 to 0.19) 5 4 RCTs, n=161	MD: -0.20 (-0.30 to -0.10) 7 RCTs, n=300	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wang *et al.*, 2022	MD: 1.25 (0.88 to 1.62) 5 RCTs, n=140	MD: -1.49 (-2.30 to -0.68) 3 RCTs, n=68	MD: -0.39 (-0.81 to 0.03) 3 RCTs, n=84	MD: -1.30 (-3.18 to 0.58) 2 RCTs, n=69	MD: 0.06 (-0.76 to 0.89) 2 RCTs, n=69	Not reported	Not reported	Not reported	Reported as narrative
Yue *et al.*, 2022	MD: 1.10 (0.89 to 1.30) 7 RCTs, n=336	SMD: -0.64 (-1.03 to -0.25) 7 RCTs, n=291	SMD: -1.05 (-1.27 to -0.83) 8 RCTs, n=382	SMD: -0.83 (-1.33 to -0.34) 2 RCTs, n=69	Not reported	Not reported	Not reported	Not reported	OR: 0.99 (0.22 to 4.53) 4 RCTs, n=137
Rammal & Mogharbel, 2023	MD: 1.12 (0.91 to 1.33) 11 RCTs; n=482	MD: -0.98 (-1.53 to -0.44) 8 RCTs, n=328	MD: -0.26 (-0.43 to -0.09) 8 RCTs, n=318	MD: -0.93 (-1.71 to -0.15) 2 RCTs, n=69	MD: 0.08 (-0.59 to 0.75) 2 RCTs, n=69	MD: 1.32 (0.59 to 2.05) 3 RCTs, n=115	Not reported	Not reported	Not reported
Martinez *et al.*, 2023	Did not performed MA	Did not performed MA	Did not performed MA	Did not performed MA	Did not performed MA	Did not performed MA	Did not performed MA	Did not performed MA	Reported as narrative

Notes
VAS: Visual Analog Scale
VSS: Vancouver Scar Scale
SBSES: Stony Brook Scar Evaluation Scale
OSAS: Observer Scar Assessment Scale
PSAS: Patient Scar Assessment Scale
MD: mean difference
SMD: standard mean difference
MA: meta-analysis
RCT: randomized controlled trial
OR: odds ratio
RR: relative risk
CI: confidence interval

Patient satisfaction was reported both as a dichotomous outcome (as risk ratio [RR] or odds ratio [OR] ranging from 1.19 to 25.76; reported by 46.7% of the SRs) (Zhang *et al.,* 2016; Guo *et al.*, 2020; Wang *et al.,* 2019b; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022) or as a continuous outcome (ranging from 1.51 to 1.84 points higher; more is better, favors intervention; reported by 13.3% of the SRs) (Guo *et al.*, 2020; Song *et al.*, 2020).

Adverse events were reported both as a continuous outcome (RR that ranged from 0.36 to 2.49; reported by 26.7% of the SRs) (Wang *et al.*, 2019*a*; Qiao *et al.*, 2021; Fu *et al.*, 2022; Yue *et al*., 2022), as well as narratively (mostly local transient adverse events, reported by 46.7% of the SRs, see Appendix 7) (Wang *et al.,* 2019b; Song *et al.*, 2020; Zhang *et al.*, 2020; Yang & Li, 2020; Guo *et al.*, 2020; Wang *et al.,* 2022; Martinez *et al.*, 2023). However, 26.7% of the included SRs (Zhang *et al.,* 2016; Chen *et al.,* 2020; Ji *et al.*, 2022; Rammal & Mogharbel, 2023) did not provide information on these safety outcomes.

Discussion

The objective of this overview of reviews was to synthesize the evidence from SRs of RCTs about the effects of local injection of BT in preventing hypertrophic and/or keloid scars in individuals who have undergone or will undergo surgical skin trauma. We identified 15 SRs, all classified with a low or critically low overall confidence. The overlap between the included SRs was very high. According to the results reported from the meta-analysis of the included SRs, there is a potential benefit on the use of BT to improve scar appearance (in 5 different scales) and patient satisfaction. However, the direction of the effect varied in the case of adverse events.

This overview of reviews is the first to address the use of BT for the prevention of hypertrophic scars and keloids in patients with skin surgical wounds. Therefore, having the first comprehensive summary of the evidence about the effects of this intervention is useful to have a broader view of the reported benefits and harms. In addition, it helps to highlight the methodological limitations that may affect clinician's confidence when using this evidence to inform their practice.

During the development of this review, the initial point of interest was the results obtained when assessing the overall confidence of the SRs using the AMSTAR-2 tool. As mentioned earlier, all included reviews were classified with low or critically low confidence, suggesting that the reviews might not provide an accurate and comprehensive summary of the available studies. According to the developers of the AMSTAR-2 tool (Shea *et al.*, 2017), while all steps involved in conducting a SR are important, failure to meet critical domains compromises the validity of the review and, consequently, the conclusions drawn from it. In this context, failure to meet one critical domain results in a rating of low confidence, whereas failure in two or more critical domains leads to a rating of critically low confidence. Based on our findings, the most frequently unmet critical domains were the lack of protocol registration before commencement of the review (D2) and to consider the risk of bias when interpreting the results of the review (D13), both of which were absent in 80% of the SRs assessed. These were followed by the omission of a list of excluded studies along with justifications for their exclusion (D7; 66.7%) and assess the presence and likely impact of publication bias (D15; 40%). Addressing these issues in future reviews could help enhance methodological quality and, consequently, increase the level of confidence in their conclusions.

In addition to the methodological deficiencies found, we encountered various challenges that may explain the discrepancies among reviews addressing similar questions, particularly regarding the included studies. Firstly, 86.7% of the included SRs (Zhang *et al.,* 2016; Wang *et al.*, 2019*a*, Wang *et al.,* 2019b; Chen *et al.,* 2020; Guo *et al.*, 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Ji *et al.*, 2022; Wang *et al.,* 2022; Yue *et al*., 2022) declared they only included studies with a RCT design; however, we noticed some inconsistencies among reviewers in the classification of study designs (e.g. (Wilson, 2006), which was included by the (Zhang *et al.,* 2016) and (Qiao *et al.*, 2021) SRs, but excluded from the (Wang *et al.*, 2019*a*), (Guo *et al.*, 2020), and (Song *et al.*, 2020) SRs as it did not correspond to an RCT). We also identified a study (Liu, 2018) that used a growth factor gel as a placebo (could be considered a co-intervention), which could explain why only one SR (Yang & Li, 2020) included it. Another study (Xiao *et al.*, 2009) was included by the (Zhang *et al.,* 2016) SR, which aimed to investigate the effects of BT for the prevention of hypertrophic scars and keloids; however, the participants already had an established hypertrophic scar at the time of the intervention. This same situation was observed with the study by (Elshahed *et al.*, 2020), included by the (Qiao *et al.*, 2021) SR. We want to emphasize that the 40% of the included reviews (Wang *et al.,* 2019b; Zhang *et al.*, 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Wang *et al.,* 2022; Rammal & Mogharbel, 2023) included only studies published in English. This language restriction in the search and/or selection of studies may lead to the exclusion of relevant research that could contribute valuable data to the evidence synthesis, resulting in findings and conclusions based on a limited subset of the available evidence. In our analysis, this issue is exposed through discrepancies observed among the studies included in SRs addressing similar research questions, particularly those involving studies from Asia published in languages other

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than English. Based on our own experience, we recognize that one of the main challenges faced by evidence synthesis teams is the retrieval of primary studies indexed in repositories that list only English-language titles, along with the limitations of conducting search strategies in a single language. Additional barriers include the reading and analysis of studies published in languages other than the reviewers' native language or English. Overcoming these challenges would not only broaden the scope and enhance the validity of SRs, but also promote the more equitable inclusion of study populations that might otherwise remain underrepresented in the international scientific literature.

The findings reported by the included reviews suggest that there could be a benefit from the use of BT for the prevention of hypertrophic scars and keloids measured as scar appearance (reported in 5 out of the 6 scales used) and in patient satisfaction. Regarding adverse events, contradictory findings were observed and should be interpreted with caution due to the inconsistency and imprecision of the reported effect estimates. This variability can be attributed primarily to the varied approaches used by the SRs to synthesize adverse event data: 26.7% conducted a meta-analysis, 46.7% reported the data narratively, and 26.7% did not report adverse events at all. This lack of uniformity hinders the ability to draw consistent conclusions and limits the certainty with which one can state that cases without adverse events were more common than those with them. Only one SR (Zhang *et al.,* 2020) explored the potential cause of a specific adverse event—palpebral ptosis following treatment as reported in the study by (Huang *et al.,* 2019)—attributing it to the injection site being located just 0.5 mm from the eyelid, with the condition resolving spontaneously within six weeks without the need for additional treatment. It is worth noting that other reported adverse events, such as local pain, pruritus, facial asymmetry, and headache, have been described as transient, infrequent, self-resolving, and expected following BT administration (Goodman *et al*., 2020). Finally, it is important to note that there is a high overlap across the SRs, implying that the conclusions drawn are likely based on the same body of evidence. Moreover, 73.3% of the included SRs (Zhang *et al.,* 2016; Wang *et al.*, 2019*a*, Wang *et al.,* 2019b; Chen *et al.,* 2020; Song *et al.*, 2020; Yang & Li, 2020; Zhang *et al.,* 2020; Qiao *et al.*, 2021; Fu *et al.*, 2022; Wang *et al.,* 2022; Rammal & Mogharbel, 2023) did not consider the risk of bias results in the analysis of the meta-analysis results. As a result, the real effect may differ from the one reported.

One of the strengths of this review is the exploration of overlap. It is our attention that there is a very high overlap of primary studies, both in the overall and in the analysis by nodes (pairs of reviews). It is important to take this into consideration since the effects of the intervention show a benefit in the appearance of the scar and in patient satisfaction, but since the overlap is very high, the reviews that report these results share the majority of the included primary studies. Therefore, the results that come from the different analyses of the reviews could potentially be redundant. One limitation of this work is that we did not conduct a new meta-analysis; therefore, we did not calculate new estimators on the effects of the intervention or perform subgroup analyses. While having these new data would allow us to increase the power of the meta-analysis, it is important to acknowledge that the included reviews presented considerable methodological limitations, so the data obtained in this exercise would not be a faithful reflection of the real effects.

Therefore, we consider it appropriate to conduct a new systematic review that takes into account the critical methodological aspects outlined in AMSTAR-2, in order to obtain solid conclusions for decision-making. This would also allow data from the primary studies to be reported individually, to avoid having possible redundant conclusions due to analysis of aggregated data reported by the reviews (given the high overlap). It is essential to collaborate with experts who facilitate access to evidence from Asia, given the abundance of relevant articles and the challenges posed by publications in languages other than English. Moreover, an assessment of the certainty of the evidence would facilitate the use of these findings to inform decision-making.

We believe it is important to consider the data used for the calculation of the overlap. CCA shows the percentage of overlap existing in the primary studies included in the different SRs, it can also be adjusted by structural zeros, which are defined as an intersection in the evidence matrix that cannot take a value other than 0 (Bracchiglione *et al.*, 2022). For example, a SR published in 2016 cannot include studies from 2018; therefore, there is a chronological structural gap (described in our matrix as clocks). Other structural gaps may arise from different inclusion criteria among the SRs, for example, a review focused only on cleft lip patients while others included other anatomical segments, therefore, part of the primary studies cannot be included in the first review. In our analysis, we obtained a CCA of 23.36%, and when we adjusted for structural zeros it increased to 54.27% showing more overlap. While optional, this adjustment may provide a clearer picture of overlap, though further studies are required. We believe it is worth noting how values change after adjustment, which in practical terms aims to calculate overlap on a "truer" denominator. Finally, it is relevant to highlight that the authors of the tool used for CCA calculation mention that the thresholds to classify the overlap (slight, moderate, high, and very high) (Bracchiglione *et al.*, 2022) are based on the first publication of the CA, (Pieper *et al.*, 2014) we believe they could be reviewed, given the massive increase in published SRs.

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Conclusion

In this review we synthesized the data from SRs of RCTs that suggest a potential benefit on the use of BT to improve scar appearance (in 5 different scales) and patient satisfaction. In adverse events the direction of effect varied. These results should be interpreted with caution, given serious methodological limitations of the included SRs, and considering the patient's clinical context.

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Ethics

Ethical approval was not required.

Declaration of conflict of interest

The authors declare that they have no conflicts of interest.

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