

Intralesional Botulinum Toxin A for Keloid Treatment: A Review of Efficacy, Safety, and Clinical Applications

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Background: Keloids are fibroproliferative disorders characterized by excessive scarring, functional impairment, and aesthetic concerns. Despite the availability of various treatments, recurrence rates remain high, highlighting the need for alternative therapies with favorable safety profiles. Botulinum toxin A (BTX-A) has emerged as a potential option for keloid treatment; however, its therapeutic role is still not fully elucidated. The aim of this study was to evaluate the efficacy and safety of BTX-A in the treatment of keloids through a structured review of available literature.

Methods: This literature review was conducted from three scientific databases: PubMed, Scopus, and Cochrane. The following keywords used were “botulinum toxin”, “BTX-A”, “botulinum toxin A”, and “keloids”. Original studies published in English between 2014 and 2024 that involved human subjects and investigated the use of BTX-A in the treatment of keloids were included.

Results: A total of eleven randomized controlled trials were included in this review. Of these, eight studies reported statistically significant improvements in keloid characteristics such as height, pliability, and vascularity following intralesional BTX-A treatment, as measured by validated scales like the Vancouver Scar Scale (VSS). Two studies demonstrated comparable efficacy between BTX-A and intralesional triamcinolone acetonide (TAC). Adverse events were rare and generally limited to mild local reactions. In addition, BTX-A has been shown to be safe for use as a keloid therapy even in the pediatric population.

Conclusion: BTX-A showed satisfactory efficacy and safety. In addition, BTX-A showed significant improvement in subjective symptoms in keloid lesions, making BTX-A a promising alternative option for keloid therapy.

Keywords: botulinum toxin, keloid, BTX-A, intralesional, botulinum toxin A

Introduction

Keloids represent a challenging dermatological condition characterized by abnormal wound healing, resulting in the overgrowth of scar tissue beyond the original wound boundaries.¹ The pathogenesis of keloids involves dysregulated collagen turnover, aberrant growth factor signaling (notably TGF- β and CTGF), immune dysfunction, genetic predisposition, inflammatory responses to sebum, and mechanical factors such as skin tension and stretching at wound edges.²

Clinically, keloids often present with aesthetic disfigurement, pain, pruritus, and in some cases, restriction of movement or other functional impairments.^{2,3} Up until now, there is no standardized consensus on therapeutic modality of keloids,⁴ and the evidence-based literature is still limited.⁵ Despite the various therapeutic interventions available, including corticosteroid injections, surgery, radiation, and laser therapy, achieving consistent and satisfactory outcomes remains difficult due to high recurrence rates and varying treatment efficacy.^{2,3} Although intralesional corticosteroids remain a mainstay of therapy, up to 50% recurrence has been reported, and side effects such as skin atrophy and hypopigmentation are not uncommon.⁴

This therapeutic gap highlights the need for safer, more effective, and well-tolerated alternatives. Botulinum toxin (BTX), a neurotoxin derived from *Clostridium botulinum*, has long been utilized for both cosmetic and medical indications. Among its seven serotypes (A–G), only types A and B are approved for clinical use.^{5,6} In recent years, botulinum toxin A (BTX-A), a neurotoxin primarily known for its muscle-relaxing properties, has emerged as a potential therapeutic option for keloid management.^{3,4,7} Research shows that intralesional BTX-A significantly relieve subjective complaints and reduce the size and height of keloids.^{2,7} Preliminary studies suggest that BTX may reduce wound site tension, inhibit fibroblast proliferation, and decrease collagen synthesis, thereby preventing formation and recurrence of keloids.^{3,8} BTX-A has been reported to have good efficacy, safety, tolerable adverse effects (AEs), and a high level of patient satisfaction for keloid management.⁹ These findings warrant a review of the available evidence. Therefore, this review aims to comprehensively assess the efficacy, safety, and clinical applicability of intralesional BTX-A for the treatment of keloids.

Methods

Search Strategy

The review process began with a literature search using three scientific databases: PubMed, Scopus, and Cochrane. The literature was selected based on the predetermined inclusion and exclusion criteria. The search used the following terms: botulinum toxin, BTX-A, botulinum toxin A, and keloid. Original studies written or available in English-language on the treatment of keloids involving human subjects using BTX-A from 2014 to 2024, including cohort, cross-sectional, case-control, and randomized control trials (RCTs) were included. Study was conducted according to PRISMA guideline. After this initial filtering process, we reviewed the remaining articles for their relevance to our subjects.

Results

A total of 346 articles were identified through literature search using the platforms mentioned above. After reviewing full-text articles relevant to our subjects, 63 duplicate studies were excluded. At the title and abstract screening stages, 272 studies were excluded because they were unrelated to the efficacy and safety of BTX-A on the treatment of keloids. Eleven articles were included in the final analysis, and all of these articles were RCTs (Figure 1).

Among 11 studies obtained, eight studies were from Egypt, two studies originated from Iran, and one study was from Thailand. Among the 11 studies obtained, five studies compared intralesional BTX-A injection with other intralesional injection therapies, three studies administered intralesional BTX-A injection as monotherapy, and two studies administered intralesional BTX-A injection in combination with other treatments. As for evaluation, most studies used the Vancouver Scar Scale (VSS),^{5,7,9–13} although other subjective scales, such as the Verbal Rating Scale (VRS),^{7,14} Patient and Observer Scar Assessment Scale (POSAS),¹¹ Modified Vancouver Scar Scale (mVSS),¹⁵ Observer Scar Assessment Scale (OSAS),⁵ Patient Scar Assessment Scale (PSAS),⁵ and Stony Brook's Scar Evaluation Scale (SBSES)¹⁴ were also used. In addition, some studies have conducted objective assessments with dermoscopy,⁹ histopathological and immunohistochemical,^{5,9,12} skin analysis cameras,¹³ and ultrasonography examinations.¹⁴ The intervention details and evaluation used in each study are shown in Table 1, while the risk of bias is shown in Figure 2.

Discussion

Keloids not only cause discomfort but also physical disorders, including contractures and aesthetic disturbances, which can reduce patients' quality of life and interfere with their self-confidence.^{17,18} A study by Anaba et al¹⁹ found that there was a significant decrease in the quality of life of keloid patients compared to controls, where the quality of life was generally impaired in 93.7% of keloid patients before treatment and improved to 65.6% after treatment.¹⁹

BTX-A has high efficacy in the management of keloids because BTX-A can reduce activated dermal fibroblasts. Several studies have suggested that transforming growth factor- β 1 (TGF- β 1) and connective tissue growth factor (CTGF) are considered key factors in keloid formation, as they not only regulate cell adhesion and growth, but also cause excessive collagen accumulation. BTX-A has an effective mechanism of action on keloids because BTX-A regulates the fibroblast cell cycle, and also reduces TGF- β 1^{2,13} and CTGF expression in fibroblasts.²

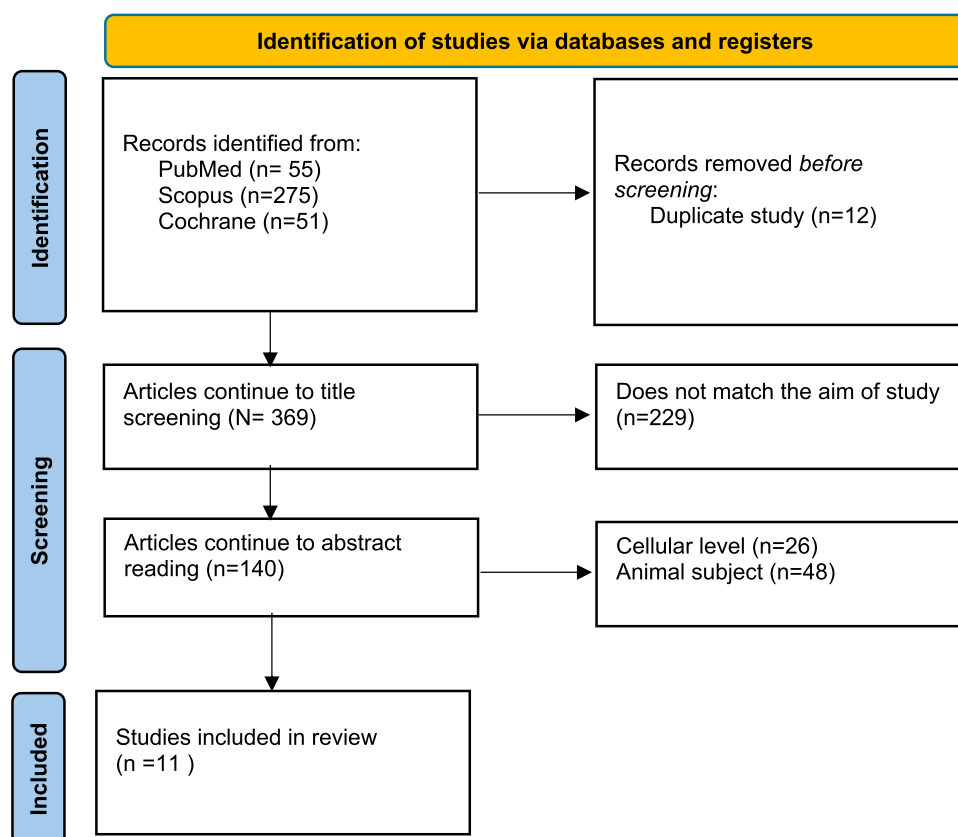


Figure 1 Flowchart of the article selection process.

Subjective symptom improvement following intralesional BTX-A injection is thought to be related to its capacity to directly interact with neuropeptides⁷ present in keloids that cause itching, pain, and allodynia,^{2,7} as well as its capacity to paralyze local muscles and reduce skin tension brought on by muscle pull, thereby neutralizing small fiber neuropathy.²

Efficacy

The assessment of keloid treatment outcomes often relies on both subjective and objective measures.^{13,20} Currently, one of the most widely used subjective scales is the VSS that evaluates four indicators: vascularity (0–3), pigmentation (0–3), pliability (0–5), and height (0–3). The most severe scar formation was indicated by a maximum score of 14 points.^{11,21,22} The VSS established a standard for systematic scar assessment by gathering subjective evaluations and employing a semiquantitative approach, as used in most of these studies.^{21,22}

BTX-A showed variable efficacy across these studies, with most studies mentioning significant improvement in keloid lesions, such as the study by Khatery et al⁵ conducted on 12 patients with keloids and eight patients with HTS. Both groups were given BTX-A 2.5 U/cm,³ repeated monthly for three sessions. A highly statistically significant difference regarding VSS, OSAS, and PSAS between the baseline and after each sessions of injection was observed, with the greatest improvement observed after the third session and after the six-month follow-up for each group. On histopathological evaluation, there was a significant improvement in the quantity and quality of collagen and elastic fibers.⁵ In line with previous studies, a study by Elfiky et al¹² that used intralesional BTX-A 5 U/cm³ injection repeated monthly for four sessions in 30 patients with HTS and keloids showed highly significant differences regarding the epidermal thickness and area of the dermal fibroblasts between the baseline and after treatment. Additionally, there was a significant decline in the VSS between the baseline and after treatment with a highly significant improvement in the pliability and height of the scars.¹²

Table I Clinical Trials Using BTX-A in Keloid Lesions

No	Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Lesions Duration	Follow-Up Duration (Months)	Evaluation	Responses	Recurrences (%)	Adverse Effects
1	Shaarawy et al ² 2015 (Egypt)	RCT	● A: TAC 10 mg/mL, 4-week interval for 6 treatment sessions/or complete improvement ● B: BTX-A 5 U/cm³, 8-week interval for 3 sessions/or complete improvement of the keloid	24 patients with keloid randomly divided into two groups ● A: 12 patients ● B: 12 patients	Mean 2.8 ± 1.474 years	The total duration of the treatment plan was 6 months	● Objective parameters (hardness, elevation, and redness) ● Subjective complaints (itching, pain, and tenderness) ● Scale of 0 (none) to 3 (maximum), score 0 revealing minimum complaint and score 3 revealing maximum complaint.	● Significant decrease in the lesions volume in all patients 7 months after treatment compared with baseline ● Significant softening of lesions in all patients 7 months after treatment compared with baseline, with statistically significant softening in group A ● Significant decrease in height of lesions and in redness in all patients 7 months after treatment compared with baseline ● Significant reduction of the subjective complaints starting 2 months after the treatment, these subjective symptoms improved more significantly in group B ● Group A: Six (50%) of patients were highly satisfied, five (42%) patients were satisfied, and only one (8%) patient was unsatisfied with the results ● Group B: Nine (75%) of patients were highly satisfied, and three (25%) of patients were satisfied with the results.	N/A	● Group A and B: Mild pain or discomfort, during and few hours after the procedure ● Group A: Skin atrophy and telangiectasia in three patients (25%)
2	Pruksapong ⁹ 2017 (Thailand)	RCT	● A: TAC 10 mg/mL, were injected 7 days after stitch removal, repeated in the first, second and third month ● B: BTX-A 1.5 U/cm wound length injected 7 days after stitch removal (one dose)	50 keloids after the scar excision A: 25 lesions B: 25 lesions	N/A	Follow-up: 14 days, 1 month, 3 month, 6 month	VSS	● Improvement of VSS in both groups after injections at 1-, 3-, and 6-month. ● In the first and third-month follow-up, the outcome in group B was more favorable than the group A, whereas the outcome in group A was more favorable than the group B in the 6 months follow-up.	N/A	N/A

3	Rasaii et al ⁶ 2018 (Iran)	RCT	● A: TAC 20 mg/mL plus normal saline ● B: TAC 20 mg/mL plus BTX-A 20 U/mL ● Maximal dose TAC 40 mg/session, and BTX-A 20 U/session ● 4-week interval, 3 treatment sessions	20 patients with a cumulative of 40 keloids A: 20 lesions B: 20 lesions	Mean 11.2 ± 0.6 months	Follow-up: 1 month after treatment	● VSS ● VAS	● VRS: No significant difference between treatment arms for height, vascularization, pliability, and scores. Group A had significant decreases in pigmentation scores compared to group B ● VAS: Significant decrease in the pain and pruritus score was noted in both groups. Group B had significant decreases in pain and pruritus scores compared to group A	N/A	N/A
4	Sabry et al ¹⁰ 2018 (Egypt)	RCT	● A: BTX-A 2.5 U/cm³, maximum dose 100 U/sessions, monthly for 4 treatment sessions ● B: 10,600 nm fractional CO₂ laser, power 25 w, dwell time 1000 us, spacing 800 um for keloids and power 15 w, dwell time 600 us, spacing 800 um for HTS, followed by topical application of BTX-A within 2 mins, covered with silicon sheet for 2 hours, monthly for 4 treatment sessions	20 patients consist of 10 keloids and 10 HTS	Mean 1.6 ± 0.5years	Follow-up: 6 months after treatment.	● VSS ● POSAS	● VSS: HTS: After both treatments, total VSS score in group B was significantly higher than group A Keloid: After both treatments, the percentage of improvement in vascularity and pliability in group A was significantly higher than in group B ● POSAS: HTS: significantly lower in patients in group B than group A Keloid: significantly lower in patients in group A than group B	N/A	Pain and pruritus which were not significantly different before and after treatment
5	Taheri et al ¹⁴ 2019 (Iran)	RCT	● A: BTX-A 4 U/cm³, monthly for a total 3 months ● B: Serum saline 0.9%, monthly for a total of 3 months	5 HTS patients and 5 Keloid patients randomly assigned to group A or group B.	At least for one year	Follow-up: 6 months for one visit every month	mVSS	BTX-A reduced (not significantly) mVSS including pliability, vascularity, pigmentation, and height, but did not affect the pruritus and pain.	N/A	N/A

(Continued)

Table I (Continued).

No	Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Lesions Duration	Follow-Up Duration (Months)	Evaluation	Responses	Recurrences (%)	Adverse Effects
6	Khatery et al ⁵ 2022 (Egypt)	RCT	● A: BTX-A 2.5 U/cm³ ● B: BTX-A 2.5 U/cm³ ● 4-weekly interval for 3 sessions	A: 12 keloid lesions B: 8 HTS lesions	● 0–3-month-old (20%) ● 4–6-month-old (15%), ● 7–12 month-old (20%) ● 12 months old (45%) of the lesions.	Follow-up: 3 months after the last session (6 months), and at the end of follow-up (9 months).	● VSS ● OSAS ● PSAS ● Histological and histochemical evaluation (collagen grading, Orcein stained sections for qualitative assessment of dermal elastic fibers)	● VSS: Greatest improvement was seen after the third session and after the 3 months follow-up. ● OSAS: Greatest improvement was after the third session and the end of follow-up ● Collagen grading score, collagen area %, Orcein stain grading score for elastic tissue: statistically significant before injection of BTX and 1 month after the third session ● Elastic tissue area %: highly statistically significant before injection of BTX and 1 month after the third session	10% A: 1 patients B: 1 patients	Usual pain experienced with any simple injection in both groups. A: No side effects B: No side effects
7	Gamil et al ¹³ 2019 (Egypt)	RCT	● A: BTX-A 2.5 U/cm³ on one side of the body, and TAC 0.1 mL/cm³ on the other side ● B: Combination of BTX-A 2.5 U/cm³ and TAC 0.1 mL/cm³ in the same lesion ● Monthly interval for 3 sessions	A: 26 keloid lesions B: 24 keloid lesions	Mean A: 35.2 ± 11.6 months B: 40.2 ± 10.2 months	Follow-up: 6 months after treatment	● SBSES ● CDU	● SBSES: Statistically significant increase in group A, significant increase in Group B ● CDU: Significant decrease in thickness and surface area of the keloids and improvement in transverse and longitudinal axis in group B versus group A.	N/A	● A: pain (11.5%) and skin atrophy (7.7%) ● B: No side effects

8	Neinaa et al ⁸ 2021 (Egypt)	RCT	● A: BTX-A 5 U/cm³, maximum dose 60 U/session ● B: autologous PRP 0.1 mL/injection point ● C: TAC 20 mg/mL, maximum dose 20 mg/session ● 4-week interval, 3 sessions	A: 20 keloid lesions B: 20 keloid lesions C: 20 keloid lesions	Mean A: 5.20 ± 1.32 months B: 4.70 ± 0.71 months C: 5.10 ± 0.99 months	Follow-up: 12 weeks	● VSS ● VRS ● Dermoscopic ● Histopathological ● Immunohistochemical	● VSS: All studied groups showed significant reduction of VSS at the end of follow-up period, with significant improvement in group A and B more than group C ● VRS: All studied groups showed significant improvement of VRS at the end of follow-up period in all studied groups in comparison with baseline ● Dermoscopic: remarkable improvement in group A and B than group C at the end of follow-up period ● Histological: significant reduction of collagen deposition, with more improvement of collagen bundles orientation ● Immunohistochemical: significantly reduced to grade 1 in group A, grade 2 in group B, and grade 3 in group C.	No patient reported recurrence of keloid lesions in all studied groups.	● A: No side effects ● B: No side effects ● C: 4 (20%) patients reported hypopigmentation
9	Ismail ¹⁶ 2021 (Egypt)	RCT	● A: BTX-A 2.5 U/cm³, maximum dose of 100 U/session, monthly interval until reaching complete flattening of the lesion or for a maximum of 6 sessions ● B: 5-FU 50 mg/mL, maximum dose 2 mL/session, weekly interval, until reaching complete flattening of the lesion or for a maximum of 6 sessions	A: 34 keloid lesions B: 35 keloid lesions	Mean: A: 2.43 ± 1.54 years B: 2.09 ± 1.04 years	Follow-up: Monthly for up to 3 months after the last session	● Flattening of lesions assessed as a reduction of keloid height ● Itching and Pain	● Degree of flattening of the lesions was significantly better in group A than group B ● A significant reduction of subjective symptoms was achieved after both treatment modalities.	● A: 8.8% ● B: 31.4%	● A: None of the lesions showed hyperpigmentation; 5.9% had hypopigmentation ● B: 14.3% post-treatment hyperpigmentation; 2.9% had hypopigmentation

(Continued)

Table 1 (Continued).

No	Authors, Years, Country	Study Design	Treatment Arms(s)	Participants	Lesions Duration	Follow-Up Duration (Months)	Evaluation	Responses	Recurrences (%)	Adverse Effects
10	Elfiky ¹¹ 2021 (Egypt)	RCT	BTX-A 5 U/cm ³ , maximum dose 100 U/session, monthly for 4 sessions	30 patients consist of 19 HTS and 21 keloid scars	Mean: 2.36 ± 2.62 years	Follow-up: Monthly, and 6 months after 4 monthly treatment sessions	• VSS • Histopathology • Immunohistochemical	• VSS: Highly significant difference between the mean VSS before treatment and after treatment with BTX, with highly significant decrease in the mean height, vascularity, and pliability of the lesions with BTX injection • Histopathology and immunohistochemistry: significant difference in epidermal thickness and fibronectin area% in dermis before and after treatment	N/A	N/A
11	Tawfik et al ¹² 2022 (Egypt)	RCT	• A: BTX-A 5 U/cm³, maximum dose 100 U/session, every month for 6 months. • B: The other part was left as a control	15 children patients consist of 10 HTS and 5 keloid scars	Mean: 56.3 ± 41.5 months	Follow up: 1 month and 6 months following the last treatment	• VSS • Antera[®] skin analysis camera system	• VSS: A comparison between the VSS in group A and group B revealed a highly significant difference clinically and statistically. A dramatic improvement in the vascularity, pliability, and height of the lesions in group A • Antera[®] camera: marked changes in the vascularity and height in group A	N/A	No side effects were reported.

Abbreviations: BTX, botulinum toxin; BTX-A, botulinum toxin A; CDU, Color Doppler Ultrasound; mVSS, Modified Vancouver Scar Scale; N/A, not available; OSAS, Observer Scar Assessment Scale; POSAS, Patient and Observer Scar Assessment Scale; PSAS, Patient Scar Assessment Scale; RCT, randomized control trials; SBSES, Stony Brook's Scar Evaluation Scale; TAC, triamcinolone acetone; VRS, the Verbal Rating Scale; VSS, the Vancouver Scar Scale.

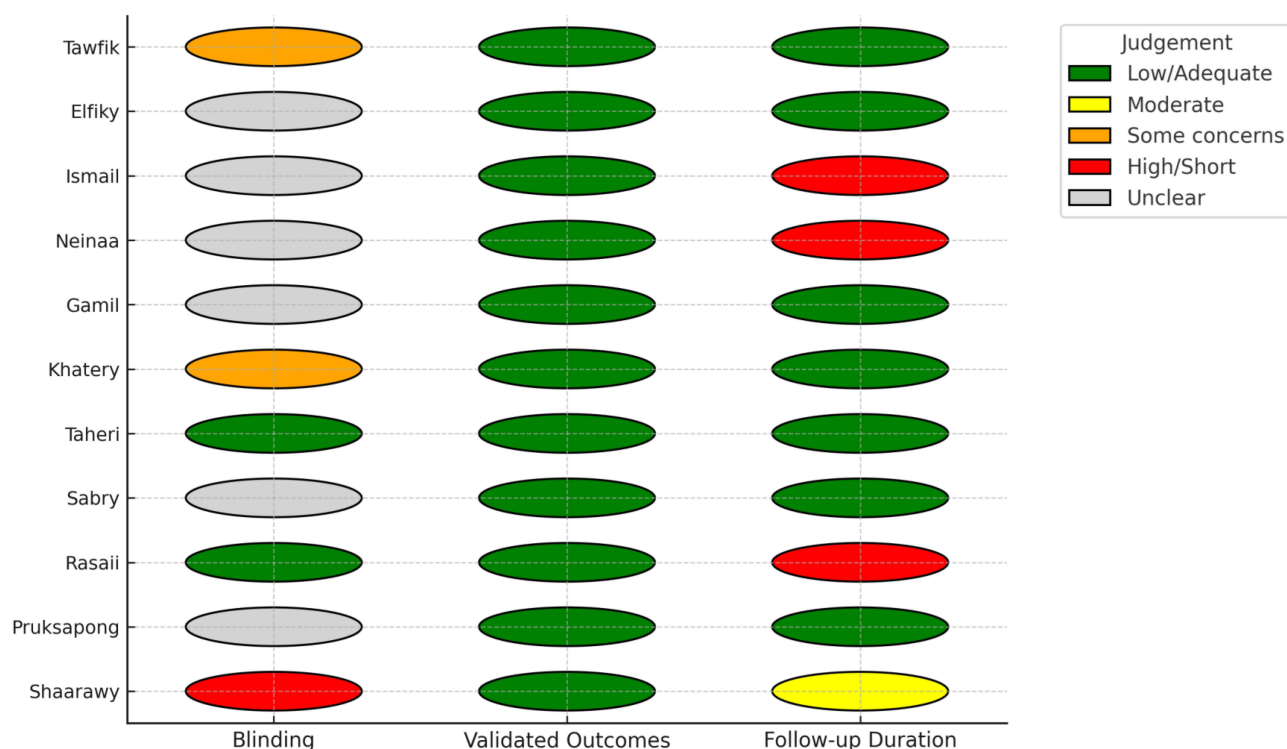


Figure 2 Risk of bias: blinding, outcome measures validated, and follow-up adequate (≥ 6 months) or inadequate (≤ 3 months) of the studies.

However, contradicting the results of other studies, one study by Taheri et al,¹⁵ conducted on 10 patients with HTS and keloids administered intralesional BTX-A 4 U/cm³ injection repeated monthly for three months, reported that BTX-A reduced mVSS, including flexibility, vascularity, pigmentation, and height, but not significantly. This study also found that BTX-A did not affect pruritus or pain in keloid lesions.¹⁵

Among the 11 studies, three studies reported that intralesional BTX-A injection improved VSS scores in terms of vascularity, height, and pliability, but did not affect the pigmentation of keloid lesions.^{7,11,12} Based on these studies, the fastest therapeutic effects are seen in the second month of treatment¹⁴ with the most therapeutic effect on average seen at three months of treatment.^{5,14}

Safety

Various studies that have been conducted report that BTX-A is safe, although AEs can still be observed. The most common local AEs are pain, edema, erythema, and bruising at the injection site.^{6,23} Systemic AEs arise when BTX-A spreads through blood vessels,^{23,24} including dysphagia, dyspnea, botulism, and death. In addition, there are other side effects that have been reported, such as headache, blurred vision, ptosis, diplopia, dysarthria, dysphonia, generalized muscle weakness, and urinary incontinence.²⁴ The ensuing AEs and complications are typically minor and transient.^{6,23}

The majority of studies did not find any serious AEs associated with intralesional BTX-A injection during treatment or observation. The most commonly reported AEs were local reactions, which can be caused by the injection itself. Minimal AEs are thought to be due to increased collagen and fibrosis in the keloid, limiting the amount of toxin that can reach the underlying muscles. These in turn reduce the local tension surrounding the scar without causing muscular paralysis.⁵

Among the 11 studies, two studies^{2,11} reporting AEs such as mild pain, pruritus, or discomfort. In the two studies that reported AEs, patients received intralesional BTX-A 2.5 U/cm³ injections monthly for four treatment sessions¹¹ and intralesional BTX-A 5 U/cm³ injections every eight weeks for three sessions or until full keloid improvement.² In addition to the side effects described, one study found that intralesional BTX-A injection caused hypopigmentation in 5.9% of patients.¹⁶

Aside from the safety profile and reversible effects,²⁵ BTX-A has also been shown to be well tolerated by pediatric patients, with the most commonly reported AEs in the pediatric patients following treatment being typically transient, mild, and self-limiting.²⁶ Recently, BTX-A has been utilized to treat a number of clinical conditions in the pediatric population,²⁵ including blepharospasm associated with dystonia, strabismus, lower-limb spasticity, focal spasticity in patients with cerebral palsy, and neurogenic detrusor overactivity.²⁶

In addition, research on the use of intralesional BTX-A injection as a treatment for keloids and HTS has also been conducted in pediatric population. Tawfik et al¹³ in Egypt conducted an RCT involving 15 children ranging from 2–15 years old with post-burn keloid and HTS who received intralesional BTX-A 5 U/cm³ injection on one part of the keloid or HTS lesion, where the other part of the lesion was left as a control. This intervention was conducted every month for six months. Clinical evaluation showed significant improvement on vascularity, pliability, and height of the lesions on six months after treatment. Furthermore, the vascularity and height of the lesions in the BTX-A group changed significantly from the evaluation with the Antera[®] camera. None of the patients had any AEs at the end of the study. This study demonstrates that BTX-A is a safe and effective treatment for keloids and HTS, even in the pediatric population.¹³

Influencing Factors

Dosage

There are currently no established recommendations for the dosage of intralesional BTX-A injection in keloids, hence the dose of BTX-A used in these studies was variable. Among the monotherapy and comparative studies, the administered dose ranged from 1.5 U/cm,¹⁰ to 5 U/cm³ ^{2,9,12,13} with the maximum dosage varying from 20 U/session,⁷ to 100 U/session.^{11–13} The details of intralesional BTX-A injection doses reported in monotherapy and comparative studies in this study are shown in Figure 3, while in studies using BTX-A as combination therapy, the doses given were 2 and 2.5 U/cm³.^{11,14}

Interval

In this study, there were different intervals of intralesional BTX-A injection in each study. The shortest interval found in these studies was monthly or 4-weekly intervals, while the longest was 8-weekly intervals. Nine out of 11 studies (81%) delivered at monthly or 4-weekly intervals^{5,7,9,11–16} with the number of sessions varying from three to six, whereas the remaining studies had 8-week intervals with three sessions.²

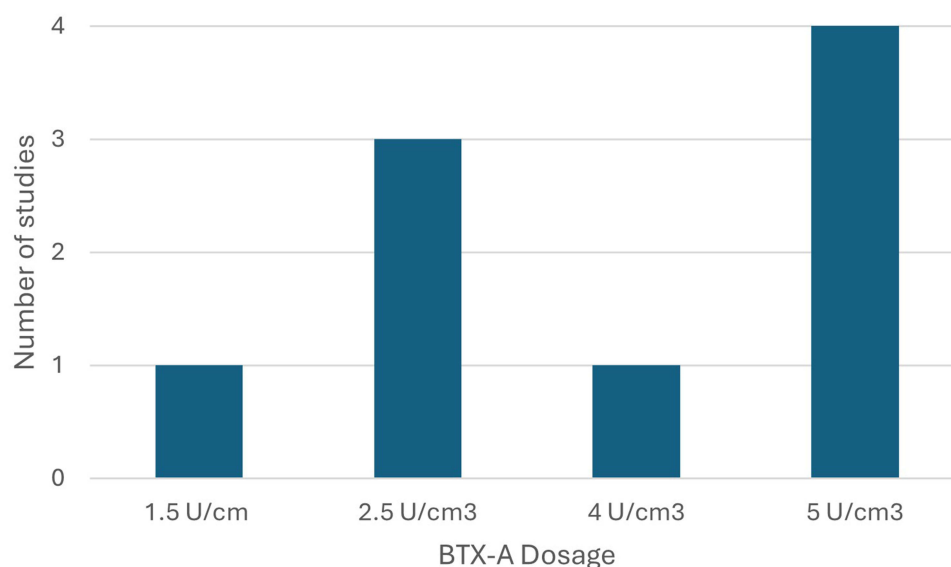


Figure 3 Dosage of BTX-A in all monotherapy and comparative studies.

Duration of the Lesions

There was significant variation in duration of the lesion between studies from 4.70 ± 0.71 months to 56.3 ± 41.5 months. Among 11 studies, 10 studies agreed that there was no significant correlation between clinical improvement and duration of keloid lesions.^{5,11,13,16} However, one study found that there was a correlation between the duration of keloid lesions on treatment response because the longer the duration of keloid lesions, the less improvement or decrease in the height of keloid lesions.¹²

Comparative Studies of Intralesional BTX-A

Several studies have also compared the efficacy of BTX-A versus other therapeutic modalities, with the most common comparator agent being triamcinolone acetonide (TAC), followed by 5-fluorouracil (5-FU), normal saline, and platelet-rich plasma (PRP).

Comparison to Other Intralesional Therapy

Comparison to Intralesional TAC

Corticosteroids remain the recommended first-line treatment of HTS and keloids.^{2,27} Corticosteroids reduce scar volume through several mechanisms of action, namely 1) reducing local inflammation, 2) inhibiting collagen production, and 3) reducing fibroblast proliferation. On a molecular level, corticosteroids are known to inhibit TGF- β 1 expression, resulting in decreased collagen synthesis.^{2,27}

Given their non-invasive nature, treatment efficacy, and relatively low recurrence rate (9–50%),²⁸ intralesional corticosteroids—including TAC—have been established as one of the most effective treatment methods for pathologic scars.²⁷ However, TAC has many AEs including telangiectasia, hypopigmentation, dermal atrophy, delayed wound healing, and scar widening.⁵

A study by Shaarawy et al² compared intralesional BTX-A 5 U/cm³ injection at 8-week interval for three sessions or until complete improvement to intralesional TAC 10 mg/mL injection at 4-week interval for six treatment sessions or until complete improvement. At the end of follow-up, there was a significant decrease in the volume and a significant softening of the keloid lesions in all patients, with a greater percentage in the TAC group than in the BTX-A group (82.7% vs 79.2%, respectively). Along with a significant decrease in the height of lesions and redness score, this study found a significant reduction in the subjective complaints, with subjective symptoms improved more dramatically in the BTX-A group. However, three patients in the TAC group experienced telangiectasia and skin atrophy, while the BTX-A group showed no AEs. In addition, the BTX-A group experienced higher satisfaction than the TAC group (75% vs 50%, respectively).²

This finding aligns with a study by Pruksapong et al,¹⁰ conducted on 50 post excision keloid lesions. Among 50 lesions, 25 lesions were treated with intralesional TAC 10 mg/mL injection and 25 lesions were treated with intralesional BTX-A 1.5 U/cm length injection a week after stitch removal. This study also reported comparable results with improvement of VSS in both groups at 1, 3-, and 6-month after injections. At the first and third month follow-ups, the outcome in the BTX-A group was more favorable than those in the TAC group, whereas at the sixth-month follow-up the outcome in the TAC group was more favorable than those in the BTX-A group. Nonetheless, intralesional TAC injection showing a superior effect on keloid formation than intralesional BTX-A injection might be due to the fact that intralesional TAC injection was administered more frequently than BTX-A, which was only done once.¹⁰

Comparison to Intralesional 5-FU

5-FU is an analog of the pyrimidine uracil which inhibits nucleic acid synthesis and cellular proliferation.^{27,29} This agent exhibits remarkable anti-metabolic activity by inserting directly into the nucleotide sequence during DNA and RNA synthesis. In addition, 5-FU has an effective mechanism of action as a cancer therapy because 1) it reduces the formation of monomeric building blocks through the inhibition of thymidylate synthase²⁷ and 2) the formation of faulty DNA and RNA due to 5-FU incorporation inhibits the hypermetabolic fibroblast proliferation state seen in HTS and keloid.^{27,29} In addition, 5-FU inhibits angiogenesis and TGF- β -induced expression of type I collagen without causing any tissue necrosis.²⁹ Through these mechanisms of action, 5-FU may be therapeutic in the treatment of keloids and HTS.²⁷

A study by Ismail et al¹⁶ compared intralesional BTX-A 2.5 U/cm³ injection repeated monthly and intralesional 5-FU 50 mg/mL injection repeated weekly on 50 patients with keloid for a maximum of six sessions showed that the BTX-A group had a more significant flattening of lesion than the 5-FU group. A significant reduction in subjective symptoms was observed in both groups after treatment with both modalities. Furthermore, the BTX-A group showed less recurrence at three month after the last sessions than the 5-FU group (8.8% vs 31.4%, respectively). However, 5.9% of patients in the BTX-A group experienced hypopigmentation, whereas in the 5-FU group, hyperpigmentation was found in 14.3% of patients, and hypopigmentation in 2.9% of patients.¹⁶

Comparison to Placebo (Normal Saline 0.9%)

A comparative study by Taheri et al¹⁵ conducted on five patients administered intralesional BTX-A 4 U/cm³ injection while another five patients were administered intralesional normal saline 0.9% injection monthly for three sessions reported that BTX-A reduced mVSS, including pliability, vascularity, pigmentation, and height, but not significantly and did not affect pruritus and pain in patients with keloids or HTS.¹⁵

Comparison to Intralesional Autologous PRP

PRP is an autologous platelet concentrate that stimulates tissue repair and accelerates wound healing.^{28,29} This mechanism occurs through a number of growth factors released by activated platelets which accelerate wound healing²⁹ by reducing inflammation,²⁸ increasing angiogenesis, remodeling and repair of collagen structures,^{28,29} also tissue restoration.²⁹

Neinaa et al⁹ compared BTX-A, autologous PRP, and TAC injected intralesionally in 60 patients with keloids. Twenty patients received BTX-A 5 U/cm³, while another 20 patients received 0.1 mL/injection point of autologous PRP, and 20 patients received TAC 20 mg/mL, repeated four weekly for three sessions. All studied groups showed a significant reduction in VSS; however, significant improvements in VSS were observed more dramatically in the BTX-A and PRP groups than in the TAC group. In terms of pain, significant improvements after treatment were observed in all studied groups compared to baseline. Moreover, remarkable improvement on dermoscopic examination was seen in the BTX-A and PRP groups compared to the TAC group, and histologically significant reduction of collagen deposition, with greater improvement of collagen bundle orientation were seen significantly in the BTX-A and PRP group compared with TAC group at the end of the follow-up period. However, AEs were also observed more frequently in the TAC group than BTX-A group and PRP group, including hypopigmentation in 20% of patients.⁹

Combination Treatments

Several studies have examined the intralesional effectiveness of BTX-A in combination with other agents including TAC and fractional CO₂ laser.

Comparison to Combination of Intralesional BTX-A with TAC

Studies comparing intralesional BTX-A injections alone with a combination of intralesional BTX-A and TAC injections have reported mixed results. Rasaii et al⁷ compared the efficacy and safety of TAC and combination of TAC-BTX-A in 20 patients with multiple keloids. Patients were randomly assigned into two groups: group A received TAC 20 mg/mL plus normal saline, while group B received TAC 20 mg/mL plus BTX-A 20 u/mL both injections intralesionally repeated four weekly for three sessions. Effectiveness was not significantly different between the two groups at 3-month follow-up. In terms of pain and pruritus, significant improvements after treatment were observed in both groups as compared to baseline with more significant improvements in the combination of TAC-BTX-A group compared to the TAC group alone. However, this study demonstrates that the combination of TAC-BTX-A in keloid had no significant difference in effectiveness compared with TAC alone, but it had a significant effect on symptomatic control (eg, pain and pruritus).⁷

On the other hand, a similar study by Gamil et al¹⁴ demonstrated different outcomes. In this study, 50 keloids patients received combination of intralesional TAC-BTX-A injections in comparison to intralesional TAC or BTX-A injection alone. In contrast to the previous study, 24 patients received a combination of intralesional BTX-A 2.5 U/cm³ plus TAC 0.1 mL/cm³ injection in the same keloid lesion. In comparison, another 26 patients received intralesional BTX-A 2.5 U/

cm³ injections on one side of their keloid and intralesional TAC 0.1 mL/cm³ injection on the other keloid lesion. This intervention was repeated every four weeks for three sessions. The SBSES score increased statistically significant in both groups during the second and third treatments; however, at the end of follow-up, the combination of intralesional TCA-BTX-A injection group showing a greater improvement than either the intralesional TCA injection or intralesional BTX-A injection groups alone. The Color Doppler Ultrasound (CDU) results demonstrated a significant decrease in the thickness and surface area of the keloids as well as an improvement in their transverse and longitudinal axes in the combination of intralesional TCA-BTX-A injection group than intralesional TCA injection or intralesional BTX-A injection group alone. This study concluded that the combination of intralesional TAC-BTX-A injection appears to be superior to either therapy alone, also providing safer and more effective outcomes with fewer AEs.¹⁴

Aligned with study by Gamil et al,¹⁴ a meta-analysis by Liu et al³⁰ reported that corticosteroids combined with BTX-A are more effective in keloids and HTS with more notable improvements in VSS, VAS, scar thickness, pruritus level, and patient satisfaction compared to corticosteroid alone. Furthermore, the combination of intralesional corticosteroid and BTX-A injection as a treatment of keloids and HTS offers greater safety, easier administration, and fewer complications compared to corticosteroid alone.³⁰

Comparison to Combination of Fractional CO₂ Laser with Topical BTX-A

Recently, laser-assisted drug delivery (LADD) has been employed as an alternative to intralesional injection in the treatment of keloids and HTS. LADDs have been recognized for enhancing topical absorption of various drugs by increasing skin permeability through the formation of vertical micro-channels in the skin.²⁷

Sabry et al¹¹ compared the combination of 10,600 nm fractional CO₂ laser followed by topical application of BTX-A with intralesional BTX-A 2.5 U/cm³ injection repeated monthly for four sessions. In the HTS patients, the improvement in vascularity, pigmentation, pliability, height, and total VSS with the combination of fractional CO₂ laser-BTX-A group was significantly higher than that in the intralesional BTX-A injection group alone. Likewise, patients with HTS were more satisfied with the combination of fractional CO₂ laser-BTX-A based on POSAS scores.¹¹

Meanwhile, in keloid patients, there was a significant improvement after completion of the treatment protocol, except for pigmentation in the intralesional BTX-A injection group and pigmentation and vascularity in the combination of fractional CO₂ laser-BTX-A group. The improvement in vascularity and pliability after intralesional BTX-A injection was significantly higher than the combination of fractional CO₂ laser-BTX-A group. Likewise, patients with keloids were more satisfied with intralesional BTX-A injection based on the POSAS scores.¹¹

Conclusion

Current evidence suggests that intralesional BTX-A may offer clinical benefit in improving certain characteristics of keloids and HTS —particularly vascularity, pliability, and scar height—with a favorable safety profile and minimal adverse effects. BTX-A may be considered as an adjunctive option, particularly when standard therapies such as corticosteroids are contraindicated or poorly tolerated.

However, the strength of this conclusion is tempered by notable limitations in the existing body of research. Most studies to date are small in scale, limited in geographic and ethnic diversity, and marked by short follow-up durations. Variability in study design, BTX-A dosing, treatment intervals, and outcome measures hinders direct comparison and broad clinical application. Furthermore, many studies rely on subjective or semi-quantitative assessment tools, and robust data on long-term outcomes are lacking.

Future research should prioritize large-scale, multicenter randomized trials with standardized protocols to determine optimal dosing, injection intervals, and treatment duration. Studies should also incorporate objective and validated outcome measures, assess recurrence over longer follow-up periods, and explore the efficacy of BTX-A across diverse populations and healthcare settings. Until such evidence is available, the use of BTX-A should be guided by individual patient characteristics and integrated within a multi-modal, patient-centered approach to keloid management.

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