International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	BOTULINUM TOXIN TYPE A IN SCAR MODULATION: PREVENTION AND TREATMENT OF HYPERTROPHIC SCARS AND KELOID
DOI	https://doi.org/10.31435/ijitss.2(50).2026.6138
RECEIVED	11 March 2026
ACCEPTED	17 June 2026
PUBLISHED	24 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

BOTULINUM TOXIN TYPE A IN SCAR MODULATION: PREVENTION AND TREATMENT OF HYPERTROPHIC SCARS AND KELOID

Aleksandra Kujach *(Corresponding Author, Email: aleksandra.kujach@gumed.edu.pl)*
M.D., University Clinical Centre, Gdańsk, Poland
ORCID ID: 0009-0004-8338-136X

Julia Góralska
Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0004-7594-0387

Melania Popielarczyk
Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0000-0658-069X

Katarzyna Napiórkowska
M.D., Nicolaus Copernicus Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0002-9736-9252

Dominik Płaza
Scientific Circle of Neurotraumatology, Department of Emergency Medicine, Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0000-6251-3969

ABSTRACT

Hypertrophic scars and keloids are fibroproliferative disorders of the dermis that arise from dysregulated wound healing and are characterized by excessive extracellular matrix deposition, persistent inflammation, fibroblast activation, and variable recurrence after treatment. Despite the availability of silicone therapy, pressure therapy, corticosteroids, 5-fluorouracil, bleomycin, lasers, cryotherapy, surgery, and radiotherapy, no universally effective treatment algorithm has been established. Botulinum toxin type A (BoNT-A) has emerged as a promising scar-modulating agent with potential value in both early postoperative scar prevention and treatment of established hypertrophic scars and keloids. Initially, its effect was attributed mainly to chemodenervation and reduction of mechanical tension across wound edges. However, accumulating experimental and clinical evidence suggests broader mechanisms, including modulation of fibroblast proliferation, suppression of transforming growth factor-β/connective tissue growth factor signaling, reduction of α-smooth muscle actin and collagen I/III expression, interference with neurogenic inflammation through the substance P–neurokinin-1 receptor pathway, regulation of macrophage polarization, and effects on intracellular profibrotic pathways such as JAK2/STAT3, BMP4/Smad, and PARP14/SOCS2-mediated signaling. Clinical studies and meta-analyses indicate that BoNT-A may improve scar width, pliability, vascularity, height, patient-reported symptoms, and overall aesthetic quality, particularly when used immediately after wound closure or as part of multimodal therapy. Nevertheless, evidence remains heterogeneous, with substantial variation in dose, timing, injection technique, anatomical site, outcome measures, and follow-up duration. This review summarizes current evidence on BoNT-A in scar modulation, emphasizing mechanisms, postoperative prevention, treatment of established scars, combination strategies, safety, limitations, and future directions.

KEYWORDS

Botulinum Toxin Type A; Hypertrophic Scar; Keloid; Scar Prevention; Neurogenic Inflammation; Macrophage Polarization; Intralesional Therapy

CITATION

Aleksandra Kujach, Julia Góralska, Melania Popielarczyk, Katarzyna Napiórkowska, Dominik Płaza. (2026) Botulinum Toxin Type A in Scar Modulation: Prevention and Treatment of Hypertrophic Scars and Keloid. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.6138

1. Introduction

Hypertrophic scars and keloids are pathological outcomes of cutaneous wound healing. Both entities are characterized by excessive fibroblast activity, increased extracellular matrix deposition, and prolonged inflammatory remodeling. However, they differ clinically: hypertrophic scars remain confined to the boundaries of the original wound and may partially regress, whereas keloids extend beyond the initial wound margins, tend to enlarge progressively, and rarely resolve spontaneously. These lesions can cause pruritus, pain, tenderness, burning, contracture, functional impairment, cosmetic disfigurement, and psychological distress, particularly when located on visible or high-tension anatomical sites such as the chest, shoulders, upper back, neck, face, and earlobes (Lai et al., 2026).

The management of hypertrophic scars and keloids remains challenging because recurrence is common and responses to monotherapy are inconsistent. Intralesional triamcinolone acetonide remains one of the most established first-line approaches, but it may be associated with dermal atrophy, telangiectasia, hypopigmentation, pain, and incomplete long-term control. Other modalities, including 5-fluorouracil, bleomycin, verapamil, silicone sheeting, pressure therapy, cryotherapy, lasers, radiotherapy, and surgical excision, are widely used, but no single intervention is universally effective (Naik, 2022).

Botulinum toxin type A (BoNT-A) has been introduced as a scar-modulating treatment because of its ability to reduce dynamic wound tension and possibly modulate cellular and molecular pathways involved in fibrosis. The earliest rationale was based on chemodenervation: by temporarily weakening adjacent muscles, BoNT-A may reduce repetitive mechanical forces across a healing incision. This concept is particularly relevant in mobile areas such as the face, perioral region, neck, and periocular area. However, newer evidence suggests that BoNT-A may also act directly on fibroblasts, inflammatory cells, neurogenic mediators, and profibrotic signaling pathways, which may explain its effects in anatomical sites where muscle paralysis alone is unlikely to account for scar improvement (Santillan et al., 2024)(Atiyeh & Chahine, 2022).

This review summarizes the current evidence regarding BoNT-A in scar modulation, with particular focus on prevention of postoperative scars and treatment of established hypertrophic scars and keloids. The review integrates clinical trials, systematic reviews, meta-analyses, network meta-analyses, mechanistic studies, animal models, and combination-treatment reports.

2. Methods

This article is a targeted narrative review based on the predefined corpus of publications selected for the manuscript topic. Priority was given to clinical studies, randomized controlled trials, systematic reviews, meta-analyses, network meta-analyses, and mechanistic studies evaluating BoNT-A in postoperative scar prevention, hypertrophic scars, and keloids. Studies evaluating BoNT-A as monotherapy, adjunctive therapy, or part of multimodal scar management were included. Experimental studies were considered when they addressed plausible mechanisms of BoNT-A action, including fibroblast activity, collagen deposition, TGF-β-related signaling, neurogenic inflammation, macrophage polarization, adipogenic transdifferentiation, and intracellular profibrotic pathways.

Because the available studies differ substantially in design, anatomical site, scar type, injection timing, BoNT-A preparation, dilution, dose, injection depth, number of sessions, comparator, and outcome measures, no quantitative synthesis was performed. Findings are therefore presented narratively, with attention to the distinction between postoperative scar prevention and treatment of established hypertrophic scars or keloids.

3. Pathophysiological Rationale for BoNT-A in Scar Modulation

3.1. Mechanical tension and chemodenervation

Mechanical tension is one of the central determinants of pathological scar formation. Wounds located in high-tension areas, such as the sternum, shoulders, back, neck, and perioral region, are more likely to develop widened, hypertrophic, or keloidal scars. Tension activates mechanotransduction pathways, enhances fibroblast activity, promotes collagen deposition, and sustains local inflammation. BoNT-A may reduce these forces by inducing temporary chemodenervation of adjacent skeletal muscles, thereby decreasing repetitive traction across the wound during the early proliferative phase (Santillan et al., 2024).

This mechanism is most plausible for facial and perioral incisions, where dynamic muscle activity directly affects wound tension. It is less sufficient as a sole explanation for scar improvement in areas such as the sternum, abdomen, back, or breast, where superficial injections may not meaningfully paralyze deeper muscles. This has led authors to propose that the clinical effects of BoNT-A cannot be reduced to neurotoxicity alone and may involve cytokine, fibroblast, inflammatory, and wound-healing pathways (Atiyeh & Chahine, 2022).

3.2. Fibroblast activity, collagen deposition, and profibrotic signaling

Hypertrophic scars and keloids are characterized by excessive fibroblast proliferation, myofibroblast differentiation, and deposition of collagen I, collagen III, and other extracellular matrix components. BoNT-A appears to influence several fibroblast-related markers, including TGF-β1, connective tissue growth factor, α-smooth muscle actin, myosin II, and collagen expression. In vitro studies summarized in a dermatologic review reported that BoNT-A decreased fibroblast proliferation in scar-derived fibroblasts, reduced TGF-β-related signaling, and affected markers associated with myofibroblast contraction and collagen deposition (Santillan et al., 2024).

A review on novel keloid therapies similarly described BoNT-A as an agent capable of modulating fibroblast activity by decreasing TGF-β1 and connective tissue growth factor, preventing fibroblast-to-myofibroblast differentiation, and altering expression of genes related to angiogenesis and extracellular matrix remodeling, including VEGF, MMP1, S100A, and PDGFA(Naik, 2022).

3.3. BMP4/Smad-mediated adipogenic transdifferentiation

One mechanistic study investigated the effect of BoNT-A on primary keloid myofibroblasts. Keloid tissues showed increased expression of α-SMA, collagen I, and collagen III compared with normal skin. In TGF-β1-induced keloid myofibroblasts, BoNT-A increased adipocyte markers PPARγ and C/EBPα, promoted lipid droplet accumulation, and decreased α-SMA, collagen I, and collagen III expression. These effects were associated with upregulation of BMP4 and phosphorylated Smad1/5/8, and they were reversed by Noggin, a BMP4 antagonist. The authors concluded that BoNT-A may promote transdifferentiation of primary keloid myofibroblasts into adipocyte-like cells through activation of BMP4/Smad signaling (Dai & Lei, 2021).

This mechanism is important because it suggests that BoNT-A may not merely suppress fibroblast activity but may also alter the cellular phenotype of scar-associated myofibroblasts. However, these findings are experimental and require cautious interpretation before translation into clinical dosing or patient selection.

3.4. Neurogenic inflammation and the SP–NK1R axis

Neurogenic inflammation is increasingly recognized as a contributor to hypertrophic scar symptoms and biology. Substance P released from sensory nerve endings may promote pain, pruritus, vasodilation, inflammation, and fibroblast activation through neurokinin-1 receptor signaling. BoNT-A may reduce scar-related pain and pruritus partly by inhibiting neuropeptide release, including substance P (Santillan et al., 2024).

A mechanistic study specifically linked hypertrophic scar formation with cutaneous neurogenic inflammation through the substance P-neurokinin-1 receptor pathway. The study proposed that BoNT-A may exert therapeutic effects by interfering with this SP-NK1R axis and thereby attenuating neurogenic inflammation in hypertrophic scars (Zhang, Li, et al., 2022).

3.5. Macrophage polarization and the PARP14/SOCS2 axis

Scar formation depends not only on fibroblasts but also on immune-cell phenotype and persistence of inflammatory signaling. A 2025 experimental study showed that BoNT-A reduced dermal thickness, epidermal hyperplasia, collagen deposition, fibrosis, proliferation, angiogenesis, and M2 macrophage markers in a mouse hypertrophic scar model. Mechanistically, BoNT-A suppressed PARP14 and SOCS2, while PARP14 overexpression restored M2 polarization and partially reversed the scar-ameliorating effects of BoNT-A. Additional SOCS2 silencing counteracted the effects of PARP14 overexpression, suggesting that BoNT-A may reduce hypertrophic scarring through inhibition of PARP14-mediated SOCS2 RNA stabilization and subsequent M2 macrophage polarization (Ali et al., 2025).

These data broaden the proposed mechanism of BoNT-A from neuromuscular modulation to immune-fibrotic regulation. Nevertheless, the authors acknowledged that the causal relationship between PARP14 and the observed phenotype remains inferential without direct validation in PARP14-knockout models, and further genetically modified models are needed (Ali et al., 2025).

3.6. JAK2/STAT3 pathway

The JAK2/STAT3 pathway is another profibrotic signaling axis implicated in hypertrophic scar fibroblast proliferation, migration, and fibrosis. In a mechanistic study, hypertrophic scar tissues and hypertrophic scar fibroblasts showed increased JAK2 and STAT3 phosphorylation. BoNT-A inhibited the JAK2/STAT3 pathway, reduced fibroblast viability, proliferation, migration, and fibrosis, and promoted wound healing while reducing collagen deposition in vivo. Activation of the pathway weakened the antifibrotic effects of BoNT-A, supporting the relevance of JAK2/STAT3 signaling in its mechanism (Fan et al., 2024).

4. BoNT-A for Prevention of Postoperative Scarring

4.1. Timing of administration

The strongest preventive rationale for BoNT-A is early administration near the time of wound closure. Immediate postoperative injection may reduce dynamic tension during the inflammatory and proliferative phases of wound healing and may also influence fibroblast activation before excessive matrix deposition becomes established. In a recent prospective, double-blind randomized controlled trial, BoNT-A was injected immediately after surgical excision and closure, with follow-up at 7 days, 15 days, 1 month, 3 months, and 6 months. Scar quality was assessed using the modified Stony Brook Scar Evaluation Scale (Shi et al., 2025).

That trial included 46 patients with benign skin tumors and compared saline with three BoNT-A concentrations: 1, 2.5, and 5 U/0.1 mL. Experimental groups had higher mSBSES scores at all follow-up points, and the optimal dose appeared to depend on anatomical risk. A concentration of 5 U/0.1 mL performed best at high-risk scar sites; 2.5 and 5 U/0.1 mL were similar at intermediate-risk sites; and 1 U/0.1 mL appeared sufficient at low-risk sites. No severe complications were reported, and 86.5% of patients were satisfied with treatment (Shi et al., 2025).

The same study emphasized that higher concentrations or repeated injections may increase scar-preventive efficacy but may also impair local movement, muscle strength, exercise stability, or physiological function, although such effects are usually reversible. This point is particularly relevant when considering BoNT-A in functional anatomical regions (Shi et al., 2025).

4.2. Cleft lip repair scars

Cleft lip repair provides a clinically important model for BoNT-A scar prevention because the upper lip is subject to repetitive movement and tension from the orbicularis oris muscle. A systematic review and meta-analysis of BoNT-A for cleft lip and/or palate scarring included four randomized controlled trials with 161 patients. BoNT-A significantly reduced scar width and improved Visual Analog Scale scores, but no statistically significant difference was found in Vancouver Scar Scale scores. The pooled mean difference for scar width was -0.20, and the VAS mean difference was 1.30, while the VSS difference did not reach statistical significance (Ji et al., 2022).

The review noted that most studies injected BoNT-A immediately after cleft lip repair, whereas one study used preoperative injection. The doses in infants generally ranged from 1 to 2 U/kg, and injections were most often delivered into the orbicularis oris muscle rather than purely into the dermis or subcutaneous tissue. The authors also emphasized that dose, dilution, timing, and injection method varied across studies, limiting subgroup analysis (Ji et al., 2022).

Another systematic review of BoNT-A for scar quality after cleft lip repair included five studies and 216 patients. Four studies involved primary cleft lip repair during infancy, and one involved older patients undergoing revision. All four studies that measured scar width and included a saline control arm reported significantly reduced scar width after BoNT-A injection. Improvement in VAS and VSS was reported in three of five and two of five studies, respectively, and no BoNT-A- or surgery-related complications were reported (Martinez et al., 2024).

Together, these data support BoNT-A as a promising adjunct for cleft lip scar prevention, particularly for scar width and subjective aesthetic assessment. However, heterogeneity in injection timing, dose, surgical technique, and assessment tools limits definitive recommendations.

4.3. Facial, cervical, and periocular scars

Facial and cervical scars are among the most biologically plausible indications for BoNT-A because mechanical forces from mimetic muscles can directly influence wound remodeling. Meta-analytic evidence summarized in a letter to the editor indicated that a systematic review by Qiao et al. identified 17 controlled trials with 633 cases and concluded that BoNT injections significantly improved postoperative scar quality and cosmetic appearance. A related review by Chen et al. included 267 patients from eight placebo-controlled, double-blind clinical trials and found that local BoNT-A injection could mitigate scar formation, although trial quality was heterogeneous (Atiyeh & Chahine, 2022).

The same commentary argued that reliance on muscle paralysis as the exclusive mechanism may be too narrow, especially because some studies involve superficial injections or anatomical areas in which deep neuromuscular blockade is unlikely. This critique supports a more balanced interpretation: facial and cervical scar improvement may involve both tension reduction and direct modulation of fibroblast, cytokine, inflammatory, and neurogenic pathways (Atiyeh & Chahine, 2022).

5. BoNT-A for Established Hypertrophic Scars and Keloids

5.1. Intralesional BoNT-A monotherapy

Intralesional BoNT-A has been evaluated as a treatment for established hypertrophic scars and keloids. In a prospective clinical and pathological study, 20 patients were enrolled: 12 with keloids and 8 with hypertrophic scars. Patients received intralesional BoNT-A monthly for three sessions. The dose was adjusted to 2.5 U per cubic centimeter of lesion, and outcomes were assessed using the Vancouver Scar Scale, Observer Scar Assessment Scale, and Patient Scar Assessment Scale, with histologic and morphometric evaluation of collagen and elastic tissue (Khatery et al., 2022).

This study reported statistically significant improvement from baseline after each injection session and at follow-up. Mean VSS decreased from 9.45 at baseline to 3.15 at the end of follow-up; OSAS decreased from 29.20 to 11.85; and PSAS decreased from 29.05 to 10.15. Histopathological findings also differed significantly before and after treatment, supporting clinical and tissue-level effects of intralesional BoNT-A (Khatery et al., 2022).

Although these findings are encouraging, the study was small, non-placebo-controlled, and included both hypertrophic scars and keloids. Therefore, it supports feasibility and biological plausibility rather than establishing BoNT-A as a first-line monotherapy.

5.2. Comparative evidence against other intralesional agents

Intralesional therapy for keloids frequently includes triamcinolone acetonide, 5-fluorouracil, bleomycin, verapamil, and BoNT-A. A network meta-analysis comparing five intralesional drugs - triamcinolone, 5-fluorouracil, bleomycin, verapamil, and BoNT-A - included 20 randomized controlled trials and 1114 patients. It found that BoNT-A alone and triamcinolone plus 5-fluorouracil had significantly better efficacy than 5-fluorouracil, triamcinolone, and verapamil, with no significant difference in efficacy between BoNT-A and triamcinolone plus 5-fluorouracil. No significant differences were noted in adverse-event rates between BoNT-A, triamcinolone plus 5-fluorouracil, 5-fluorouracil, and triamcinolone (Yang et al., 2024).

Another network meta-analysis focused on both efficacy and recurrence risk in hypertrophic scars and keloids emphasized that recurrence is underreported despite being central to long-term success. This analysis framed BoNT-A among the major intralesional therapies, alongside triamcinolone, 5-fluorouracil, bleomycin, and verapamil, but noted that small sample sizes, inconsistent outcome definitions, and heterogeneous protocols continue to limit robust treatment ranking (Lai et al., 2026).

In a randomized comparison of intralesional insulin, BoNT-A, and corticosteroid for keloids, all three groups showed significant volume reduction, but insulin and corticosteroids were statistically superior to BoNT-A for pigmentation, thickness reduction, and symptom relief. The authors concluded that BoNT-A may be promising but is better positioned as an adjuvant therapy rather than a standalone replacement for mainstay modalities (Elradi et al., 2025).

These findings illustrate a clinically important nuance: BoNT-A is not consistently superior to established intralesional treatments in all settings. Its value may be greatest in selected scars, in combination regimens, or when pain, pruritus, dynamic tension, and tolerability are major considerations.

6. Combination Strategies

6.1. BoNT-A with corticosteroids

Combination therapy is increasingly favored in scar management because monotherapy often fails to address the multiple biological drivers of hypertrophic scars and keloids. A systematic review of combined scar-modulating agents found that several drug combinations show increased efficacy and similar or fewer adverse events compared with triamcinolone monotherapy. The strongest and most consistent evidence was observed for triamcinolone plus 5-fluorouracil, whereas evidence for other combinations, including those involving BoNT-A, remains more limited and variable (Bernabe et al., 2024).

A meta-analysis comparing corticosteroid alone versus corticosteroid plus BoNT-A suggested better treatment outcomes with the combined approach, but a subsequent letter raised methodological concerns regarding the search strategy, outcome interpretation, and follow-up duration. Specifically, the letter noted that one included study had only three months of follow-up, whereas BoNT-A effects may be more apparent at six months, potentially affecting pooled estimates (Yue & Ju, 2022).

Therefore, the combination of corticosteroids and BoNT-A is biologically plausible but not yet standardized. Future trials should distinguish between additive efficacy, steroid-sparing effects, symptom relief, recurrence prevention, and adverse-event reduction.

6.2. BoNT-A with hyaluronic acid and microneedle delivery

Microneedle delivery of BoNT-A combined with hyaluronic acid has been evaluated in multiple sternal keloids among patients with oily skin. In a retrospective investigation of 58 patients receiving monthly steroid injections, 32 patients received additional BoNT-A/hyaluronic acid injection on the same day as the first steroid injection, whereas 26 served as controls. At 24 weeks, average sebum production and transepidermal water loss increased in controls but were reduced relative to baseline in the intervention group. Sternal keloid relapse was observed in 88.5% of controls and in none of the intervention-group patients. VSS and VAS scores were also significantly lower in the BoNT-A/hyaluronic acid group, and satisfaction was higher (Zhang, Peng, et al., 2022).

These data suggest that BoNT-A may be useful not only through antifibrotic activity but also by modulating sebum production, barrier function, and symptoms in selected keloid phenotypes. However, the retrospective design, concomitant steroid therapy, and specific focus on oily sternal keloids limit generalization.

6.3. BoNT-A after surgical excision of ear keloids

Auricular keloids are difficult to manage because of frequent recurrence after excision. A retrospective study evaluated 33 consecutive patients who received immediate BoNT-A injections after surgical excision of ear keloids. Follow-up ranged from 7 to 18 months. Only one recurrence occurred, and no adverse effects were reported. VSS and VAS improved significantly, and patient satisfaction was high (Li et al., 2024).

The authors concluded that concomitant surgical excision and immediate BoNT-A injection could be a safe and effective method for ear keloids, while acknowledging the limitations of small sample size and need for longer follow-up (Li et al., 2024).

6.4. BoNT-A with radiotherapy after keloid surgery

Post-excision radiotherapy is a recognized strategy for reducing keloid recurrence, particularly in high-risk sites. A randomized controlled trial of 60 patients with medium and large chest keloids compared surgical resection followed by BoNT-A plus superficial radiotherapy with surgical resection followed by superficial radiotherapy alone. After six months, the combined BoNT-A and superficial radiotherapy group had a higher total effective rate, higher patient satisfaction, lower VSS score, and lower recurrence rate than radiotherapy alone (Gao et al., 2025).

These findings support multimodal postoperative management for high-risk keloids, but longer follow-up is needed because keloid recurrence may occur beyond six months.

6.5. BoNT-A with lasers and device-based therapy

Lasers and energy-based devices are frequently incorporated into scar management protocols. Their potential synergy with BoNT-A is based on different mechanisms: lasers may target vascularity, collagen remodeling, and texture, while BoNT-A may reduce tension, fibroblast activity, neurogenic inflammation, and symptoms. However, available evidence remains heterogeneous and often involves small cohorts or multimodal regimens in which the independent contribution of BoNT-A is difficult to isolate.

A postoperative scar protocol for Asian patients supports intraoperative BoNT-A in selected high-risk individuals at the time of skin closure and proposes multimodal treatment for recalcitrant keloids, including intralesional steroids, BoNT-A, lasers, surgery, and radiotherapy (Gill et al., 2024).

7. Injection Techniques, Dose, and Anatomical Considerations

The optimal dose and injection technique remain unsettled. Existing studies vary in BoNT-A product, dilution, concentration, injection plane, spacing, volume, timing, and number of sessions. Preventive protocols commonly use injection immediately after wound closure, whereas treatment protocols for established scars often use intralesional injection repeated monthly or every several weeks.

The dose-dependent randomized controlled trial is particularly useful because it evaluated anatomical risk categories. The study suggested 5 U/0.1 mL for high-risk sites, 2.5-5 U/0.1 mL for intermediate-risk sites, and 1 U/0.1 mL for low-risk sites. These results are preliminary but clinically relevant because they imply that fixed-dose protocols may be less appropriate than site-specific dosing (Shi et al., 2025).

For established hypertrophic scars and keloids, one clinical-pathological study used 2.5 U per cubic centimeter of lesion, injected intralesionally once monthly for three months (Khatery et al., 2022).

For cleft lip repair, doses in pediatric studies generally ranged from 1 to 2 U/kg and were administered into the orbicularis oris muscle, most often immediately after repair (Ji et al., 2022).

A long-term clinical study comparing dual-plane micro-drop BoNT-A injection with traditional methods for hypertrophic scars in tension zones proposed that injection plane and distribution pattern may influence outcomes. In that study, patients were randomized to dual-plane micro-drop BoNT-A, triamcinolone acetonide, or fractional CO2 laser, with monthly interventions for three sessions and POSAS follow-up up to 24 months. The BoNT-A approach was designed to address scars in tension-prone areas and to distribute the agent across different tissue planes (Jiang et al., 2024).

8. Safety and Tolerability

Across the available studies, BoNT-A was generally well tolerated. In the dose-dependent postoperative prevention trial, no severe complications were reported among 46 patients (Shi et al., 2025).

In the cleft lip systematic review including 216 patients, no complications related to BoNT-A injection or surgery were reported (Martinez et al., 2024).

In the retrospective ear-keloid study, no adverse effects were reported during follow-up (Li et al., 2024).

Nevertheless, safety must be interpreted anatomically. Injections near the perioral, periocular, cervical, or hand regions may impair function if excessive diffusion or dosing occurs. Potential concerns include transient weakness, asymmetry, speech or oral competence changes, impaired facial expression, eyelid malposition, or reduced local muscle performance. These risks are usually reversible but must be considered when using BoNT-A for scar prevention in functionally sensitive areas.

9. Proposed Clinical Positioning of BoNT-A

BoNT-A should not be viewed as a universal replacement for established scar therapies. Instead, it is best understood as a scar-modulating adjunct with several potential roles.

First, BoNT-A appears most justified for early postoperative scar prevention in high-risk wounds, especially in mobile or tension-prone areas. Immediate injection after closure may reduce mechanical forces and influence early fibro-inflammatory activity before scar hypertrophy becomes established (Shi et al., 2025).

Second, BoNT-A may be useful for facial, cervical, and perioral scars, where dynamic muscle activity plays a clear role in wound tension. The evidence is particularly suggestive in cleft lip repair, where BoNT-A reduced scar width and improved VAS outcomes in meta-analysis (Ji et al., 2022).

Third, BoNT-A may be considered for symptomatic hypertrophic scars and keloids, especially when pruritus, pain, tightness, and patient-reported symptoms are prominent. This may reflect effects on neurogenic inflammation, substance P signaling, and scar contractility (Santillan et al., 2024) (Zhang, Li, et al., 2022).

Fourth, BoNT-A may have a role in multimodal keloid protocols, particularly after surgical excision, with radiotherapy, corticosteroids, hyaluronic acid, microneedle delivery, or lasers. The most appropriate combination likely depends on scar site, scar phenotype, recurrence risk, prior treatments, patient skin type, and tolerance of corticosteroid-related adverse effects.

10. Future Directions

Future studies should prioritize standardized, scar-specific trial designs. Important variables include anatomical site, Fitzpatrick skin type, scar type, baseline scar duration, prior therapy, recurrence history, wound tension, and genetic or family predisposition. Trials should distinguish postoperative prevention from treatment of established hypertrophic scars and keloids.

Dose-ranging studies are needed for different anatomical sites and BoNT-A preparations. The existing dose-dependent RCT provides a useful framework, but replication is required before universal dosing recommendations can be adopted.

Future research should include longer follow-up, preferably at least 12-24 months for keloids, because recurrence is a major determinant of treatment success. Recurrence should be defined consistently and reported separately from short-term flattening or symptom improvement.

Mechanistic studies should be linked to clinical endpoints. Biopsies, ultrasound, elastography, transcriptomics, immunohistochemistry, and scar-symptom scales could help determine whether BoNT-A-responsive scars have specific molecular signatures, such as increased neurogenic inflammation, high tension biology, dominant myofibroblast activity, or macrophage polarization patterns.

Finally, future trials should compare BoNT-A as monotherapy, BoNT-A plus corticosteroid, BoNT-A plus 5-fluorouracil, BoNT-A plus laser, and BoNT-A plus surgery/radiotherapy in clearly defined scar phenotypes.

11. Conclusions

BoNT-A is an increasingly supported scar-modulating agent with potential roles in both postoperative scar prevention and treatment of established hypertrophic scars and keloids. Its effect is likely multifactorial. Mechanical tension reduction through chemodenervation remains important, particularly for facial and perioral wounds, but current evidence also supports direct effects on fibroblasts, myofibroblasts, collagen deposition, neurogenic inflammation, macrophage polarization, and profibrotic signaling pathways.

Clinical evidence is strongest for early postoperative use in selected scars and for cleft lip repair scar prevention, where BoNT-A appears to reduce scar width and improve subjective aesthetic outcomes. Intralesional BoNT-A may also improve established hypertrophic scars and keloids, but its role as monotherapy remains less certain. In many patients, BoNT-A may be best positioned as part of multimodal treatment, especially when combined with surgery, radiotherapy, corticosteroids, hyaluronic acid, microneedle delivery, or laser-based approaches.

At present, BoNT-A should be considered a promising but incompletely standardized adjunct in scar management. Future high-quality randomized trials with standardized dosing, anatomical stratification, longer follow-up, and recurrence-focused endpoints are required to define its optimal role.

REFERENCES

1. Ali, M., Xie, B., Li, P., Chen, S., Lu, Y., Qi, F., Xiong, Z., & Li, J. (2025). Botulinum toxin A prevents hypertrophic scarring by suppressing PARP14/SOCS2-mediated M2 polarization of macrophages. *Biochimica et Biophysica Acta - Molecular Cell Research, 1872*(7). https://doi.org/10.1016/j.bbamcr.2025.120003
2. Atiyeh, B. S., & Chahine, F. (2022). Comment on the efficacy and safety of botulinum toxin injections in preventing postoperative scars and improving scar quality: A systematic review and meta-analysis—is the observed effect due to botulinum neurotoxicity? *Aesthetic Plastic Surgery, 46*(Suppl. 1), 182–183. https://doi.org/10.1007/s00266-021-02279-3
3. Bernabe, R. M., Won, P., Lin, J., Pham, C., Madrigal, P., Yenikomshian, H., & Gillenwater, T. J. (2024). Combining scar-modulating agents for the treatment of hypertrophic scars and keloids: A systematic review. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 88*, 125–140. https://doi.org/10.1016/j.bjps.2023.10.065
4. Dai, X., & Lei, T. C. (2021). Botulinum toxin A promotes the transdifferentiation of primary keloid myofibroblasts into adipocyte-like cells. *Basic & Clinical Pharmacology & Toxicology, 129*(6), 462–469. https://doi.org/10.1111/bcpt.13661
5. Elradi, M., Selim, H., & Hamed, D. E. (2025). Intralesional insulin is superior to intralesional botulinum toxin-A in the treatment of keloids. *Dermatologic Surgery, 51*(6), 593–598. https://doi.org/10.1097/dss.0000000000004566
6. Fan, Y., Guo, X., Tian, Y., Li, J., & Xi, H. (2024). Botulinum toxin type A inhibits the formation of hypertrophic scar through the JAK2/STAT3 pathway. *Biomolecules & Biomedicine, 25*(1), 249–258. https://doi.org/10.17305/bb.2024.10906
7. Gao, Y., Li, W., Li, Z., Wu, F., & Wang, J. (2025). Clinical efficacy analysis of botulinum toxin type A combined with superficial radiotherapy after chest keloid surgery. *Aesthetic Plastic Surgery, 49*(22), 6333–6338. https://doi.org/10.1007/s00266-025-04886-w
8. Gill, H. S., O-Wern, L., Tiwari, P., Gill, G. K. S., Goh, C., Hung, J., Lee, J. T., Lim, T. C., Lim, J., Yap, Y. L., & Nallathamby, V. (2024). Postoperative scar management protocol for Asian patients. *Aesthetic Plastic Surgery, 48*(3), 461–471. https://doi.org/10.1007/s00266-023-03696-2
9. Ji, Q., Tang, J., Hu, H., Chen, J., & Cen, Y. (2022). Botulinum toxin type A for preventing and treating cleft lip scarring: A systematic review and meta-analysis. *Journal of Cosmetic Dermatology, 21*(6), 2331–2337. https://doi.org/10.1111/jocd.14941
10. Jiang, B., Zhang, J., Yang, W., Wang, Y., Huang, S., Qiu, J., Bian, B., Zhang, L., & Zu, W. (2024). Comparison of dual-plane micro-drop injection of botulinum toxin type A with two traditional methods for treating hypertrophic scars in the tension zone: A long-term clinical application study. *Journal of Cosmetic Dermatology, 23*(10), 3182–3188. https://doi.org/10.1111/jocd.16401
11. Khatery, B. H. M., Hussein, H. A., Abd-el-Raheem, T. A., El Hanbuli, H. M., & Yassen, N. N. (2022). Assessment of intralesional injection of botulinum toxin type A in hypertrophic scars and keloids: Clinical and pathological study. *Dermatologic Therapy, 35*(10). https://doi.org/10.1111/dth.15748
12. Lai, I.-C., Huang, G.-L., Lee, K.-C., & Wu, P.-Y. (2026). Comparative efficacy and recurrence risk of intralesional therapies for hypertrophic scars and keloids: A network meta-analysis. *Aesthetic Surgery Journal, 46*(2). https://doi.org/10.1093/asj/sjaf182
13. Li, S. H., Shan, X. J., Wang, Z. H., & Tao, S. J. (2024). Immediately injections of botulinum toxin A after surgical excision for ear keloids: A retrospective study. *The Journal of Craniofacial Surgery, 35*(8), 2386–2389. https://doi.org/10.1097/scs.0000000000010649
14. Martinez, P. F., Rogers, A. E., Mantilla-Rivas, E., Hughes, H., Melo Leal, D., Rana, M. S., Manrique, M., Rogers, G. F., & Oh, A. K. (2024). Botulinum toxin to improve scar quality in cleft lip repair: A systematic review. *The Cleft Palate-Craniofacial Journal, 61*(11), 1828–1835. https://doi.org/10.1177/10556656231190535
15. Naik, P. P. (2022). Novel targets and therapies for keloid. *Clinical and Experimental Dermatology, 47*(3), 507–515. https://doi.org/10.1111/ced.14920
16. Santillan, M. R., Ozog, D., & Wu, W. (2024). Using neuromodulators to improve scar formation, keloids, rosacea, and antiaging. *Dermatologic Surgery, 50*(9S), S91–S96. https://doi.org/10.1097/dss.0000000000004353
17. Shi, H., Zhang, P., Zhang, J., Sun, J., & Lv, T. (2025). Dose-dependent effects of botulinum toxin type A on prevention of postoperative scars in various regions in the body: A prospective, double-blind randomized controlled trial. *Aesthetic Plastic Surgery, 49*(3), 862–874. https://doi.org/10.1007/s00266-024-04351-0
18. Yang, H. A., Jheng, W. L., Yu, J., Huang, J. Y., Cheng, K. Y., & Lee, J. J. (2024). Comparative efficacy of drug interventions for keloids: A network meta-analysis. *Annals of Plastic Surgery, 92*(1S Suppl. 1), S52–S59. https://doi.org/10.1097/sap.0000000000003759
19. Yue, S., & Ju, M. (2022). Letter to the editor: Evaluation of efficacy of corticosteroid and corticosteroid combined with botulinum toxin type A in the treatment of keloid and hypertrophic scars: A meta-analysis. *Aesthetic Plastic Surgery, 46*(4), 2095–2096. https://doi.org/10.1007/s00266-021-02539-2
20. Zhang, S., Li, K., Yu, Z., Chai, J., Zhang, Z., Zhang, Y., & Min, P. (2022). Dramatic effect of botulinum toxin type A on hypertrophic scar: A promising therapeutic drug and its mechanism through the SP-NK1R pathway in cutaneous neurogenic inflammation. *Frontiers in Medicine, 9*. https://doi.org/10.3389/fmed.2022.820817
21. Zhang, S., Peng, Y., Fan, H., Zhang, Y., & Min, P. (2022). Microneedle delivery of botulinum toxin type A combined with hyaluronic acid for the synergetic management of multiple sternal keloids with oily skin: A retrospective clinical investigation. *Journal of Cosmetic Dermatology, 21*(11), 5601–5609. https://doi.org/10.1111/jocd.15216