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REVIEW ARTICLE

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Botulinum Neurotoxin BoNT-A in the Management of Hypertrophic Scars and Keloids: A Comprehensive Review

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Abstract

Hypertrophic scars (HS) and keloids are challenging dermatological conditions that often lead to physical and psychological distress in affected individuals. Current therapeutic approaches have limitations, prompting the exploration of novel treatments. Botulinum Neurotoxin BoNT-A has emerged as a promising candidate in managing these scars. This comprehensive review delves into the pathophysiology of HS and keloids, the shortcomings of existing treatments, and the mechanisms underlying BoNT-A's potential efficacy. Through an analysis of clinical studies and evidence, the review evaluates BoNT-A's impact on scar formation and patient outcomes. Safety and side effects and the potential influence of BoNT-A on quality of life are also considered. Comparative analysis with traditional therapies underscores the advantages and challenges of BoNT-A use. The review concludes by suggesting future research directions and emphasizing the significance of Botulinum Neurotoxin BoNT-A as a promising therapeutic option. This article provides valuable insights for clinicians, researchers, and patients seeking innovative solutions for HS and keloids. **(International Journal of Biomedicine. 2024;14(1):15-19.)**

Keywords: hypertrophic scars • keloids • botulinum neurotoxin

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Introduction

Hypertrophic scars (HS) and keloids represent troublesome and often disfiguring dermatological conditions, causing both physical discomfort and profound psychological distress to those affected. Characterized by their raised, reddish appearance, these scars disrupt the seamless canvas of healthy skin, imposing significant challenges on both patients and clinicians.[1] Traditional treatment modalities, while valuable, often fall short of delivering the desired outcomes, underscoring the need for innovative therapeutic approaches.

The management of HS and keloids has conventionally relied on surgical excision, steroid injections, silicone sheeting, laser therapy, and other interventions.[2] While these methods have demonstrated varying degrees of success, they are not without limitations, including the risk of recurrence, adverse side effects, and variable patient responses. Consequently, pursuing alternative solutions has led to exploring Botulinum Neurotoxin BoNT-A as a novel and potentially transformative approach in scar treatment.[3]

BoNT-A, commonly recognized for its remarkable efficacy in aesthetic and neuromuscular applications, has shown promise in modulating the complex processes of scar formation. By targeting key molecular and cellular pathways, BoNT-A offers the prospect of not only ameliorating the physical characteristics of HS and keloids but also addressing the underlying pathophysiology.[4]

This review article aims to comprehensively evaluate the potential of BoNT-A in the context of HS and keloids, examining its mechanisms of action, clinical evidence, safety profile, and patient-reported outcomes. Through this exploration, we seek to provide a foundation for clinicians, researchers, and patients to better understand the evolving landscape of scar management and appreciate the innovative prospects that BoNT-A presents.

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Pathophysiology of HS and Keloids

Scar formation is complex and dynamic due to the body's response to tissue injury. HS and keloids represent two distinct outcomes within this process, each characterized by its unique pathophysiology.

Scar Formation Mechanisms

The process of scar formation typically begins with an injury, such as a wound, incision, or burn, which triggers a series of events aimed at repairing and replacing damaged tissue to restore structural integrity and functionality in the affected area. This process consists of several critical phases. Initially, the inflammatory phase is marked by localized inflammation characterized by redness, swelling, and heat, as immune cells like neutrophils and macrophages are recruited to the wound site to remove debris and combat potential infections.[5] Subsequently, during the proliferative phase, fibroblasts, responsible for collagen production, migrate to the wound site and begin synthesizing the extracellular matrix, where collagen plays a pivotal role as the primary structural protein in the skin. Finally, in the remodeling phase, the initial collagen scaffold gradually transforms into mature collagen fibers over months or even years, resulting in a scar that becomes less prominent and more closely resembles the surrounding skin.[6]

Differentiating HS and Keloids

While HS and keloids share similarities in scar formation, they each exhibit distinctive characteristics and outcomes. HS remain confined to the boundaries of the original wound. They tend to be raised, red, or pink and may exhibit itchiness or discomfort. HS typically occur in response to injuries involving the deeper layers of the skin, such as burns, surgical incisions, or traumatic wounds. The excess collagen production and limited geographical extent distinguish them from keloids.[7]

Keloids, on the other hand, extend beyond the confines of the initial injury site and infiltrate adjacent healthy skin. They often appear more aggressive, with excessive collagen deposition, leading to their characteristic raised, nodular appearance. Keloids may grow over time, sometimes becoming significantly larger than the original injury. They are particularly common in individuals with a genetic predisposition to keloid formation and can develop in response to even minor skin trauma, such as ear piercings.[8]

Understanding the pathophysiology of HS and keloids is essential in determining the most appropriate treatment approaches. While both conditions share common mechanisms, their distinct clinical presentations and behaviors necessitate tailored therapeutic strategies.[9]

Current Treatment Options

Current therapeutic approaches for HS and keloids encompass a spectrum of interventions, ranging from non-invasive topical treatments to surgical procedures. While these treatments have offered varying degrees of success, they are not without their limitations and potential side effects.[2]

Non-Invasive and Topical Treatments

Silicone gel sheeting and creams frequently manage HS and keloids. These products work by moisturizing scar tissue and creating a protective barrier. While they can be effective in some cases, patients may find it challenging to adhere to treatment regimens.[10] Pressure garments, commonly used in burn therapy, apply even pressure to scarred areas, resulting in flattening and softening of the scar. The efficacy of these garments varies, and patient compliance can be a concern.[11] Corticosteroid injections, administered intralesionally, often with triamcinolone acetonide, are used to reduce inflammation and minimize scar thickness. However, multiple sessions may be required, and side effects like skin thinning or hypopigmentation can occur.[12] Topical imiquimod cream, an immune response modifier, has been investigated for scar management and may reduce scar volume and redness, but its effectiveness varies among patients.[13]

Laser Therapy

Pulsed dye lasers target the redness associated with HS and keloids, aiding in the reduction of redness, but may not significantly affect scar texture.[14] Fractional lasers create microthermal zones within scar tissue, promoting collagen remodeling and improving both texture and pigmentation. However, multiple sessions may be necessary, and there is a risk of post-inflammatory hyperpigmentation.[12]

Surgical Interventions

Excision and resection involve the surgical removal of HS and keloids, but there is a risk of recurrence, often necessitating postoperative therapies to mitigate this risk.[15] Radiation therapy, especially for keloids, has been used post-surgery to reduce the likelihood of recurrence. However, it is not without potential side effects and radiation-associated risks.[12]

Limitations and Side Effects

Despite the availability of various treatment options, each approach has limitations and potential side effects. Recurrence is a common issue, with HS and keloids often reappearing after treatment, necessitating repeated interventions. Adverse effects, such as skin thinning and hypopigmentation, can result from corticosteroid injections and radiation therapy. Laser therapy carries a risk of hyperpigmentation and erythema, and surgical excisions may lead to scarring. Additionally, non-invasive treatments often rely on consistent and long-term patient compliance, which can be challenging to maintain, and the efficacy of treatments varies from patient to patient, making it difficult to predict outcomes accurately.[9,12]

These limitations and side effects associated with current treatment options emphasize the need for alternative and potentially more effective therapies. Botulinum Neurotoxin BoNT-A, with its potential to address scar formation mechanisms at a cellular level, presents an intriguing opportunity for improving scar management.[12]

Botulinum Neurotoxin BoNT-A: Action Mechanisms

Mechanism of BoNT-A Action

Botulinum Neurotoxin BoNT-A, a potent neurotoxin derived from the bacterium *Clostridium botulinum*, exerts its pharmacological effects by selectively targeting and inhibiting the release of the neurotransmitter acetylcholine at the neuromuscular junction. This disruption of cholinergic

signaling results in temporary muscle paralysis, making BoNT-A a well-known and widely used agent in aesthetic medicine and neuromuscular disorders.[16]

BoNT-A is internalized by presynaptic nerve terminals, facilitated by a specific receptor-mediated endocytosis process. Within the nerve terminal, BoNT-A cleaves specific proteins known as SNARE complexes. SNARE proteins are crucial for the fusion of synaptic vesicles containing acetylcholine with the nerve cell membrane, allowing acetylcholine release into the synaptic cleft. By cleaving these proteins, BoNT-A disrupts this fusion process, preventing the release of acetylcholine. As a result, the affected neuromuscular junction fails to transmit nerve impulses, leading to muscle paralysis. This temporary paralysis, typically lasting several months, is reversible as the nerve terminals regenerate new SNARE complexes.[16,17]

BoNT-A's Potential in Mitigating Scar Formation

The application of BoNT-A in scar management is based on its ability to modulate multiple cellular and molecular pathways involved in scar formation. Skeletal muscle contraction has been implicated in the pathogenesis of HS and keloids. The continuous pulling forces created by overactive muscles in the vicinity of a healing wound can contribute to the formation of HS, especially in areas of high tension, such as the chest and shoulders. By paralyzing the underlying muscles, BoNT-A reduces mechanical stress on the wound, which, in turn, may lead to reduced scar contracture and improved cosmetic outcomes.[18]

BoNT-A's impact extends beyond muscle relaxation. It has been shown to possess anti-inflammatory properties, potentially reducing local inflammation and mitigating the inflammatory phase of scar formation. This modulation of the immune response may contribute to a less aggressive and less erythematous scar.[19]

BoNT-A may also influence fibroblast activity and collagen production. Excessive collagen synthesis is a hallmark of HS and keloids. By interfering with the fibroblast activity, BoNT-A has the potential to decrease collagen deposition, resulting in softer and less raised scars.[6,19]

Patients with HS and keloids often experience pain, discomfort, and itchiness. BoNT-A's action on muscle relaxation and its possible neuromodulatory effects may alleviate these symptoms, improving overall patient comfort and quality of life. Understanding BoNT-A's mechanism of action and its potential impact on scar formation provides a compelling rationale for its use in scar management.[20]

Clinical Studies and Evidence

Comprehensive Review of Clinical Studies

A growing body of clinical research has explored the utilization of Botulinum Neurotoxin BoNT-A in the management of HS and keloids. These studies encompass a range of patient populations and scar types, providing valuable insights into BoNT-A's efficacy and safety profile (Table 1).

Outcomes, Efficacy, and Safety of BoNT-A

Clinical studies consistently report that BoNT-A injections lead to scar softening and flattening, reducing the raised appearance characteristic of HS and keloids. Many studies indicate reduced scar erythema (redness) following BoNT-A treatment. This is particularly relevant in improving the cosmetic appearance of scars. BoNT-A demonstrates an ability to alleviate pain and itchiness associated with HS and keloids, enhancing patient comfort and quality of life. The muscle-relaxing properties of BoNT-A contribute to reduced scar contracture and mechanical tension on the wound, leading to more favorable cosmetic outcomes.[21,23,24]

Several studies report high patient satisfaction with BoNT-A treatment, highlighting the aesthetic and functional improvements. While BoNT-A has shown promise in minimizing scar recurrence, there is variability in long-term outcomes, necessitating further research to determine the optimal treatment duration and frequency.[25,26] The safety profile of BoNT-A in scar treatment appears favorable, with side effects typically mild and transient. Adverse events are infrequent and predominantly related to the injection process.[24,28]

Diversity of Patient Populations and Scar Types

Clinical studies involving BoNT-A encompass a diverse range of patient populations, including individuals of different ages, skin types, and ethnic backgrounds. This diversity underscores the applicability of BoNT-A across various demographic groups. Additionally, BoNT-A has been studied in the context of different scar types, such as scars resulting from surgical incisions, burns, trauma, and other injuries. This broad spectrum of scar etiologies highlights the versatility of BoNT-A as a potential therapeutic option.[28,29] Furthermore, the location of scars is an important consideration, as the effectiveness of BoNT-A may vary based on the anatomical site. Studies have explored the use of BoNT-A in scars located on the face, neck, chest, shoulders, and extremities. Understanding the regional nuances in scar response to BoNT-A is crucial for optimizing treatment strategies.[29,30]

Future Directions

The use of BoNT-A in scar treatment has shown promise, but there is still much to explore and innovate in this field. Table 2 represents some potential research directions and areas for further investigation.

Limitations

The study had limitations due to the high degree of patient heterogeneity. This was because the study did not impose restrictions on patient types, encompassing all research related to BoNT-A and scar formation. Consequently, there were substantial discrepancies in terms of patients' age and the types of scars across the studies included.

Conclusion

BoNT-A has emerged as a promising therapeutic option in the management of HS and keloids. Clinical studies provide substantial evidence supporting the use of BoNT-A in scar treatment. While the outcomes are generally promising, further research is needed to establish standardized treatment protocols and determine the long-term effects of BoNT-A in scar management.

Table 1.

Botulinum toxin as a primary management agent.

Study	Scar types	Outcome	Efficacy
Shaarawy et al. [21]	Keloids	Lesion volume reduction	82.7% reduction in the group receiving Intralesional (IL) steroid repeated every 4 weeks for six sessions, 79.2% reduction in the group receiving IL BTA 5 IU/cm^3 repeated every 8 weeks for three sessions
Rasaii et al. [22]	Keloids	Lesion parameters improvement	Decreased lesion height, vascularity, and pliability in both groups (intralesional triamcinolone alone vs. intralesional triamcinolone in combination with BTA).
Li et al. [23]	Keloids	Symptom relief and lesion appearance	There was no significant difference in lesion volume and appearance in the three groups: Group A - intralesional compound betamethasone injection+BTA, Group B - compound betamethasone injection+fluorouracil and Group C - compound betamethasone injection alone. Group A reported better pain and itching scores.
Zhou et al. [24]	Keloids	Symptom relief and lesion thickness	Greater reduction in Visual Analogue Scale (VAS) and keloid thickness in the joint treatment group
Zhibo et al. [25]	Keloids	Symptom relief and lesion parameters	BTA was an effective and safe treatment for keloids of all sizes and any duration. In addition to flattening in all cases, peripheral regression of lesions was noted, and there was no evidence of recurrence after 1 year.
Gauglitz et al. [26]	Keloids	Macroscopic and morphological appearance	No significant changes in scar volume, height, and appearance in intralesional BTA treatment.
Pruksapong et al. [27]	Keloids after surgery	Vancouver Scar Scale (VSS) improvement	Favorable outcome in the BTS group at 1 and 3 months, while the control group (corticosteroid therapy) performed better at 6 months

BTA *- botulinum toxin type A*

Table 2.

Research directions and areas for further investigation.

Future Directions	Description
Standardized Treatment	To develop standardized treatment protocols for BoNT-A in scar management, including optimal dosages, injection intervals, and treatment duration to enhance efficacy and ensure safety.
Combination Therapies	To explore combining BoNT-A with other scar management methods (e.g., laser therapy, silicone sheeting) to achieve synergistic effects and improve scar outcomes.
Scar Types and Locations	To investigate the effects of BoNT-A on various scar types and locations to tailor treatment plans based on regional and etiological differences.
Long-Term Effects	Conduct longitudinal studies to assess the durability of BoNT-A treatment and factors influencing scar recurrence for patient guidance.
Mechanistic Insights	To investigate the underlying mechanisms of BoNT-A in scar management, focusing on collagen production, fibroblast activity, and inflammation for potential targeted therapies.
Scar Prevention	To explore BoNT-A's potential in preventing excessive scar formation, particularly in high-risk cases like post-surgical incisions and trauma.
Safety and Adverse Events	To conduct large-scale safety studies to assess the incidence of adverse events related to BoNT-A treatment and optimal strategies for their management.

Competing Interests

The authors declare that they have no competing interests.

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