Review Article

Use of botulinum toxin for the treatment of keloid scars: scoping review

Utilização da toxina botulínica para o tratamento de cicatriz queloide: revisão de escopo

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■ **ABSTRACT**

Introduction: Visible scars can cause problems, whether aesthetic, psychological, functional, or social, mainly of great extension and volume, such as keloids. The discovery of new treatments for keloids is not easy, given the presence of some methodological and ethical obstacles, and it is an area that is little explored. Botulinum toxin has been presented as a therapeutic alternative in national and international studies, requiring a compilation and highlighting of the main studies that can support clinical practice. Thus, the objective was to present a scoping review on the therapeutic use of botulinum toxin for the treatment of keloid scars. **Method:** The review was carried out using the PICO strategy and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. It was carried out in the PubMed/ Medline, Virtual Health Library, and SciELO databases, considering studies from 2016 to September 2021. **Results:** Overall, 34 articles related to the topic were found. After filtering and selection, the review was constructed with the support of 5 articles. The studies varied between cohorts, case reports, randomized clinical trials, and case-control. It was possible to observe as main results of the short-term action of botulinum toxin in reducing keloids, greater effectiveness in reducing symptoms, and possibilities of clinical use for different populations and clinical manifestations. **Conclusion:** The mechanism of action of botulinum toxin can facilitate the treatment of keloids and reduce symptoms, requiring more robust studies to define effective scar management protocols.

Keywords: Keloid; Therapeutic Human experimentation; Botulinum toxins, type A; Reconstructive surgical procedures; Evidence-based practice.

■ **RESUMO**

Introdução: Cicatrizes visíveis podem acarretar agravos, sejam estéticos, psicológicos, funcionais ou sociais, principalmente de grande extensão e volume, como os queloides. A descoberta de novos tratamentos de queloides não é fácil, visto a presença de alguns entraves metodológicos e éticos, sendo uma área pouco explorada. A toxina botulínica tem sido apresentada como alternativa terapêutica em estudos nacionais e internacionais, sendo necessária uma compilação e destaque dos principais estudos que possam subsidiar a prática clínica. Assim, o objetivo foi apresentar uma revisão de escopo sobre a utilização terapêutica da toxina botulínica para o tratamento de cicatrizes queloides. **Método:** A revisão foi realizada através da estratégia PICO e utilizando o *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews*. Foi realizada nas bases de dados PubMed/ Medline, Biblioteca Virtual em Saúde e SciELO, considerando estudos do período de 2016 até setembro de 2021. **Resultados:** Foram encontrados 34 artigos no geral relacionados ao tema. Após filtragem e seleção, a revisão foi construída com apoio de 5 artigos. Os estudos variaram entre coorte, relatos de caso, ensaio clínico randomizado e

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Article received: July 10, 2023.
Article accepted: February 4, 2024.

Conflicts of interest: none.

DOI: 10.5935/2177-1235.2024RBCP0841-EN

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caso-controle. Foi possível observar como principais resultados a ação a curto prazo da toxina botulínica na redução de queloides, maior efetividade na redução dos sintomas e possibilidades de utilização clínica para diferentes populações e manifestações clínicas. **Conclusão:** O mecanismo de ação da toxina botulínica pode facilitar o tratamento de queloides e redução de sintomas, sendo necessários estudos mais robustos para definição de protocolos cínicos de gestão de cicatrizes.

Descritores: Queloide; Experimentação humana terapêutica; Toxinas botulínicas tipo A; Procedimentos cirúrgicos reconstrutivos; Prática clínica baseada em evidências.

INTRODUCTION

Scars are generally a matter of concern for patients undergoing surgical procedures, especially if they are likely to appear in more visible areas of the body[1]. Surgical wounds in regions such as the face tend to have a greater aesthetic impact during the healing process, and there may also be greater tension in the surgical wound in some myofascial structures, resulting in scars[2].

Keloid is characterized as a scar of considerable thickness, raised, resulting from the abnormal growth of scar tissue, which, unlike hypertrophic scars, extends beyond the limits of the surgical wound[3]. Due to their physiology, keloids do not develop in animals, which makes the process of developing new therapies difficult, as testing on animals cannot be carried out[1]. Furthermore, the presence of scars can lead to biopsychosocial repercussions, whether physiological or social limitations due to aesthetics[4]. With these aspects in mind, several treatments are used to reduce these problems.

There is still no consensus on a single treatment that is considered the best alternative for keloid scars. The Virtual Health Library[5], with support from the *Sociedade Brasileira de Cirurgia Dermatológica* and the *Sociedade Brasileira de Dermatologia*, presents the main treatments for keloids: local radiotherapy, silicone plates, drug injections, occlusive tapes, surgery, cryotherapy, and laser therapy. These treatment options mainly aim to reduce symptoms, with their regression or reduction being less frequent alternatives that are still being studied.

Aiming for better therapy, research using botulinum toxin is gaining more and more space. Botulinum toxin type A (BTA) acts to reduce tension at the edges of surgical wounds during the healing process, thus contributing to improving the scar aspect, and reducing the possibilities of development and/or progression of keloids[6].

OBJECTIVE

With this in mind, the present study aims to present a scoping review on the therapeutic use of botulinum toxin for the treatment of keloid scars.

METHOD

The PICO model, based on Santos et al.[7], was used to formulate the guiding questions of this study, considering: (P) studies that considered patients with keloid scars, (I) studies in which the main objective was to perform or describe interventions and strategies using botulinum toxin for these patients, (C) studies with or without a control group, (O) studies that reported the development and results of interventions in the short, medium and long term. Studies carried out until September 2021 were included in this review if they met the PICO criteria.

The review was constructed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews: PRISMA-ScR[8]. The search was carried out in the PubMed/Medline, Virtual Health Library (VHL), and SciELO databases to identify articles on the treatment of keloid scars with botulinum toxin. The search was carried out by combining the terms "botulinum toxin", "keloid", "scar" and "treatment". The terms were used in combination, according to the order mentioned above. The terms are based on descriptors present in the Health Sciences Descriptors (DECs).

Articles of any design, except reviews, in any language were considered, as long as they were related to the central theme. The exclusion criteria were: unpublished reports, literature reviews, symptom assessment studies, articles published in the period before 2016, and studies with no full text. Articles that met the eligibility criteria were selected based on title and abstract by two reviewers and articles that did not meet the inclusion criteria were excluded. After title and abstract screening, studies were submitted to a public reference manager (Mendeley v.1.17.9) to eliminate duplicates. The result of this selection can be seen in Figure 1.

Subsequently, the remaining full-text articles were examined by a third reviewer. Any disagreement was resolved through discussion until consensus was reached, or with the involvement of a fourth reviewer. Then, the following points were extracted from each study, when available: authorship, year of

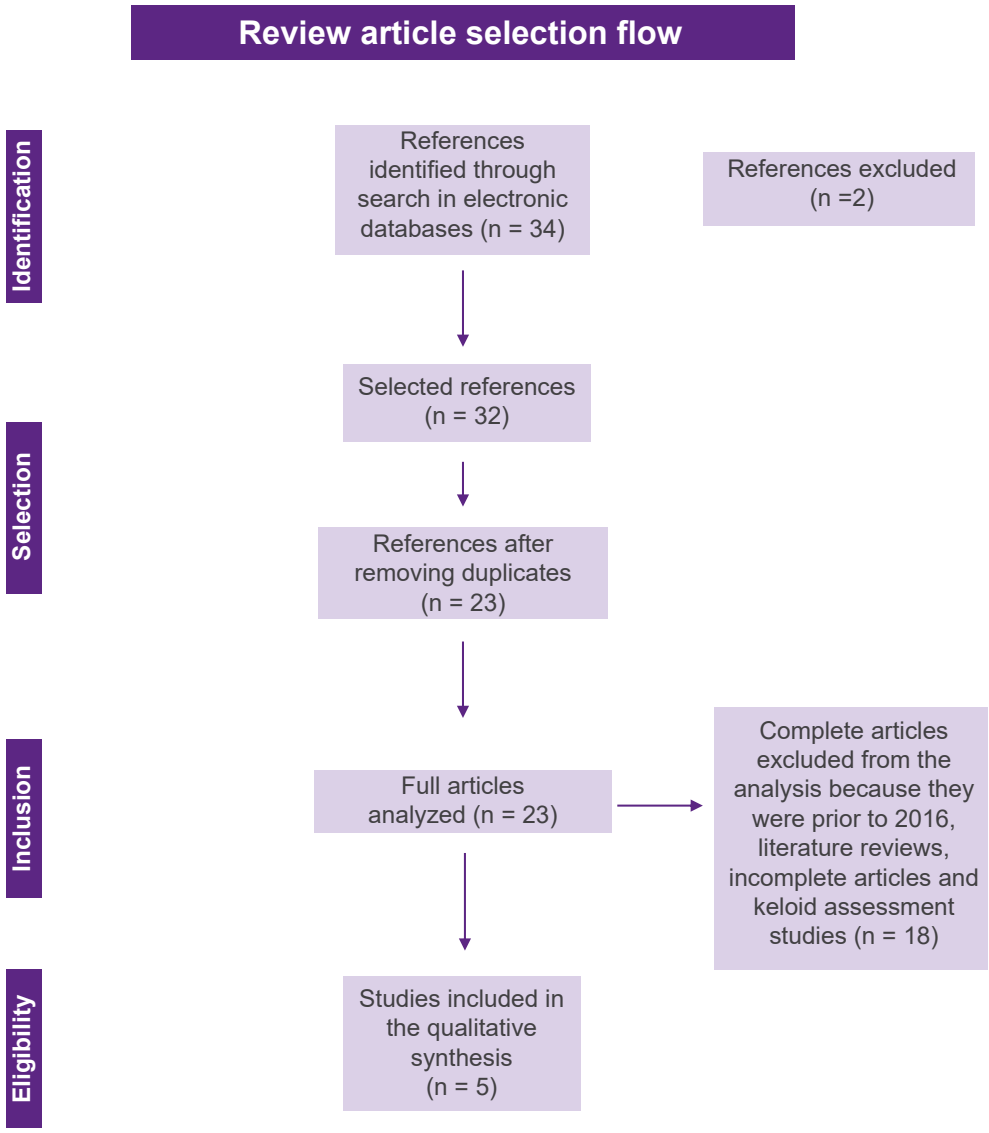

Figure 1. Flowchart for selecting review articles.
Source: Adapted from Tricco et al.[8]

publication, title, objectives, and results. These data were arranged in tables in Microsoft Word 2016, for final inclusion analysis.

RESULTS

The initial literature search found 34 studies. Of these, 12 studies were identified using PubMed/Medline, 20 using the VHL, and 2 in SciELO. After selection by title and abstract, 32 articles were run in Mendeley to eliminate duplicates. The resulting 23 full-text articles were reviewed to establish whether the publication met the inclusion criteria and 5 were considered eligible (Figure 1).

Of the 5 articles eligible for this review, 1 is a cohort study, 2 are case reports, 1 is a randomized clinical trial and 1 is a case-control study (Chart 1). The search strategy and study inclusion and exclusion criteria are detailed in Figure 1.

Regarding treatments, the studies present variations concerning their populations, methods, and clinical criteria, as shown in Chart 2.

The selected studies present different outcomes and conclusions regarding the use of BTA. In Chart 3 it is possible to observe the treatments used, results, and conclusions of the studies analyzed.

Chart 1. Presentation of studies according to year, authorship, and type of study.

Reference	Title	Study type
Cardoso et al. (2016)[2]	Application of botulinum toxin in secondary intention healing	Case report
Pruksapong et al. (2017)[9]	Efficacy of Botulinum Toxin A in Preventing Recurrence of Keloids: Double Blinded Randomized Controlled Trial Study: Intraindividual Subject	Randomized Clinical Trial
Zhou et al. (2017)[10]	Evaluation on efficacy and adverse reactions of combined therapy with botulinum toxin type A in treatment of keloid	Case-control
Rasaii et al. (2019)[11]	Intralesional triamcinolone alone or in combination with botulinium toxin A is ineffective for the treatment of formed keloid scar: A double blind controlled pilot study	Cohort
Pires et al. (2020)[12]	Botulinum toxin type A in the treatment of hypertrophic burn scars in pediatric age: Clinical Case	Case report

Source: Production of the authors.

Chart 2. Presentation of studies according to authorship and methods.

Reference	Method	Clinical criteria
Cardoso et al. (2016)[2]	N=1 Age = 36 years Botulinum toxin application type A	Scar resulting from Mohs micrographic surgery in the supralabial region; Operative scar measuring 3 x 1.6cm; Application in the immediate postoperative period
Pruksapong et al. (2017)[9]	N=25 patients, 50 keloids Average age = 26 years Control group = injection of corticosteroid therapy Study group = toxin botulinum type A	Present two scars keloids; Not being pregnant or breastfeeding; Scars larger than 10cm; not be allergic to toxin, lidocaine; Do not present undesirable medical conditions and use anticoagulant drugs or antiplatelet agents
Zhou et al. (2017)[10]	N=58 Control group = injection of betamethasone and topical hyaluronic acid Study group = toxin combined type A botulinum with injection of betamethasone and topical hyaluronic acid	Present scars keloids; No restrictions on the pharmacological components of the study
Rasaii et al. (2019)[11]	N=23 Average age = 23 years Control group = intralesional triamcinolone acetonide plus placebo Study Group = botulinum toxin type A combined with saline solution	Present two scars keloids; Do not be pregnant or breastfeeding; Absence of neuromuscular junction disease or use of neuromuscular junction blockers
Pires et al. (2020)[12]	N=1 Age = 12 years Application of botulinum toxin type A with prior topical analgesia with lidocaine + prilocaine 25 mg/g cream	Scars resulting from 2nd and 3rd burns on the face, scalp, ear pinna, neck, anterior side of the chest, and upper limbs; Application to the right axillary scar and radial border of the first finger of the right hand; Application 5 months post-burn

Source: Production of the authors.

Chart 3. Studies according to authorship, treatment, results, and conclusions.

Reference	Treatment	Results	Conclusions
Cardoso et al. (2016)[2]	8 units of BTA in the surgical wound, with healing by secondary intention.	Complete wound healing in 18 days with formation of slightly erythematous scar tissue on the upper lip, with slight extension to the supralabial region, maintained in the late postoperative period, favoring aesthetics and functionality.	The molecular properties of BTA suggest that its action is best at the beginning of healing, when the fibroblasts are still in the proliferative phase and have intense apoptotic activity, requiring further studies on this process in secondary healing.
Pruksapong et al. (2017)[9]	Control group = Injection of triamcinolone acetonide (10mg/cc) seven days after stitch removal, repeated in the first, second, and third months. Study group = intradermal BTA, with a dose of 1.5 units / 1cm length (Botox® 50 units of toxin with 0.9% NSS for injection 2.5cc, concentration 2 units per 0.1cc) seven days after stitch removal (one dose).	In the first and third months, the outcome in the toxin group was more favorable than in the control group, while the outcome in the control group was more favorable than in the toxin group in the sixth month of follow-up.	The use of BTA is significantly better at preventing keloids from recurring when compared to corticosteroid therapy after one and three months. However, corticosteroid therapy offers significantly better results at 6-month follow-up.
Zhou et al. (2017)[10]	Control group = Betamethasone and topical hyaluronic acid injection. Study group = botulinum toxin type A combined with betamethasone and topical hyaluronic acid injection. Both groups of patients were locally injected with betamethasone once every 4 weeks, 3 consecutive times, and topical hyaluronic acid was used daily. Patients in the combined treatment group were injected with botulinum toxin type A into the periphery of the skin lesion after the first injection of betamethasone.	The aesthetics of the skin lesions in the study group improved better after 3 applications. Pain and itch scores in the control group decreased during 1 month of treatment but gradually increased at 2 and 3 months; in contrast, in patients in the study gradually decreased within 3 months of treatment, this difference being statistically significant. Over the course of 3 months of treatment, the thickness of skin lesions in the study group gradually decreased, but the reduction in the control group was not significant. The pain, itching symptoms, and skin thickness of patients in the control group increased 2 weeks after each injection, while the combination treatment group did not experience recurrence. The incidence of adverse reactions in the control group was 26.7% and in the study group it was 25.0%, with no significant difference between the two groups.	BTA combined with local injection of betamethasone and topical hyaluronic acid for the treatment of keloids is more effective than local injection of betamethasone and topical hyaluronic acid alone, and there is no significant difference in the incidence of adverse reactions, being favorable for clinical application.

BTA: botulinum toxin type A.
Source: Production of the authors.

DISCUSSION

Aesthetic and functional issues related to scars, especially keloids, end up generating discomfort and dissatisfaction on the part of people who have them. Studies such as that by Motoki et al.[13] present negative results from interviewees concerning dimorphic disorders of the self-concept and the body, and also

state that people with keloids in socially more seen regions such as the face, chest, and upper limbs report a greater negative impact on their body image.

The development of treatment strategies for this condition is a challenge for the scientific community since keloids do not develop in animals, which limits the possibilities for research and testing of new therapeutic elements[1]. As possibilities, the clinical and scientific community uses strategies already tested in other conditions, in addition to studies with in vitro cells to generate new options[14]. Lee et al.[15] present combined therapy as the main alternative in the treatment of keloids, whether this therapy involves lasers, cryotherapy, or intralesional drug injection, presenting greater safety and efficacy when compared to individual monotherapies.

As an emerging therapeutic, the use of botulinum toxin type A is gaining increasing attention from the clinical and scientific communities. This greater interest can be observed when this work initially found 34 studies that related the use of BTA for the treatment of keloids. In this review, five studies were eligible, ranging from cohort studies, case reports, randomized clinical trials, and case-control studies. Due to the previously mentioned difficulties in developing new research in the area, there is still little variation in the types of studies, which can be seen as an obstacle to treating the condition.

The studies analyzed present variations in their populations and clinical criteria, but it is possible to observe that in two studies[10,11] combined therapy was used, as advocated by Lee et al.[15], these two studies presented results favorable to the replication of combined therapy for treatment of keloid. Concerning samples and methodologies, the absence of application protocols and considerable methodological deficiencies can be highlighted, mainly regarding sample size and uniformity of treatments.

It was also observed that the studies highlighted the exclusion of participants who are allergic to the components of the treatment, pregnant and lactating women, who use anticoagulant or antiplatelet drugs, as well as those with neuromuscular junction disease or the use of neuromuscular junction blockers, being the effectiveness of treatment with BTA has not been tested in these populations, therefore, without indication of scientific evidence and clinical replicability for them[9-11].

The five studies applied BTA intradermally, either at the edge of the scar/operative wound or directly at the site. Sohrabi & Goutos[16] add to these studies when they state, in their review, that other research also points to the application of BTA in keloids as a growing treatment to minimize tension on the scar edge and optimize the activity of fibroblasts, directly implicated in the pathogenesis of the formation of scars. In the present study, variation in the dosage of BTA was still observed. As it is composed of studies with different populations, ages, and clinical conditions, this review was unable to define a dosage standard for the toxin, as this dosage is linked to and dependent on the clinical manifestation, size of the scar, and the event that triggered the healing process.

Despite these variations, the five studies observed are related to the findings resulting from BTA-based therapy. It is possible to highlight as the main results the acceleration of the healing process of surgical wounds and reduction of scar formation[2], significant short-term results in the reduction of keloids[9], and improvement and maintenance of aesthetic, functional, and symptomatic aspects, especially pain and itching[10-12]. In other reviews[5,16] it was also possible to find the replicability of these results, with the use of BTA for keloid a possibility being of effective clinical treatment and with evidence already presented in clinical and scientific circles.

The use of botulinum toxin type A for the treatment of keloid scars is justified mainly by its chemoimmobilizing mechanisms of the muscles in the region, and its action on fibroblastic activity. Studies conclude that the use of botulinum toxin type A has a better effect at the beginning of the healing process, with direct action on fibroblasts[2], that this treatment presents fewer adverse reactions and better short-term results when compared to other injectable pharmacological treatments[9,10], that this alternative acts better in managing symptoms in different populations and clinical manifestations[5], even in pediatric age[16], thus encouraging the clinical community to consider BTA as a therapeutic alternative for selected and well-analyzed cases of keloids, always taking into account the clinical particularities and manifestation of the condition.

CONCLUSION

The most recent studies suggest a good potential for the use of botulinum toxin type A for the treatment of keloid scars, mainly for short-term results, and reduction of local symptoms such as pain and itching when compared to other pharmacological treatments. However, there are deficiencies in the studies as they have small populations, short follow-up periods, and lack of homogeneity in the results found. Therefore, it is necessary to develop larger studies with better methodologies, aiming to better

define the use of BTA for the treatment of keloids in different situations, and the development of unified scar management protocols for better clinical replicability.

COLLABORATIONS

ELM Analysis and/or data interpretation, Final manuscript approval, Data curation, Conceptualization, Conception and design study, Resources Administration, Project Administration, Investigation, Methodology, Writing - Original Draft Preparation.

KLSQ Analysis and/or data interpretation, Final manuscript approval, Conceptualization, Conception and design study, Project Administration, Investigation, Methodology, Writing - Review & Editing, Supervision, Visualization.

TAMA Analysis and/or data interpretation, Final manuscript approval, Data curation, Conceptualization, Conception and design study, Project Administration, Investigation, Methodology, Writing - Review & Editing, Supervision, Validation, Visualization.

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