

## Botulin Toxin Use in Scars/Keloids Treatment

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### Abstract

**Citation:** Scala J, Vojvodic A, Vojvodic P, Vlaškovic-Jovicevic T, Peric-Hajzler Z, Matovic D, Dimitrijevic S, Vojvodic J, Sijan G, Stepic N, Wollina U, Tirant M, Thuong NV, Fioranelli M, Lotti T. Botulin Toxin Use in Scars/Keloids Treatment. Open Access Maced J Med Sci. 2019 Sep 30; 7(18):2979-2981. <https://doi.org/10.3889/oamjms.2019.783>

**Keywords:** Botulin toxin; Scars; Keloids

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**Received:** 12-Jun-2019; **Revised:** 06-Jul-2019; **Accepted:** 07-Jul-2019; **Online first:** 30-Aug-2019

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**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist

Botulinum toxin (BTX) is a neurotoxin protein derived from the *Clostridium botulinum* bacterium that inhibits the release of acetylcholine at the neuromuscular junction level whose effects has been used for many years to treat a variety of muscular/neuromuscular conditions and more recently also for cosmetic use.

BTX has experimented in some dermatological conditions which include scar prevention and treatment with good results. The complex mechanism underlying those results is not completely understood but several mechanisms were proposed: release inhibition of different substances like (TGF)- $\beta$ , substance P, calcitonin gene-related peptide (CGRP) and glutamate thus modulating cutaneous inflammation and wound healing.

We analysed the published data on BTX off label applications on scars and keloids retrieved from PubMed.

### Introduction

Botulinum toxin (BTX) is a neurotoxin protein derived from the *Clostridium botulinum* bacterium that inhibits the release of acetylcholine at the neuromuscular junction level causing temporary chemical denervation. At the synaptic level, BTX cleaves a docking protein (synaptosomal-associated protein of 25 kDa or SNAP-25) on the internal surface of neuronal membranes inhibiting vesicle fusion and thus the release of acetylcholine [1]. BTX effects are temporary and as SNAP-25 regenerates, contractility

is restored in the affected muscles after a variable time of a few months.

BTX effects have been used for many years to treat a variety of muscular/neuromuscular conditions and starting from 2002 also for cosmetic use [2].

More recently, BTX has experimented in some dermatological conditions which include scar prevention and treatment with good results [3], [4], [5]. The good results of those off label uses could be explained with the widely known interaction between skin and nervous system and is supposed that BTX

may inhibit the release of other substances like (TGF)- $\beta$ , substance P, calcitonin gene-related peptide (CGRP) and glutamate thus modulating cutaneous inflammation and wound healing [5], [6], [7].

## Material and Methods

We analysed the published data on BTX off label applications on scars and keloids retrieved from PubMed. We found 163 articles, from 2011 to April 2019 using the terms “botulin scar” and correlated MeSH terms. Of these articles, only 44 were included in this review. Exclusion criteria were: case reports, duplicated studies, papers focusing on topics not related to dermatology or plastic surgery and articles written in languages other than English.

## Results

BTX has been used to treat hypertrophic scars (HS) and keloids in a number of studies [8], [9], [10], [11], [12], [13], [14] and also was successfully used in scar prevention [14], [15], [16], [17], [18], [19], [20], [21]. Only a small number of available studies were made as randomized controlled trials with the efficacy of BTX compared to placebo (saline solution) or steroids, and those studies differ for the amount of BTX used ranging from 1.5 to 5 IU every cm<sup>2</sup> and for the frequency of treatment ranging from a single treatment to multiple treatments done every month or even with longer intervals, but all gave positive results.

Moreover, some animal studies demonstrated the usefulness of BTX in scar and keloid reduction [20], [21], [22]. Despite all differences in published studies a recent meta-analysis of randomised controlled trials evaluating BTX effect in the face/neck area has found that patients who received BTX had better outcomes than those who did not receive it [24]. According to this study the scars were significantly narrower ( $P = 0.006$ ) and visual analogue scale scores were significantly better, indicating that patients treated with BTX were more satisfied with the results than those who received saline. However, the number of studies eligible for the analysis was only 9, and only 3 of these were completely unbiased.

## Discussion

The molecular mechanism of BTX usefulness on hypertrophic scars and keloids is not yet perfectly explained but in vivo studies in animals and humans have demonstrated that, in addition to the known effects on acetylcholine release, BTX inhibits fibroblast proliferation (and hence collagen production). Also, it is reported to downregulate the expression of  $\alpha$ -smooth muscle actin and myosin II proteins, which are found in fibroblasts in a dose-dependent fashion [23]. It is important to note that these phenomena were not observed in fibroblasts isolated from normal skin [27]. Other studies indicated that, along with inhibition of fibroblast proliferation, production of transforming growth factor (TGF)- $\beta$ 1 and connective tissue growth factor were also diminished [25], [26], [27]. Unexpectedly collagen production and collagen organisation were found significantly improved with intralesional BTX than with saline in a rat model of burn healing and was associated with faster vascularisation and reepithelialisation of the wound [26].

To explain this phenomenon, it has been hypothesised that BTX may increase expression of Vascular endothelial growth factor (VEGF), and thus promote angiogenesis that hastens wound healing [29] and ultimately gave a better scar appearance, although the exact mechanism for this is not known. Results from studies investigating the effect of BTX on the expression of VEGF in scar healing are still inconsistent: some appear to demonstrate benefit, but others show no effect [28].

One particularly favourable aspect of BTX treatment is its ability to control the subjective symptoms of hypertrophic scars. We already know that BTX can immobilize the local muscles of a scar and reduce skin tension caused by the muscle pull which exacerbates inflammation and leads to overproduction of collagen and glycosaminoglycans, thus improving the cosmetic result of the scar, but also relieves trapped nerve fibers in keloids, neutralizing the itch and pain associated with small-fiber neuropathy [30], [31]. The last known effect reported of BTX treatment is related to the inhibition of inflammatory mediators release such as substance P and calcitonin gene-related peptide (CGRP) [32], [33]. The reduction and control of local skin inflammation mediated by those cytokines may allow better overall healing resulting in a less evident scar.

In conclusion, the innovative applications for BTX use in scar prevention or reduction, even if his complex mechanism is not completely understood, show very promising results. To better understand its therapeutic potential in dermatology, future studies should investigate the link between BTX and the cutaneous neuroimmune system and skin-nervous system interaction. Also, a consensus on the dose and regimen would be desirable to standardise the treatment.

## References

- Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. *Nature*. 1993; 365(6442):160-163. <https://doi.org/10.1038/365160a0> PMID:8103915
- França K, Kumar A, Fioranelli M, Lotti T, Tirant M, Rocchia MG. The history of Botulinum toxin: from poison to beauty. *Wien Med Wochenschr*. 2017; 167(1):46-48. <https://doi.org/10.1007/s10354-017-0553-7> PMID:28299552
- França K, Castillo D, Lotti T. Non-cosmetic dermatological use of botulinum neurotoxin. *Dermatol Ther*. 2017; 30(4). <https://doi.org/10.1111/dth.12495> PMID:28425626
- Guida S, Farnetani F, Nisticò SP, Giorgio Mariarosaria C, Babino G, Giovanni Pellacani G, Fulgione E. New trends in botulinum toxin use in dermatology. *Dermatol Pract Concept*. 2018; 8(4):277-282. <https://doi.org/10.5826/dpc.0804a05> PMID:30479855 PMID:PMC6246063
- Schlessinger J, Gilbert E, Cohen JK, Kaufman J. New Uses of AbobotulinumtoxinA in Aesthetics. *Aesthet Surg J*. 2017; 37(1): S45-S58. <https://doi.org/10.1093/asi/sjx005> PMID:28388720 PMID:C5434494
- Steinhoff M, Stander S, Seeliger S, Ansel JC, Schmeiz M, Luger T. Modern aspects of cutaneous neurogenic inflammation. *Arch. Dermatol*. 2003; 139:1479-1488. <https://doi.org/10.1001/archderm.139.11.1479>
- Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. *J. Investig. Dermatol*. 1996; 106:198-204. <https://doi.org/10.1111/1523-1747.ep12330326> PMID:8592075
- Elhefnawy AM. Assessment of intralesional injection of botulinum toxin type A injection for hypertrophic scars. *Indian J. Dermatol. Venereol. Leprol*. 2016; 82:279-283. <https://doi.org/10.4103/0378-6323.173586> PMID:27088929
- Shaarawy E, Hegazy RA, Abdel Hay RM. Intralesional botulinum toxin type A equally effective and better tolerated than intralesional steroid in the treatment of keloids: A randomized controlled trial. *J. Cosmet. Dermatol*. 2015; 14:161-166. <https://doi.org/10.1111/jocd.12134> PMID:25810045
- Xiao Z, Zhang F, Cui Z. Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: A preliminary report. *Aesthet. Plast. Surg*. 2009; 33:409-412. <https://doi.org/10.1007/s00266-009-9334-z> PMID:19357910
- Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. *Plast. Reconstr. Surg*. 2009; 124:275e-277e. <https://doi.org/10.1097/PRS.0b013e3181b98ee7> PMID:20009818
- Jablonska EM, Sherris DA, Gassner HG. Botulinum toxin to minimize facial scarring. *Facial Plast Surg*. 2012; 28(5):525-535. <https://doi.org/10.1055/s-0032-1325641> PMID:23027220
- Gauglitz GG. Management of keloids and hypertrophic scars: current and emerging options. *Clin Cosmet Investig Dermatol*. 2013; 6:103-114. <https://doi.org/10.2147/CCID.S35252> PMID:23637546 PMID:PMC3639020
- Gauglitz GG, Bureik D, Dombrowski Y, Pavicic T, Ruzicka T, Schaubert J. Botulinum toxin A for the treatment of keloids. *Skin Pharmacol Physiol*. 2012; 25(6):313-318. <https://doi.org/10.1159/000342125> PMID:22948093
- Kim YS, Lee HJ, Cho SH, Lee JD, Kim HS. Early postoperative treatment of thyroidectomy scars using botulinum toxin: A split-scar, double-blind, randomized controlled trial. *Wound Repair Regen*. 2014; 22:605-612. <https://doi.org/10.1111/wrr.12204> PMID:24898579
- Ziade M, Domergue S, Batifol D, Jreige R, Sebbane M, Goudot P, Yachouh J. Use of botulinum toxin type A to improve treatment of facial wounds: A prospective randomized study. *J. Plast. Reconstr. Aesthet. Surg*. 2013; 66:209-214. <https://doi.org/10.1016/j.bjps.2012.09.012> PMID:23102873
- Gassner HG, Brissett AE, Otleigh CC, Boahene DK, Boggust AJ, Weaver AL, Sherris DA. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. *Mayo Clin Proc*. 2006; 81:1023-1028. <https://doi.org/10.4065/81.8.1023> PMID:16901024
- Galárraga IM. Use of botulinum toxin in cheiloplasty: A new method to decrease tension. *Can J Plast Surg*. 2009; 17(3):e1-e2. <https://doi.org/10.1177/229255030901700313> PMID:20808741 PMID:PMC2740606
- Chang CS, Wallace CG, Hsiao YC, Chang CJ, Chen PK. Botulinum toxin to improve results in cleft lip repair. *Plast Reconstr Surg*. 2014; 134(3):511-516. <https://doi.org/10.1097/PRS.0000000000000416> PMID:25158709
- Wilson AM. Use of botulinum toxin type A to prevent widening of facial scars. *Plast. Reconstr. Surg*. 2006; 117:1758-1766. <https://doi.org/10.1097/01.prs.0000209944.45949.d1> PMID:16651948
- Chen M, Yan T, Ma K, et al. Botulinum toxin type A inhibits  $\alpha$  smooth muscle actin and myosin II expression in fibroblasts derived from scar contracture. *Ann Plast Surg*. 2016; 77(3):e46-e49. <https://doi.org/10.1097/SAP.0000000000000268> PMID:25144422
- Xiao Z, Qu G. Effects of botulinum toxin type a on collagen deposition in hypertrophic scars. *Molecules*. 2012; 17(2):2169-2177. <https://doi.org/10.3390/molecules17022169> PMID:22354193 PMID:PMC6268678
- Jeong HS, Lee BH, Sung HM, et al. Effect of botulinum toxin type A on differentiation of fibroblasts derived from scar tissue. *Plast Reconstr Surg*. 2015; 136(2):171e-178e. <https://doi.org/10.1097/PRS.0000000000001438> PMID:26218391
- Zhang DZ, Liu XY, Xiao WL, Xu YX. Botulinum toxin type A and the prevention of hypertrophic scars on the maxillofacial area and neck: a meta-analysis of randomized controlled trials. *PLoS One*. 2016; 11(3):e0151627. <https://doi.org/10.1371/journal.pone.0151627> PMID:26985661 PMID:PMC4795777
- Xiao Z, Zhang M, Liu Y, Ren L. Botulinum toxin type a inhibits connective tissue growth factor expression in fibroblasts derived from hypertrophic scar. *Aesthetic Plast Surg*. 2011; 35(5):802-807. <https://doi.org/10.1007/s00266-011-9690-3> PMID:21455826
- Xiao Z, Zhang F, Lin W, Zhang M, Liu Y. Effect of botulinum toxin type A on transforming growth factor beta1 in fibroblasts derived from hypertrophic scar: a preliminary report. *Aesthetic Plast Surg*. 2010; 34(4):424-427. <https://doi.org/10.1007/s00266-009-9423-z> PMID:19802513
- Huang C, Akaishi S, Hyakusoku H, Ogawa R. Are keloid and hypertrophic scar different forms of the same disorder? A fibroproliferative skin disorder hypothesis based on keloid findings. *Int Wound J*. 2014; 11(5):517-522. <https://doi.org/10.1111/i.1742-481X.2012.01118.x> PMID:23173565
- Haubner F, Leyh M, Ohmann E, Sadick H, Gassner HG. Effects of botulinum toxin A on patient-specific keloid fibroblasts in vitro. *Laryngoscope*. 2014; 124(6):1344-1351. <https://doi.org/10.1002/lary.24456> PMID:24122729
- Wilgus TA, Ferreira AM, Oberyszyn TM, Bergdall VK, Dipietro LA. Regulation of scar formation by vascular endothelial growth factor. *Lab Invest*. 2008; 88(6):579-590. <https://doi.org/10.1038/labinvest.2008.36> PMID:18427552 PMID:PMC2810253
- Viera, M.H.; Amini, S.; Valins, W.; Berman, B. Innovative therapies in the treatment of keloids and hypertrophic scars. *J. Clin. Aesthet. Dermatol*. 2010; 3:20-26.
- Uyesugi B, Lippincott B, Dave S. Treatment of painful keloid with botulinum toxin type A. *Am. J. Phys. Med. Rehabil*. 2010; 89:153-155. <https://doi.org/10.1097/PHM.0b013e3181c1ec11> PMID:19884811
- Kellogg Jr DL, Pérgola PE, Piest KL, Kosiba WA, Crandall CG, Grossmann M, Johnson JM. Cutaneous active vasodilation in humans is mediated by cholinergic nerve cotransmission. *Circ. Res*. 1995; 77:1222-1228. <https://doi.org/10.1161/01.RES.77.6.1222> PMID:7586235
- Carmichael MM, Dostrovsky JO, Charlton MP. Peptide-mediated transdermal delivery of botulinum neurotoxin type A reduces neurogenic inflammation in the skin. *Pain*. 2010; 149:316-324. <https://doi.org/10.1016/j.pain.2010.02.024> PMID:20223589