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Botulin Toxin Use in Scars/Keloids Treatment

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Abstract

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)-β, 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)-β, 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^2 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 α-smooth muscle actin and myosin II proteins, which are found in fibroblasts in a dose-dependent fashion [23]. 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)-β1 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 know 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.

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