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Botulin Toxin Use in Rosacea and Facial Flushing Treatment

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Abstract

Botulinum toxin (BTX) is a neurotoxin 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 Rosacea and facial flushing treatment with good results. The complex mechanism underlying those results is not completely understood but was proposed a release inhibition of acetylcholine from peripheral autonomic nerves of the cutaneous vasodilatory system combined with the blockade substance P and calcitonin gene-related peptide (CGRP) thus modulating blood vessel dilatation.

We analysed the published data on BTX off label applications rosacea and flushing retrieved from PubMed.

Introduction

Botulinum toxin (BTX) is a neurotoxin derived from the *Clostridium botulinum* bacterium that exerts its effect at the neuromuscular junction cleaving a docking protein (synaptosomal-associated protein of 25 kDa [SNAP-25]) on the internal surface of neuronal membranes, thereby inhibiting vesicle fusion and release of acetylcholine thus causing a temporary chemical denervation [1] . BTX effects in the targeted muscles diminish over time as SNAP-25 regenerates, and contractility is restored in a variable time of a few months.

Those effects, used for many years to treat a variety of muscular/neuromuscular conditions in 2002 was also approved for cosmetic use to treat complex glabellar muscles that form frown lines first and to treat lateral orbicularis oculi muscles that form crow's feet later [2].

More recently, BTX has experimented in some dermatological conditions which include Rosacea and facial flushing treatment with good results [3], [4], [5], [6]. 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 substance P, calcitonin gene-related peptide (CGRP) and glutamate modulating cutaneous inflammation and wound healing.

Material and Methods

We analysed the published data on BTX off label applications on rosacea and facial flushing retrieved from PubMed. We found 39 articles, from 2005 to April 2017 using the terms “botulin rosacea” and “botulin flushing” plus all correlated MeSH terms. Of these articles, only 30 were included in this review. Exclusion criteria were: duplicated studies, papers focusing on topics not related to dermatology or plastic surgery (like many papers on flushing related to Frey syndrome) and articles written in languages other than English.

Results

BTX has been used to treat rosacea or facial flushing in a small number of studies [7], [8], [9], [10], [11], [12], [13], [14] and only one was made as randomized controlled trials with the efficacy of BTX compared to placebo (saline solution). All works, randomised and not, while all using intradermal injections, differ for the amount of BTX used ranging from 1 to 6 IU every cm2 of affected skin and for the frequency of treatment ranging from a single treatment to three treatments done with different intervals, but all gave positive results.

Single-arm pilot studies involving patients with facial flushing were done and showed an improvement within a variable time ranging from 2 weeks to 3 months after a single treatment of a variable dose of BTX (from 1 to 2 IU/cm2) [9], [10], [12], [13], [14], while the only randomized controlled trial followed for 6 months 60 patients with menopausal hot flushes treated with a single injection of 6,2 IU of BTX per cm2 versus 0,9% saline solution and showed a significant reduction in the mean number of menopausal hot flashes after 2 months. The effect of BTX was also investigated in 15 patients with rosacea. Treated with a single dose of 15–45 IU of BTX to face which resulted in a statistically significant of erythema grade, as compared to baseline, at 1, 2, and 3 months after treatment ($P < 0.05$, $P < 0.001$, and $P < 0.05$, respectively) [9].

Discussion

Facial flushing consists of an episode of redness often associated with a burning sensation. It can be primary or idiopathic and secondary to rosacea or hormonal stimuli like menopause; **r**osacea is a common inflammatory dermatosis also characterised by persistent erythema, telangiectasia, papules and pustules [15].A possible mechanism by which BTX improves flushing and rosacea is the blockade of acetylcholine release from peripheral autonomic nerves of the cutaneous vasodilatory system [16], [17]. Is also known that BTX inhibits the release of inflammatory mediators such as substance P and calcitonin gene-related peptide (CGRP) [18] that have a relevant effect in vasodilation. The reduction of all those mediators can lead to a reduction of local skin inflammation and allow erythema to fade out relieving at the same time from pain. Reported adverse effect to BTX treatment is rare and limited to a mild headache.

In conclusion, the innovative applications for BTX use in rosacea and facial flushing treatment, even if his complex mechanism is not completely understood, suggest that intradermal BTX injections are safe and efficacious for reducing erythema and flushing in rosacea. Larger, controlled, randomised studies are warranted to determine optimal dosing and duration of the activity. Moreover, 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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