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Review

Dilution of botulinum toxin type A in local anesthetics: a therapeutic opportunity in migraine treatment

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Abstract

Botulinum Toxin (BoNT) type A, derived from *Clostridium botulinum*, is widely employed in neurology for its muscle-paralyzing effects. Concurrently, local anesthetics like lidocaine offer regional pain relief. Combining BoNT-A with local anesthetics could enhance therapeutic efficacy, particularly in headache disorders. We conducted a systematic review following PRISMA guidelines, searching various databases for relevant studies. Among the 1,623 articles initially identified, 13 met inclusion criteria. Notably, no trials specifically addressed BoNT-A dilution in local anesthetics for headaches. However, studies in other contexts revealed promising findings. For instance, blending BoNT-A with lidocaine and epinephrine demonstrated superior pharmacological properties compared to saline reconstitution. Nonetheless, caution is warranted, as fatal outcomes have been reported with BoNT-A and lidocaine administration. While the literature on BoNT-A diluted in local anesthetics for migraines is scarce, existing evidence suggests potential benefits akin to other disorders. Reconstituting BoNT-A in lidocaine offers a promising avenue for optimizing headache treatment, warranting further investigation in future research endeavors.

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Introduction

Botulinum toxin refers to a group of neurotoxins with the primary mechanism of action being the inhibition of acetylcholine release into the synaptic cleft, leading to a flaccid muscle paralysis (1, 2). Derived from the gram-positive bacterium *Clostridium botulinum* through fermentation, these toxins are categorized into seven neurotoxic serotypes (A to G), with type A being extensively studied for therapeutic applications (3, 4).

While Emile van Ermengen initially described the toxin's mechanism in 1895, it was not until 1980 that Alan Scott documented its use for strabismus treatment, specifically in the extrinsic ocular muscles (5).

Presently, botulinum toxin is widely utilized for treating various conditions, including dystonia, hemifacial spasm, blepharospasm, spasticity, migraine, trigeminal neuralgia, and other chronic pains (1, 6).

Commercially, onabotulinum toxin is associated with human albumin and requires dilution for application in specific anatomical areas. Sodium chloride (NaCl) 0.9% serves as the most commonly used solvent for this purpose (6).

Local anesthetics constitute drugs known for their regional and reversible inhibition of neuronal transmission. Categorized into amides and esters, amides like Lidocaine and bupivacaine dominate clinical practice due to their thermostability, facilitating practical storage (7).

Botulinum toxin type A (BoNT-A) and peripheral nerve blocks stand as established therapeutic interventions for headache disorders. The strategic amalgamation of BoNT-A with local anesthetics through dilution offers the opportunity to synergize both approaches, potentially enhancing headache treatment efficacy through a heightened analgesic effect. This study endeavors to scrutinize the dilution of BoNT-A in local anesthetics across various conditions and assess the feasibility of applying the same methodology to optimize headache treatment.

Methods

According to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, we searched online databases, including Web of Science, PubMed, EMBASE, Scopus, Cochrane Library, ProQuest, ClinicalTrials.gov, and Google Scholar until 2023 with the terms "Botulinum toxin type A" and "Local anesthetics" (Figure 1). Afterwards, the references of the selected papers were explored.

Figure 1. Flow Chart of selected papers

Results

Our initial search yielded 1,623 articles, from which we conducted a thorough exclusion process, ultimately scrutinizing 21 publications. Subsequent removal of duplicates and meticulous examination of references led to the inclusion of 16 papers for this comprehensive review. Remarkably, no clinical trials specifically addressing the dilution of BoNT-A in local anesthetics for headache disorders were identified.

Among the selected studies, two randomized clinical trials investigated the impact of BoNT-A diluted in lidocaine in alternative clinical contexts-one incorporating epinephrine and the other without it. Notably, Gassner and Sherris (2) conducted a double-blind, randomized clinical trial assessing the paralytic effects of BoNT-A diluted in 1% lidocaine with epinephrine 1:100,000. In comparison to BoNT-A reconstituted in saline solution, they concluded that the reconstitution of BoNT-A in lidocaine with epinephrine exhibited superior pharmacological properties, inducing an immediate paralytic effect.

Discussion

Since the inception of the therapeutic application of botulinum toxin, particularly Onabotulinum toxin type A, a concerted effort by researchers has been directed towards alleviating local pain following its administration—an issue frequently reported by patients (7, 9).

The precise chemical mechanisms facilitating the dilution of BoNT-A in lidocaine remain incompletely elucidated within the current medical literature (2). Nevertheless, emerging evidence suggests potential advantages in reconstituting botulinum toxin in lidocaine with epinephrine (2). This is attributed to the immediate muscle relaxation induced by the local anesthetic and the vasoconstrictor's promotion of enhanced substance absorption through local vasoconstriction (10, 11).

It is imperative to acknowledge that these substances although not common are not devoid of adverse effects. Lidocaine, being the most extensively utilized anesthetic, is associated with a higher incidence of anaphylactic reactions, manifesting as pruritic erythematous rash, vesicles, and papules (12). Enhanced caution is warranted during medication administration, especially when dealing with special populations such as pregnant women, newborns, and the elderly (12, 13).

In 2005, a notable case emerged involving a fatal adverse reaction subsequent to the concurrent administration of BoNT-A and lidocaine for the management of cervical spasms and rigidity. The application proceeded smoothly, save for reports of a taste sensation in the mouth during the trapezius injection. However, following the completion of the 100 IU applications, the patient succumbed to shock. Notably, the patient had previously undergone therapy with the same BoNT-A and lidocaine blend a year prior, as well as took methadone (10 mg three times a day), robaxin (750 mg twice a day) and oxycodone (5 mg two times a day) rendering it challenging to pinpoint whether which drug, precipitated the unfortunate outcome (14). Although descriptions of a metallic taste sensation linked with botulinum toxin administration exist, they typically resolve spontaneously and entail no significant sequelae (15).

Regarding migraine, the inaugural clinical study with botulinum toxin in 2000 employed dilution in 0.9% sodium chloride, yielding favorable results (10). Despite subsequent studies on migraine and botulinum toxin, our thorough database search failed to uncover any literature reporting toxin reconstitution in lidocaine, with or without epinephrine, or any other type of local anesthetic.

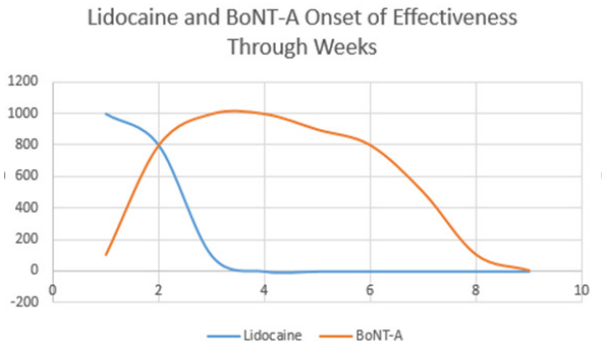

Figure 2. Hypothetical Onset of effectiveness comparison between Lidocaine and BoNT-A through weeks.

5. Conclusion

The reconstitution of BoNT-A in local anesthetics, particularly Lidocaine, not only appears to preserve its therapeutic properties but also exhibits the potential to mitigate local pain during application. This method facilitates an almost immediate paralyzing effect of the toxin, presenting a notable advantage in its therapeutic application. While literature specific to the use of BoNT-A diluted in local anesthetics for migraine treatment remains scarce, the positive effects observed in other disorders suggest a parallel potential for migraine therapy. This avenue should be actively explored as a promising therapeutic opportunity in future research endeavors.

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