Botulinum toxin for the treatment of headaches: A review of current practices and evidence based-data

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ÖZET

Baş ağrısı tedavisinde botulismus toksini; günümüzdeki uygulamalar ve kanıta dayalı verilerin derlemesi

Botulismus toksini Tip A 15 yıldan daha uzun süredir çeşitli primer baş ağrısı tiplerinin tedavisi ve profilaksisi amacı ile kullanılmaktadır. Bu ajanın baş ağrısı tedavisindeki etki mekanizması pek çok çalışmada incelenmiştir. Asetil kolin salınımı üzerindeki bilinen etkisine ek olarak bir veya daha fazla sayıda ağrı ile ilgili transmitterin salınımını bloke ederek antinosiseptif etki gösterdiği düşünülmektedir. Botulinum toksininin primer baş ağrılarındaki klinik kullanımını inceleyen körlü olmayan ilk çalışmalar, pozitif sonuçlar vermiştir, ancak son zamanlarda yapılan metodoloji açısından yeterli çalışmalar kanıta dayalı bir yaklaşımla incelendiğinde bu ajanın yaygın klinik kullanıma girmesini desteklememektedir. Bu derlemede botulinum toksininin kullanımı; etki mekanizması, enjeksiyon teknikleri ve konu hakkındaki kanıta dayalı veriler öncelikli olarak incelenmiştir.

Anahtar kelimeler: Baş ağrısı, botulinum toksini

SUMMARY

Botulinum toxin type A has been used clinically for the prophylaxis and treatment of various types of primary headache disorders for over 15 years. Several studies have been performed to demonstrate its mechanism of its effect. There is adequate data to support the idea that; beside its well-known effect on acetylcholine release, an additional antinociceptive effect related to a possible block in one or more pain transmitters exists. Earlier open-labeled studies investigating the clinical outcome of botulinum toxin in primary headache disorders have come out with positive results on the topic however recent evidence based evaluation of data do not seem to support the widespread clinical use of this agent. In this manuscript use of botulinum toxin is reviewed with special emphasize on its mechanism of effect, injection techniques and recent evidence-based data.

Key words: Headache, botulinum toxin

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Introduction

The efficacy of Botulinum neurotoxin A (BotNT-A) in headache patients was first noted in 1992 by William Binder an otolaryngologist who identified that patients with migraine headaches recovered from their attacks following Botulinum toxin injections for the treatment of facial wrinkles (Ewans, 2003). Clinical reports about both prophylactic and therapeutic use of BotNT-A have appeared since and there is a body of knowledge developing on the topic. In this review article current practices of BotNT-A use is discussed with special emphasize on evidence based data.

Why Do We Need Another Drug For Treatment Or Prophylaxis In Primary Headache Disorders?

Headache can be debilitating, causing lost productivity at work or school, impaired quality of life, and disruptions in family and social life. Moderate-to-severe adverse events are common with the available preventive medications. Tricyclic antidepressant use is associated with sedation, weight gain, dry mouth, nausea, constipation, dizziness, mental confusion, palpitations, blurred vision and urinary retention (Blumenfeld A 2004, Silberstein 2002). b-blockers are associated with drowsiness, fatigue, lethargy, sleep disorders and depression whereas calcium channel blockers can cause constipation, peripheral edema and weight gain (Blumenfeld A 2004,Silberstein 2002). Therefore any preventive measure that is more effective and associated with fewer side effects is apparently needed in primary headache disorders.

Botulinum Toxin And Its Actual Mechanism Of Effect In Different Types Of Headaches

Human exposure to botulinum toxin typically occurs in two settings: 1) as an etiologic agent in the disease botulism and 2) as a therapeutic agent for the treatment of cervical dystonia, severe primary axillary hyperhydrosis, strabismus and blepharospasm associated with dystonia (Murray 2005, Coffield 1997).

Botulinum neurotoxin exists in seven different serotypes, designated A, B, C, D, E, F and G. All seven serotypes are large proteins that act on cholinergic neuromuscular junctions to block transmitter release. The ability of botulinum toxins to cause muscle paralysis by blocking acetylcholine release at the neuromuscular junction is well known. Research on laboratory animal preparations has shown that the toxins produce this effect by proceeding through a sequence of four steps: 1) binding to receptors on the plasma membrane, 2) penetration of plasma membrane by receptor mediated endocytosis, 3) penetration of the endosome membrane by pH induced translocation and 4) intracellular expression of an enzymatic action that culminates in blockade of exocytosis (Coffield 1997, Simpson 1980). Serotype A has long been implicated in human illness and it was the first serotype to be evaluated as a medical agent.

Botulinum toxin has lately been investigated through a series of open-labeled studies as well as a few controlled randomized studies in its effect as a therapeutic and prophylactic drug for primary headache disorders especially migraine and chronic tension type headaches. Botulinum toxin type A and type B have been used for research purposes clinically for headaches. Botulinum toxin type A (BotoxR by Allergan, Inc., Irvine CA, USA or DysportR by Ipsen Ltd., Slough Berkshire, UK) or botulinum toxin type B (MyoblocR by Solstice Neurosciences Inc., South San Francisco, CA, USA). These three products have different dosing, safety and efficacy characteristics. There is no established methodology to calculate equivalent doses (Blumenfeld AM 2003). Number of studies using botulinum toxin B for the prophylaxis and treatment of headaches is rare compared to botulinum toxin A (Winner 2003, Lake 2003, Evers 2002).

The most commonly used formulation of Botulinum neurotoxin type A is BotoxR and as a drug it is a purified neurotoxin complex, in a sterile, vacuum-dried and purified form, produced from fermentation of Hall strain Clostridium botulinum type A grown in a medium containing casein hydrolisate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin and several accessory proteins. Each vial of BotoxR contains 100 Units (U) of Clostridium botulinum type A neurotoxin complex, 0.5 milligrams of Albumin (Human) and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative (Murray 2005).

Table 1: Candidates for Botulinum Toxin Type A Therapy for Headache (Blumenfeld AM 2003).

- Patients with disabling primary headaches
- Patients who have failed to respond adequately to conventional treatments
- Patients with unacceptable side effects (from existing treatments)
- Patients in whom standard preventive treatments are contraindicated
- Patients in special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments, airplane pilots, students studying and preparing for examinations)
- Patients misusing or abusing or overusing medications
- Patients with coexistent jaw, head or neck muscle spasm
- Patients who prefer this treatment

The proposed mechanism of effect of BotNT-A in chronic tension type headache is the reduction of pericranial muscle tension (Wheeler 1998, Zwart 1994). However some investigators do not support the idea of an increased muscle tension as a main generator in tension type headache and claim that due to the lack of evidence to support a 'peripheral' mechanism for chronic tension type headache a 'central' origin, eg, a disturbance of limbic pathways to the brain stem may be responsible (Rollnik 2001 ,Schoenen 1991). Results of the studies using BotNT-A for chronic tension-type headache will be further reviewed in this manuscript.

In migraine type of headache it has been proposed that factors other than a decreased pericranial muscle tension play an important role in the mechanism of the effect of BotNT-A, since the pain relief following BotNT-A injections in migraine headache may well outlast the duration of effect of the drug itself (Blumenfeld AJ 2004, Blumenfeld A 2003). Current pathophysiological models of migraine focus on the trigeminovascular system as an important generator of the sensory input leading to migraine. According to this model, trigeminal afferents innervating meningeal vessels are activated during migraine possibly by a wave of neuronal depression that spreads across the cerebral cortex (Bolay 2002). Consequently afferents in ophthalmic branch (V1) of the trigeminal nerve are stimulated to release various neuropeptides, including calcitonin gene-related peptide (CGRP). BotNT-A has been shown to directly inhibit the CGRP secretion from stimulated trigeminal neurons in an experimental model (Durham 2004). Previous studies have shown that BotNT-A inhibits the release of substance P (mediated by cleavage of the intracellular effector SNAP-25) and glutamate, another neurotransmitter involved in nociceptive processing (Blumenfeld AJ 2004, Cui 2002 Purkiss 2000, Ishikawa 1999). As a result beyond chemodenervation of skeletal muscle BotNT-A inhibits neurotransmission of pain signals from periphery to cortex. Additional research is needed to clarify further the impact of BotNT-A on the neuronal signaling pathways activated during migraine.

Choosing The Appropriate Candidate For BotNT-A Injection

Although there is no consensus on the standards for application of BotNT-A in preventing certain types of primary headaches (most commonly migraine and tension-type headache), results from clinical studies have revealed a patient population which may be more appropriate for BotNT-A application. The appropriate candidates for BotNT-A therapy for headache may be listed as shown in table 1.

Application Of BotNT-A For Headache; Is There A Consensus On The Dosage And Site of Application?

Studies on BotNT-A have mostly focused on its use for migraine and tension-type headache

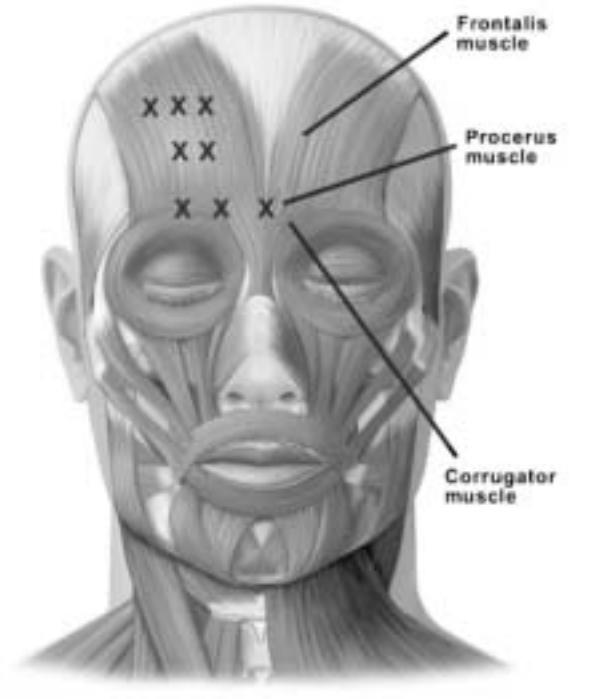

Figure 1: BotNT-A injection sites for headache; procerus, corrugator and frontalis muscles (Blumenfeld AM 2003).

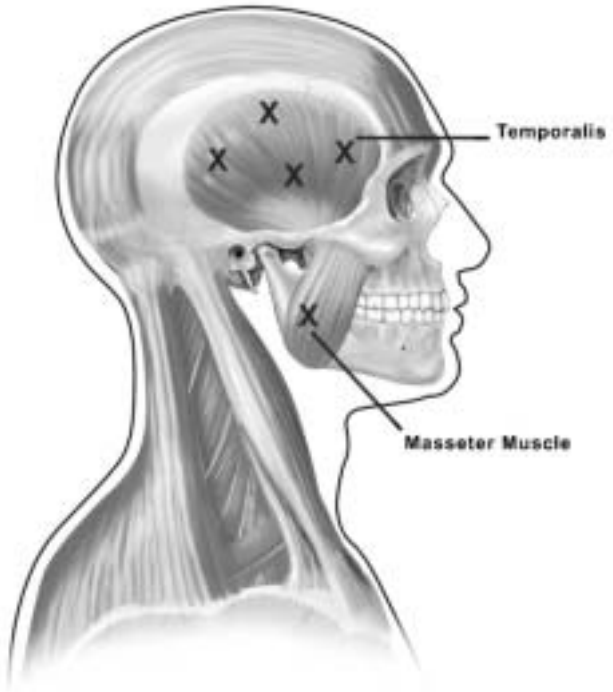

Figure 2: BotNT-A injection sites for headache; temporalis and masseter muscles (Blumenfeld AM 2003).

(TTH). Patients suffering from either migraine or TTH or both represent the vast majority of patients suffering from idiopathic headache. Investigators have used injection techniques with differing anatomical injection techniques, doses and concentrations of BotNT-A. There are mainly two types of injection techniques for BotNT-A; namely the fixed site approach or the 'follow the pain' approach. However the combination of both methods has also been reported (Mathew 2002). Other factors such as volume per injection site, number of injection sites per area, the dilution of BotNT-A, and the injection technique vary across studies and have not been consistently reported.

Side Effects And Other Important Points For Pre-Warning The Patients And Obtaining An informed Consent

Physicians should review the known side effects of BotNT-A treatment, including possible headache, rash, bruising or eyebrow and eyelid ptosis with the patient and obtain informed consent. Out of 92 patients receiving BotNT-A into the temporalis muscle 26 patients have been reported to develop 'hourglass deformity' characterized by bilateral depression of the temporal

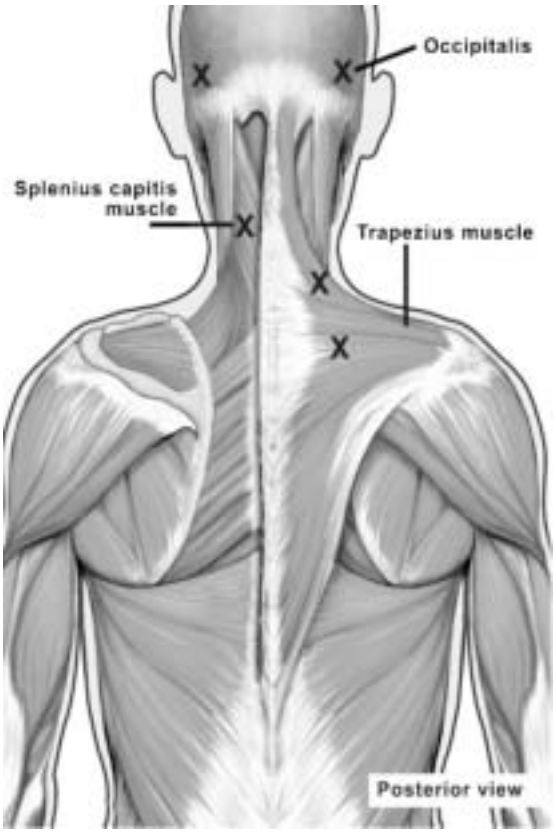

Figure 3: BotNT-A injection sites for headache; occipitalis, splenius capitis and trapezius muscles. (Blumenfeld AM 2003).

Table 2. Controlled studies on botulinum toxin in headache disorders.

	Type of headache	Number of patients	Toxin	Dose (units), application type	Result
Ondo et al 2004	CDH	60	A (Botox®)	200 B; FTP	Negative
Padberg et al 2004	TTH	40	A (Botox®)	100 B; FTP	Negative
Smuts et al 1999	TTH	41	A (Botox®)	100 B; FTP	Positive
Mathew et al 2005	CDH	355	A (Botox®)	200 B; FTP	Negative
Schmitt et al 2001	TTH	60	A (Botox®)	20 B; FS	Negative
Silberstein et al 2000	M	123	A (Botox®)	75 B, 150 B, 225 B; FS	+/- a
Silberstein 2005	CDH	702	A (Botox®)	25 B, 75 B; FS	Negative
Barrientos and Chana 2003	M	30	A (Botox®)	50 B; FS	b
Evers et al 2004	M	60	A (Botox®)	16 B, 100 B; FS	Negative
Rollnik 2000	TTH	21	A(Dysport®)	200 D; FS	Negative
Schulte-Mattler TTH and Krack 2004	112	A(Dysport“)	500 D; FS	Negative	
Gwynn et al 2003	CDH	39	B(Myobloc®)	5000 M, 7500 M; FS	Negative, c

CDH, Chronic daily headache; M, Migraine; TTH, Tension-type headache; FTP, Follow-the pain approach; FS, Fixed site approach.

a: Significant only in the 25 U, no correction for multiple hypothesis testing

b: No outcome criterion defined prospectively

c: Preliminary results, published as abstract only

region ranging from minimal to significant resembling an ‘hourglass’ (Guyuron 2004).

Patients should also be told that multiple treatment cycles may be needed to achieve an optimal therapeutic effect (Mathew 2002, Blumenfeld AM 2003). However owing to the potential risk of antibody development, BotNT-A treatments should not be repeated more frequently than every 3 months (Brin 1997).

Injection Techniques And Sites For BotNT-A

BotNT-A is used in the range of 50 to 100 units for all types of headache. The technique of delivering small doses at multiple sites reduces the occurrence of side effects and controls head pain efficiently. To achieve this, a dilution of 4 mL of normal saline to 100 units of BotNT-A is used. The dose at each site is 2,5 (0.1 cc) to 10 units (0.4 cc). Number of injected sites may vary from 10 to 25 (Blumenfeld AM 2003). The injections are administered intramuscularly to limit discomfort and side effects imported by soft tissue diffusion. Intradermal injections may produce similar clinical improvement but tend to be more uncomfortable (Ewans 2003).

Treatment with a fixed-site approach rather than follow-the-pain approach is recommended for patients with migraine or migrainous headache, because the latter may produce a suboptimal cosmetic outcome and the headaches may shift to the previously unaffected side (Ewans 2003). The fixed-site approach consists of bilateral injections even if the patient has strictly unilateral headaches. The muscles injected are the procerus, corrugators, frontalis and temporalis (Figures 1 and 2).

Follow-the-pain approach is more commonly used in chronic-tension type or chronic daily headache patients. Follow-the-pain injection sites include; the frontalis, temporalis, occipitalis, trapezius, splenius capitis, suboccipital and cervical paraspinal muscles (Figures 1, 2 and 3). Injection sites are identified by history ('Where does it hurt when you have a headache?') and ('Show me with your hands where the pain is') and by examination of the cervical shoulder girdle and temporomandibular musculature. The doses injected in the cervical shoulder girdle muscles are kept low, so as to prevent any possible weakness (Ewans 2003, Blumenfeld AM 2003).

Evidence-Based Approach For BotNT-A Use In Different Headache Types

Use of botulinum toxin in different types of headaches in an evidence-based manner has been evaluated in 2002 and later in 2006 (Schulte-Mattler 2006, Evers 2002). Most of the initial reports on botulinum toxin in tension-type headache and in migraine were positive. Unfortunately, these results were not reproduced in well-designed, randomized controlled trials (Schulte-Mattler 2006). For a systematic evaluation of the efficacy of BotNT-A in headache disorders, well-defined treatment procedures and an exact diagnosis, for headache according to the criteria of the International Headache Society (IHS) is mandatory. Appropriate study design is usually lacking in open-labeled studies that have shown positive results with BotNT-A in different types of headache patients (Blumenfeld A 2004). So far, doses from 20 U (Botox®) to 500 U (Dysport®) have been studied in patients with chronic tension-type headache, and doses from 16 to 200 U (Botox®) in patients with migraine. Experience with botulinum toxin type B (Myobloc®/ Neurobloc®) is limited. Table 2 shows the randomized controlled trials of different botulinum toxin preparations.

One of the studies performed by a study group on 355 chronic daily headache patients has reported that the primary objective of the study was not met however there were positive outcome measures eg; decreased frequency of headaches following third injection session (Dodick 2005, Mathew 2005). Side effects related to BotNT-A in this study were; muscular weakness (29%), neck pain (14%), blepharoptosis (10%) and skin tightness (6%) (Dodick 2005).

BotNT-A has also been used in patients with cervicogenic headache and cluster headache (Evers 2002) however well-designed and controlled studies with a high number of patients are still needed for a valid evaluation.

Conclusion

BotNT-A has been used clinically mostly for the prophylaxis of different types of headaches for almost 15 years. Several studies have focused both on the mechanism of its effect in different types of headaches and its clinical usefulness. Positive results in mostly migraine and tension-type headache populations have been reported in open-labeled studies. However evidence-based evaluation of the present studies reveals so far that it is not possible to recommend the widespread clinical use of botulinum toxins in headache. Therefore it is advisable to limit the further use of botulinum toxin to properly planned clinical studies.

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