

Treatment of Tension-Type Headache with Botox:

A Review of the Literature

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Abstract

Botulinum toxin has been shown to effectively treat several types of neurological disorders. It has recently been evaluated for the treatment of tension-type headaches in patients who are unable to tolerate or cannot benefit from standard therapies. Most of the open design studies seem to present positive results. However, the randomized, double-blind, placebo-controlled studies present contradictory results for the efficacy of botulinum toxin. Based on these data, further controlled trials of botulinum toxin are needed to evaluate its effects on tension headaches and to determine optimal injection sites, doses, and frequency of treatments.

Key Words: Botox, tension-type headache, headache.

Introduction

RECENT STUDIES demonstrating the effectiveness of botulinum in treating several disorders related to muscle spasticity and pain suggest a potential role for this agent in headache treatment. Botulin or botulinum toxin (BT), a polypeptide produced by the anaerobic bacterium *Clostridium botulinum*, is one of the world's deadliest substances. It is best known as a source of food poisoning; its ingestion in spoiled food can lead to death caused by muscle paralysis. The toxin interferes with presynaptic vesicular release of acetylcholine from nerve endings and interrupts neuromuscular transmission (1, 2). It also exerts a blocking action on the parasympathetic nervous system, and may inhibit release of other neurotransmitters or affect transmission of afferent neuronal impulses (2, 3).

Purified toxin injected locally into muscles causes paralysis for up to 3–4 months, after which

nerve endings regenerate and the toxin's clinical effects wear off (2, 4). The ability of this agent to reversibly alter muscle strength, with few systemic side effects, suggests its potential therapeutic usefulness in such diverse conditions as post-stroke, congenital spasticity or contractures, dystonias, regional myofascial pain syndromes, and other disorders that involve pathologic muscle hyperactivity. BT is also being studied as a treatment for a variety of pain conditions, especially those in which heightened muscle tension is believed to play a role (2). This review summarizes evidence to date regarding the use of BT in treating tension-type headaches.

The International Headache Society (IHS) began developing a classification system for headaches in 1985. Finalized in 1988, this system includes a tension-type headache category, further defined as either episodic or chronic. Headache categories are also defined by whether they are associated with pericranial muscle disorders. Episodic tension headache usually is associated with a stressful event. This headache type is of moderate intensity, self-limited, and usually responsive to nonprescription drugs. Chronic tension headache often recurs daily and is associated with contracted muscles of the neck and scalp. This type of headache is bilateral and usually occipitofrontal. Tension-type headache is the most common type of chronic, recurring head pain. In the past, pain eti-

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Accepted for publication June 2005.

ology was presumed to be the muscular contraction of pain-sensitive structures of the cranium, but the IHS intentionally abandoned the terms “muscular contraction headache” and “tension headache,” because no research supports muscular contraction as the sole pain etiology. Pain onset in tension-type headache can have a throbbing quality and is usually more gradual than onset in migraines. Compared with migraines, tension-type headaches are more variable in duration, more constant in quality, and less severe (5).

The IHS diagnostic criteria for tension-type headaches state that two of the following characteristics must be present: pressing or tightening (nonpulsatile quality), frontal-occipital location, and/or bilateral with mild/moderate intensity. Tension-type headache history is usually as follows: duration of 30 minutes to 7 days; no nausea or vomiting (anorexia may occur); photophobia and/or phonophobia; a minimum of 10 previous headache episodes; fewer than 180 days per year with headache; bilateral and occipitonal or bifrontal pain; pain described as “fullness,” “tightness/squeezing,” “pressure,” or “bandlike/viselike,” which may occur acutely under emotional distress or intense worry; insomnia; pain often present upon rising or shortly thereafter; pain not aggravated by physical activity; muscular tightness or stiffness in neck, occipital, and frontal regions; duration of more than 5 years in 75% of patients with chronic headaches; difficulty concentrating; and no prodrome. A new headache onset in elderly patients should suggest etiologies other than tension headache (5).

The physical examination serves mainly to exclude the possibility of other headache causes. Vital signs should be normal. Tenderness may be elicited in the scalp or neck, but no other positive physical exam findings should be noted. Pain should not be elicited over the temporal arteries or positive trigger zones. Some patients with occipital tension headaches may manifest tender upper cervical muscles. Pain associated with neck flexion and stretching of paracervical muscles must be distinguished from nuchal rigidity associated with meningeal irritation. The causes include stress and/or anxiety. Stress may cause contraction of neck and scalp muscles, although no evidence confirms that the origin of pain is sustained muscle contraction. Other causes include poor posture, depression, and psychological or social problems (5).

Discussion

A large number of clinical studies are available for the evaluation of botulinum toxin in the treat-

ment of tension-type headache. The results however are contradictory. After the first negative report of Zwart et al., who in an open study injected only the temporalis muscle on one side of the head and did not find an improvement in any of 6 patients treated with 30–40 U of Botox, all later case reports and open studies presented positive results (6, 7). Krack et al. first described a patient with tension-type headache who became pain-free after injection of 160 U of Dysport (European brand name for botulinum toxin) (7, 8). Relja treated 10 patients with 15–35 U of Botox using individual injection sites. She found a significant reduction in headache duration, pain intensity and pain sensitivity (7, 9). In a further 24 patients treated using the same study design, Relja found a lasting effect in long-term use over 15 months. This may be because the repeat injections had a step-like therapeutic effect: the consecutive therapeutic effect of each injection built on the effect previously achieved (7, 10). This was further seen in a study conducted by Ondo et al. They conducted a double-blind, placebo-controlled, parallel study of botulinum toxin type A for chronic tension-type headache and chronic migraine headache in 60 patients. The primary efficacy point was the number of headache-free days as assessed by diary for 12 weeks after Botox injection. Secondary efficacy points included global impressions, the use of abortive headache medications and palpation. After recruitment, subjects kept diaries for 4 weeks prior to randomization, at which time they received either 200 U of Botox or matching placebo and were followed. After the week-12 evaluation, patients were offered 200 U of Botox (open-label), and were similarly followed for another 12 weeks. Over a 12-week period after injections, headache-free days had improved in the Botox group from week 8–12 and tended to improve strongly over the entire 12-week period, but did not meet a significance criterion. The subject global impressions, subject change in headache impressions, and investigator global impressions all improved in the Botox group as compared with the placebo group. At week 24 (open label), there were more headache-free days in the twice-Botox-treated group compared with the once-injected group. Therefore, the study showed that Botox may help chronic daily headache and appears to have a cumulative effect with subsequent injections (11).

In an open study, but using a standardized injection design, Schulte-Mattler et al. reported on the use of Dysport (total of 200 U) in 9 patients with chronic tension-type headache not sufficiently responding to physical therapy and pharmacotherapy. Patients kept a headache diary from

which the area under the headache curve (AUC) 4 weeks before and after treatment was calculated. After a 4-week run-in phase, equal doses of 25 units of Botox were injected into the frontalis, temporalis, occipitalis, and sternocleidomastoid muscles. The mean AUC of the 8 patients who completed the study was significantly reduced from 404 to 196 and the product of pain duration and pain intensity was significantly reduced (12). Smuts and Barnard showed positive results in 30 of 50 patients treated with 100 U of Botox in an open and individual fashion (7, 13). Freund and Schwartz conducted a retrospective study of 21 patients with chronic tension-type headache (based on IHS criteria) who also had palpable muscle tenderness of the scalp or upper neck. Patients received botulinum toxin type A 100 U over five sites in the scalp and upper neck representing muscle points most tender to palpation. Eighteen patients experienced a >50% reduction in headache frequency, and 20 had a 50% reduction in tenderness to palpation. The investigators suggested that some chronic headaches may represent “variants of focal dystonias,” accounting for the efficacy of botulinum toxin. Although the theory is intriguing, the results of this open-label study must be interpreted with caution (2, 14).

However, when randomized, double-blind, and placebo-controlled studies were performed with patients suffering from tension-type headache, contradictory results for the efficacy of botulinum toxin were found. Schmitt et al., studying 59 patients, could not find any significant difference between 20 U of Botox and placebo (15, 16). Burch et al. also could not show a significant difference in headache frequency between treatment with Botox (50 U) and placebo injected in pericranial muscles in 41 patients. However, there was a significant decrease of pain intensity in the treatment group with Botox compared with the control group (16, 17). Rollnik et al. studied the efficacy of 200 U of Botox A (presumably Dysport) against placebo. They treated 11 patients with 200 U of Dysport and 10 patients with placebo. After 4, 8, and 12 weeks, the 21 patients showed no difference (16, 18). Gobel et al. treated 10 patients each with either 80 U of Botox or placebo. In both cases, no reduction was found either in pain intensity, pain-free days or in use of analgesics (19).

In a study by Smuts et al., 37 patients with tension-type headache received Botox type A 100 U or placebo, divided among six injection sites: two in the temporal muscles and four in the cervical muscles. Patients kept a diary of headache intensity and frequency and medication use, starting 1 month before treatment and continuing for 3

months after injections were administered. The actively treated group showed a trend toward decreased headache severity over the 3 months after injection. This improvement reached statistical significance at month 3 relative to the pretreatment month. Similarly, the number of headache-free days was greater at month 3 than at baseline. The Chronic Pain Index, a subjective indicator of pain intensity, also reflected improvement in the actively treated patients but not in the placebo group. No serious adverse events were reported (20). Relja (21) reported on her data from a prospective, randomized, double-blinded 8-week crossover trial of Botox as a treatment for chronic tension-type headache in 16 patients who were resistant to medication. Patients received either Botox 35–80 U in saline vs. saline alone by multiple injections in the most tender pericranial muscles. No other medication was administered for at least 24 hours prior to either baseline measurements or Botox injections. Tenderness was assessed by palpation of frontalis, trapezius, and sternocleidomastoid muscles. Of the placebo patients, 94% still had moderate-to-severe headaches after treatment compared with only 25% (moderate only) in the Botox group (75% had no or mild headaches after treatment) (21, 22). Relja conducted another study (in 2001) in which 27 patients were randomized to placebo or the injection of 40–95 U of Botox every 3 months over a period of 10 months. The Botox group experienced a significant reduction of headache frequency and intensity compared with the placebo group (23). In a more recent study, Relja et al. (2004) conducted a prospective, double-blind, placebo-controlled crossover study with 16 patients and an open-label, long-term study with 30 patients. The results revealed that all the patients showed reduced severity of headache, reduced pericranial muscle tenderness and increased number of headache-free days during botulinum toxin A treatment. Moreover, a constant and cumulative trend of improvement was present, indicating better quality of life during botulinum toxin treatment (24). In the double-blind study, all outcome measures showed a significant difference between Botox and placebo treatments. Botox was significantly more potent in reducing muscle tenderness. Compared with placebo, patients treated with Botox showed significantly reduced maximum severity of headache. In the open-label study, there was a constant and cumulative trend of improvement in the number of headache-free days over the 18-month period. However, in most of these studies, the number of patients in the subgroups was too small.

In addition, the dose of botulinum toxin A and the injection sites were not always standardized. In some of these controlled studies, however (Gobel

and Rollnik), there was a standardized design with defined injection sites rather than an individual selection of trigger points. Taking account of this point, Porta conducted a randomized comparative trial of tension-type headache treatment with botulinum toxin A and methylprednisolone injected into individual tender points in cranial muscles in 20 patients. A significant decrease in the median pain score at day 60 after injection of botulinum toxin A was found compared to methylprednisolone. All patients treated with botulinum toxin A experienced a gradual decrease in median pain severity scores at 30 days and 60 days after treatment. The beneficial effects of botulinum toxin A continued to increase 60 days after injection, whereas the effects of steroid therapy at this time point began to decline. Without a placebo group, however, it is not possible to assess the methodology or significance of this trial (25).

Thus, an important finding of experience to date with botulinum toxin A in therapy of tension-type headache is that the injection should be performed at the site of the pain or the trigger points, and not on a standardized basis. Just as the injection is made specifically into the affected muscle in the treatment of dystonia cases, this must also be done in the treatment of pain. It is essential that this crucial point be observed in future controlled studies and in open use. However, this point was contradicted in a study by Padberg et al. They conducted a randomized, placebo-controlled clinical trial to prove the efficacy of botulinum toxin for chronic tension-type headache. Patients were randomly assigned to receive botulinum toxin (maximum 100 U) or placebo (saline) in muscles with increased tenderness. After 12 weeks there was no significant difference between the two treatment groups in decrease of headache intensity on Visual Analog Scale (VAS), mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, and number of analgesics taken per day. There was also no significant difference in patients' assessment of improvement after week 4, 8 and 12. Botulinum toxin was not proven effective in the treatment of chronic tension-type headache. Therefore, increased muscle tenderness might not be as important in the pathophysiology of chronic tension-type headache as believed (26).

Another factor to consider is the range of doses of botulinum toxin A used, which in the positive studies ranged from 15–100 U or 160–200 U of Dysport; the total dose injected would appear to be of secondary importance. Schulte-Mattler et al. (2004) conducted a follow-up study from their previous open-label study in 1999. This study was a

prospective, multicenter, randomized, double-blind, placebo-controlled trial. Multiple pericranial muscles (frontalis, temporalis, sternocleidomastoid, auricularis, occipitalis, splenius capitus, semispinalis capitus, and trapezius) of 107 patients with chronic tension-type headache were treated either with 500 U of botulinum toxin (Dysport) or with placebo. The diagnosis was made strictly following the IHS criteria. Injections were made following a fixed scheme and not adjusted to the patient's symptoms. Patients kept a headache diary that was used to calculate the area under the curve at 6 weeks before and 12 weeks after the treatment as the main effect measure. Secondary effect measures were the number of days with headache, the number of days with intake of analgesics, the duration of nocturnal sleep, and the Beck Depression Inventory score. The results showed that there were no significant differences between the verum group and the placebo group in any of these variables. In addition, seven of the patients of the verum group had transient weakness of the eyelids, the neck, or both, indicating that a higher dose than used in this study does not seem sensible for the treatment of headache. The study significantly concluded that botulinum toxin A cannot be recommended for patients with chronic tension-type headache who do not sufficiently respond to the established therapeutic strategies (7).

It would also appear to be significant that a higher efficacy seems to result in cases where both migraine and tension-type headache exist. Most studies dealt with either one syndrome or the other (27). Klapper et al. treated patients with chronic daily headache in a double-blind, placebo-controlled trial using 25.5–72.5 U of Botox. In a subgroup with 2 injection regions they found a reduction in headache duration and in frequency of moderate and severe headaches (28). Wheeler achieved the same results in a group of 4 patients with chronic headaches associated with pericranial muscle tension, which had failed to respond to prolonged conventional treatment. The patients were injected in multiple sites with a total of 100–200 U of Botox. All of them had a significant reduction in headache severity and frequency with concomitant reduction in medication use for up to 8 months after treatment (29).

Additional studies of the prophylactic effect of botulinum toxin A on tension-type headache were either not controlled, had no exact diagnosis, had too few patients or did not define the reduction of headache frequency as the primary endpoint.

Klapper et al. enrolled 56 patients in their study. However, they separated them into four subgroups, and no exact headache diagnosis ("chronic

headache”) was given. Treatment with botulinum toxin A in both frontal and suboccipital sites caused a significant reduction of headache for one subgroup compared with the other three subgroups (28). The open study of Robbins with 79 patients treated with 24 U of Botox A had only “daily headache” as the diagnosis. After a control period of 3 months, 30% of the patients showed good or moderate improvement; 70% had no relief (30).

Rollnik et al., in another study, examined the efficacy of 500 U of botulinum toxin A (Dysport) in chronic tension-type headache and also studied the electromyography (EMG) activity of different face and neck muscles. The study was placebo controlled and parallel grouped (four patients in each group). Although the EMG activity was significantly reduced by botulinum toxin A, there was no effect on the headache (31).

Conclusion

Botulinum toxin A represents a completely new treatment option for patients with chronic pain syndromes, especially tension-type headaches. At this time, clinicians may consider botulinum toxin as a treatment for headache disorders in patients who cannot tolerate or do not benefit from standard therapies.

In our current review, the results were contradictory and inconclusive. In evaluating the open design studies, all but one seemed to show a favorable response to the treatment of tension type-headache with Botox. However, in the double-blind, placebo-controlled trials the results were contradictory for the efficacy of botulinum toxin. This may be due to the fact that varying doses of Botox were used. There were also differing injection sites: some researchers used individual injection sites or most tender muscles while in other studies there was a standardized injection design. In our own practice, patients receive a total of 100 units of Botox at standardized sites (suboccipital, frontalis, temporalis, and glabellar). Another aspect is the frequency of treatment. In the studies reviewed, it was shown that there was a cumulative effect with subsequent injections.

Therefore, further evidence is needed to determine whether this agent can serve as a first-line therapy for patients with less refractory headaches, and to determine optimal injection sites, doses, and frequency of treatment.

References

1. Simpson LL. The origin, structure, and pharmacological activity of botulinum toxin. *Parmaol Rev* 1981; 33:155–188.
2. Loder E, Biondi D. Use of botulinum toxins for chronic headaches: a focused review. *Clin J Pain* 2002; 18(6 Suppl):S169–S176.
3. Volknaand W. Commentary: the synaptic vesicle and its targets. *Neuroscience* 1995; 64:277–300.
4. Carruthers JD, Carruthers A. Botulinum A exotoxin in clinical ophthalmology. *Can J Ophthalmol* 1996; 31(7):389–400.
5. Blanda M. eMedicine - Headache, Tension 2004.
6. Zwart JA, Bovim G, Sand T, Sjaastad O. Tension headache: botulinum toxin paralysis of temporal muscles. *Headache* 1994; 34(8):458–462.
7. Schulte-Mattler WJ, Krack P, BONTTH study group. Treatment of chronic tension-type headache with botulinum A: a randomized, double-blind, placebo-controlled multicenter study. *Pain* 2004; 109:110–114.
8. Krack P, Hornig C, Dorndorf W. Resolution of chronic tension headache after botulinum toxin treatment of idiopathic blepharospasm. *Mov Disorder* 1995; 10:388.
9. Relja MA. Treatment of tension-type headache by local injection of botulinum toxin. *Euro J Neurol* 1997; 4(Suppl 2):71–72.
10. Relja MA. Treatment of tension-type headache with botulinum toxin: 1-year follow-up. *Cephalalgia* 2000; 20:336.
11. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized placebo-controlled, parallel design study. *Cephalalgia* 2004; 24(1):60–65.
12. Schulte-Mattler WJ, Wieser T, Zierz S. Treatment of tension-type headache with botulinum toxin: a pilot study. *Eur J Med Res* 1999; 4(5):183–186.
13. Smuts JA, Barnard PWA. Botulinum toxin type A in the treatment of headache syndromes: a clinical report of 79 patients. *Cephalalgia* 2000; 20: 332.
14. Freund BJ, Schwartz M. A focal dystonia model for subsets of chronic tension headache [abstract]. *Cephalalgia* 2000; 20:433.
15. Schmitt WJ, Slowey E, Fravi N, et al. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double blind, placebo-controlled trial. *Headache* 2001; 41:658–664.
16. Evers S, Rahmann A, Vollmer-Haase J, Husstedt IW. Treatment of headache with botulinum toxin A—a review according to evidence-based medicine criteria. *Cephalalgia* 2002; 22(9):699–710.
17. Burch CM, Kokoska MS, Glaser DA, Hollenbeak CS. Treatment of frontal tension headaches with botulinum toxin A. *Cephalalgia* 2001; 21:486–491.
18. Rollnik JD, Tanneberger O, Schubert M, et al. Treatment of tension-type headache with botulinum toxin A: a double-blind, placebo-controlled study. *Headache* 2000; 40:300–305.
19. Gobel H, Lindner V, Krack P, et al. Treatment of chronic tension-type headache with botulinum toxin. *Cephalalgia* 1999; 19:455.
20. Smuts JA, Baker MK, Smuts HM, et al. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. *Eur J Neurol* 1999; 6(Suppl 4):99–102.
21. Relja M. Botulinum toxin type A in the treatment of tension-type headache. Presented at: World Congress on Pain; Aug 22–27, 1999; Vienna, Austria and at the International Conference 1999. Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins; Nov 16–18, 1999; Orlando, FL.
22. Royal MA. The use of botulinum toxins in the management of pain and headache. *Pain Practice* 2001; 1(3):215–235.
23. Relja MA, Klepac N. Botulinum toxin A as prophylactic treatment in chronic tension-type headache: long-term follow-up study; *Neurology* 2001; 56(Suppl 3):A349–A350.

24. Relja MA, Telarovic S. Botulinum toxin in tension-type headache. *J Neurol* 2004; 251(Suppl)1/12–1/14.
25. Porta M. A comparative trial of botulinum toxin A and methyl-prednisolone for the treatment of tension-type headache. *Curr Rev Pain* 2000; 4:31–35.
26. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double blind, placebo-controlled clinical trial; *Cephalalgia* 2004; 24(8):675–680.
27. Gobel H, Heinze A, Heinze-Kuhn K, Jost WH. Evidence-based medicine: botulinum toxin A in migraine and tension-type headache. *J Neurol* 2001; 248 Suppl 1:34–38.
28. Klapper JA, Mathew NT, Klapper A, Kailasam J. Botulinum toxin type A (Btx-A) for the prophylaxis of chronic daily headache. *Cephalalgia* 2000; 20:292–293.
29. Wheeler AH. Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. *Headache* 1998; 38(6):468–471.
30. Robbins L. Botulinum toxin A for refractory chronic daily headache [abstract]. *Neurology* 2001; 56(Suppl 3):A349.
31. Rollnik JD, Karst M, Fink M, Dengler R. Botulinum toxin type and EMG: a key to the understanding of chronic tension-type headache? *Headache* 2002; 41(10):985–989.