Expert Opinion

Botulinum Toxin Injections for Headache

Case Histories Submitted by Randolph W. Evans, MD
Expert Opinion by Andrew Blumenfeld, MD

Key words: botulinum toxin, migraine, chronic daily headaches
(*Headache*. 2003;43:682-685)

Botulinum toxin injections for migraine? It seemed crazy to many when first suggested by otolaryngologist William Binder. In 1992, he noted that migraineurs who received injections for wrinkles reported an improvement in their headaches, and additional evidence for efficacy has accumulated since. Serendipity strikes again!

CLINICAL HISTORIES

Case 1.—A 30-year-old woman has had migraine without aura about 1 to 2 times per week for the last several years. The headaches are either left- or right-sided. Triptans often produce headache relief, but she feels "dragged out" afterwards. She has read about botulinum toxin type A therapy and wonders if this treatment might be appropriate for her.

Case 2.—A 38-year-old woman has a 10-year history of chronic daily headache with about 25 headache days per month. Her typical headaches are bilateral and possess features of both migraine and tension-type headache. Approximately 10 days per month, the headaches are unilateral and otherwise typical of migraine without aura. She has tried numerous preventive medications without clinical improvement. She currently is taking a triptan 2 days per week and no medications on the other days. She does not drink caffeinated beverages.

Questions.—For these 2 patients, what is the probability that botulinum toxin injections would significantly reduce the frequency of their headaches? Is there any evidence to recommend fixed-pattern injections over a "follow-the-pain" protocol? Can you determine if a patient is a responder after one set of injections? Is there any advantage of Botox versus Myobloc? Are there other headache types that may respond to botulinum toxin (eg, analgesic overuse headache, posttraumatic headache)?

Address all correspondence to Dr. Randolph W. Evans, Suite 1370, 1200 Binz, Houston, TX 77004 or Dr. Andrew Blumenfeld, Southern California Permanente Medical Group, Vandever Avenue, San Diego, CA 92120.

EXPERT COMMENTARY

The patient described in case 1 is an appropriate candidate for botulinum toxin type A therapy. She has frequent disabling migraine headache with triptan side effects and no medication overuse issues which would complicate treatment outcome. For patients with migraine or migrainous headache, treatment with a fixed-site approach rather than the follow-the-pain approach is preferable because the latter may produce a suboptimal cosmetic outcome, and the headaches may shift to the previously unaffected side. 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 (see Table 1). Using this fixed-site approach and having resolved any medication or caffeine (or both) overuse issues, subjective improvement can be expected in more than 80% of patients.[1]

In patients who have migraine with aura, botulinum toxin type A therapy frequently produces improvement in head pain, but the aura remains unchanged. This may be related to the mechanism of action of botulinum toxin type A in migraine, wherein the drug is hypothesized to affect the trigeminal

Table 1.—Fixed-Site Approach to Botulinum Toxin Type A Injection*

	Source, y		
	Blumenfeld,[1] 2002	Silberstein et al,[12] 2000	Smuts et al,[13] 1999
Injection site			
Procerus	5	3 or 9	Site not injected
Medial corrugator	2.5-4	1.5 or 4.5	Site not injected
Lateral corrugator	2.5	1.5 or 4.5	Site not injected
Frontalis	2.5 per site, 4-6 sites per side	2.5 or .5, 2 sites	Site not injected
Temporalis	2.5-5, 4 sites	3 or 9	9, 2 sites
Suboccipital area	5 (optional)	Site not injected	7, 2 sites
Trapezius	15-25, 3 sites	Site not injected	9, 2 sites
Botulinum toxin type A concentration	100 U/4 mL	Not reported	100 U/2 mL
Total injection sites	25	11	12

* Values expressed as units of botulinum toxin. All injections were performed bilaterally.

nerve predominantly.[2] Triptan responsiveness often improves following botulinum toxin type A treatment, but patients with allodynia will continue to have a poor response to triptans.[3] It would be interesting to study the effects of botulinum toxin type A on allodynia in patients with migraine.

Although patients improve after one treatment, repeated treatments produce even greater clinical efficacy, particularly with respect to changes in Migraine Disability Assessment (MIDAS) scores.[4-6] Three treatments of botulinum toxin type A over a 9-month period should be considered adequate to determine whether the patient will or will not be a responder to botulinum toxin therapy. To insure appropriate expectations, patients should be advised about the progressive efficacy of repeated treatments. Each successive treatment may involve higher doses and varied combinations of fixed-site and follow-the-pain approaches.[7]

The decision to use botulinum toxin type A (Botox) versus botulinum toxin type B (Myobloc) is largely physician preference. One consideration in selecting a specific product is that Myobloc has a lower pH value compared with Botox and as a result, produces greater discomfort, typically a burning sensation. Headache treatments involve multiple injection sites, and this discomfort may diminish the patient's enthusiasm for such treatment.

Because of her poor response to other preventive medications and high use of triptans, the patient described in case 2 is also an appropriate candidate for botulinum toxin type A therapy. Her headaches should improve in a manner similar to the first case, and the cost of her health care will decrease if the improvement in her headaches causes her to reduce her triptan usage.[8]

Botulinum toxin type A therapy may be effective in the management of chronic daily headache. The technique of injection involves a fixed-site approach for migrainous headaches, as for the first case, with the addition of a follow-the-pain approach for headaches with tension-type features. Follow-the-pain injection sites include the frontalis, temporalis, occipitalis, trapezius, splenius capitus, suboccipital, and cervical paraspinal muscles (Table 2). 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.

Medication overuse must be addressed in patients with chronic daily headache.[9] For patients who are willing to discontinue their medication overuse, botulinum toxin type A may serve as an excellent

Table 2.—Follow-the-Pain Injection Technique for Tension-type Headache*

	Source, y				
	Blumenfeld,[1] 2002	Relja,[14] 1997	Wheeler,[15] 1998	Relja and Korsic,[16] 1999	Freund and Schwartz,[17] 2000
Injection site					
Trapezius	2-3 sites	Site not injected	X	Site not injected	X
Splenius capitus	1 site	Site not injected	X	Site not injected	X
Semispinalis capitus	1 site	Site not injected	Site not injected	Site not injected	X
Occipitalis	1-2 sites	Site not injected	Site not injected	Site not injected	Site not injected
Sternocleidomastoid	2 sites	X	Site not injected	X	Site not injected
Temporalis	4 sites	X	X	X	Site not injected
Frontalis	4-5 sites	X	X	X	Site not injected
Corrugators	Site not injected	Site not injected	X	Site not injected	Site not injected
Rectus capitus	Site not injected	Site not injected	Site not injected	Site not injected	X
Botulinum toxin type A concentration	100 U/4 mL	Not reported	Not reported	Not reported	100 U/1 mL
Dose at each site or total dose, units	5-10 Not reported	Not reported 15-35	Not reported 197	Not reported 35-80	Not reported 100

* All injections were performed bilaterally with the exception of the procerus.

preventive treatment during the process of detoxification. Patient compliance is not an issue because treatment is administered by injection and has a duration of action of 3 months. In addition, the onset of headache relief is quicker than that experienced with standard oral preventive treatments. Initial botulinum toxin type A treatment may be combined with use of a long-acting triptan and a rapid tapering of the overused agent over a 1-week period.

Treatment of posttraumatic headache in a similar fashion produces results which are comparable with migraine and tension-type headache. Usually a combination of fixed-site and follow-the-pain approaches is used.

For all types of headache, the dose of botulinum toxin type A is in the range of 50 to 100 units. The technique of delivering small doses at multiple sites reduces the occurrence of side effects and controls head pain effectively. To achieve this, a dilution of 4 mL of normal saline to 100 units of botulinum toxin type A is used. The dose at each site is 2.5 (0.1 cc) to 5 units (0.2 cc). The injections are administered intramuscularly to limit discomfort and side effects imported by soft tissue diffusion. Intradermal injections may produce a similar clinical improvement but tend to be more uncomfortable. Owing to the potential risk of antibody development, botulinum toxin type A treatments should not be repeated more frequently than every 3 months.[10]

At the present time, no large-scale, double-blind, randomized, placebo-controlled studies have been completed to confirm the effects noted in clinical practice, in open-label studies, or in smaller, randomized, controlled trials.[11] Such studies are ongoing, however, and include evaluation of the efficacy of repeated treatment cycles.

Unless the patient has well-established chronic cluster, the effect of botulinum toxin type A in cluster headache is difficult to determine. Of 3 patients with chronic cluster, 1 improved with treatment involving a fixed-site and follow-the-pain approach (unpublished observation). Other investigators have reported a 50% success in small case series or individual case reports involving patients with cluster headaches.[11]

In summary, the 2 cases presented here are appropriate candidates for botulinum toxin type A therapy and are likely to derive clinical benefit from this preventive treatment strategy. Further studies will

help to define the subpopulation of patients with headache likely to respond to botulinum toxin therapy and the clinical guidelines required to optimize treatment response.

REFERENCES

1. Blumenfeld A. Botulinum toxin type A (BOTOX™) as an effective prophylactic treatment in headache [abstract]. *Cephalalgia*. 2002;22(suppl 1):20.
2. Guyuron B, Tucker T, Davis J. Surgical treatment of migraine headaches. *Plast Reconstr Surg*. 2002;109: 2183-2189.
3. Burstein R, Collins B, Bajwa Z, Jakubowski M. Triptan therapy can abort migraine attacks if given before the establishment or in the absence of cutaneous allodynia and central sensitization: clinical and preclinical evidence [abstract]. *Headache*. 2002;42: 390.
4. Tepper S, Sheftell F, Bigal M, Rapoport A. Botulinum toxin A for refractory headaches. Presented at: the 55th Annual Meeting of the American Academy of Neurology; March 29-April 5, 2003; Honolulu, Hawaii.
5. Troost B. Botulinum toxin type A (Botox®) therapy for intractable headache [abstract]. *Headache*. 2002; 42:435.
6. Mathew NT, Kailasam J, Meadors L. "Disease modification" in chronic migraine with botulinum toxin type A: long-term experience [abstract]. *Headache*. 2002;42:454.
7. BOTOX® [package insert] Allergan, Inc., Irvine, Calif., 2003.
8. Blumenfeld A. Decrease in headache medication use and cost after botulinum toxin type A (Botox®) treatment in a high triptan use population [abstract]. *Headache*. 2002;42:420.
9. Silberstein SD, Lipton RB. Chronic daily headache. *Curr Opin Neurol*. 2000;13:277-283.
10. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl*. 1997;6:S146-S168.
11. 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;22:699-710.
12. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. *Headache*. 2000;40:445-450.
13. Smuts J, Baker M, Smuts H, Stassen J, Rossouw E, Barnard P. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. *Eur J Neurol*. 1999;6(suppl 4):S99-S102.
14. Relja M. Treatment of tension-type headache by local injection of botulinum toxin [abstract]. *Eur J Neurol*. 1997;4(suppl 2):71-73.
15. Wheeler AH. Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. *Headache*. 1998;38:468-471.
16. Relja M, Korsic M. Treatment of tension-type headache by injections of botulinum toxin type A: double-blind placebo controlled study [abstract]. *Neurology*. 1999;52:203.
17. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. *Headache*. 2000;40:231-236.