Brief Communication

Single-Site Botulinum Toxin Type A Injection for Elimination of Migraine Trigger Points

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Background.—Botulinum toxin may be effective in suppressing migraine. Most injection regimens utilized have involved multiple sites.

Purpose.—To evaluate prospectively the effect of botulinum toxin type A injections into the corrugator supercilii muscles alone on the frequency and severity of migraine.

Methods.—Twenty-nine patients (24 women, 5 men) with migraine were enrolled in the study. Average age was 45 years (range, 24 to 63). The frequency (number of migraines per month) and intensity (recorded on an analog scale of 1 to 10, 10 being most severe) of headache were recorded before and after treatment. Twenty-five units of botulinum toxin type A was injected into each corrugator supercilii muscle, for a total of 50 units.

Results.—At 2 months, 24 (83%) of 29 patients reported a positive response to the injection of botulinum toxin type A ($P < .001$). Sixteen patients (55%) reported complete elimination of headache ($P < .001$), 8 (28%) experienced significant improvement (at least 50% reduction in frequency or intensity) ($P < .04$), and 5 (17%) did not notice a change in headache. The duration of efficacy of the botulinum toxin type A injections ranged from 6 to 12 weeks, with an average of 8 weeks. In patients who had improvement in migraine but not complete elimination, the headache frequency decreased from 6.4 to 2.1 per month on average ($P < .04$), and the intensity decreased from 8.6 to 6.1 ($P < .04$).

Conclusion.—These results support the hypothesis that focal injection of botulinum toxin type A may be an effective therapy for migraine.

Key words: corrugator supercilii muscle, botulinum toxin type A, trigger point, migraine

Abbreviation: BTXA botulinum toxin type A

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Botulinum toxin type A (BTXA) is a neurotoxin, which blocks the release of acetylcholine from presynaptic cholinergic nerve endings, but it does not affect nerve conduction or actual synthesis and storage of acetylcholine.[1] Therefore, intramuscular injection of BTXA results in cholinergic neuromuscular blockade. This phenomenon is the cornerstone of BTXA use in the treatment of abnormal muscle movements and spasticity, as well as relief of pain due to excessive involuntary muscle contraction. More recently, the use of BTXA for the temporary relief of migraine has been reported in several studies.[2-4]

Until now, researchers have based reports of improvement in the symptoms of migraineurs with BTXA injections on studies in which multiple sites in the forehead and temple areas were injected.[4] These studies, however, have not targeted a specific anatomic structure. The foundation of our work is based on the hypothesis that the contraction of corrugator supercilii muscles affects the trigeminal nerve branches, which pierce these muscles, namely the supraorbital and supratrochlear nerves, and may commonly serve as a trigger for migraine. We based this hypothesis on the finding of elimination or reduction of migraine in patients who had undergone resection of the corrugator supercilii muscles for cosmetic reasons.[5] Consequently, in this study, we focused on evaluation of

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the effect of single-site BTXA injections into the corrugator supercilii muscles alone to reduce trigeminal sensory nerve irritation in patients with migraine.

METHODS

The research team's neurologist (T.T.) performed the initial screening of patients. Patients were evaluated based on the criteria of the International Headache Society for the diagnosis of migraine.[6] Twenty-nine consecutive patients who met the criteria and agreed to participate in the study were enrolled. Of these, 24 were women and 5 were men. Average age was 45 years (range, 24 to 63). Patients with medical or neurological conditions likely to induce migraine were considered ineligible for the study, as well as those patients whose migraine responded to over-the-counter medications. Patients who were in good health, between 18 and 75 years of age, and experiencing 2 to 20 moderate to severe migraine each month were considered eligible for the study.

The patients completed a comprehensive migraine questionnaire that contained 56 items. All symptoms including frequency, duration, characteristics, and severity of headache were documented, starting 1 month before BTXA injection. Frequency was recorded as number of migraines per month, and intensity of headache was recorded on an analog scale of 1 to 10 (10 being most severe) before and after treatment. Corrugator supercilii muscle hypertrophy was clinically assessed in all patients and graded from 1 to 5. A score of 1 indicated an inability to frown. Two is given when only minor skin tension lines are formed in response to frowning, but vertical frown lines are not seen, and a score of 3 would indicate the formation of small vertical frown lines without obvious muscle hypertrophy. The score of 4 is given when multiple deep vertical frown lines with increased muscle size are observed. Finally, a score of 5 is reserved for patients with deep vertical frown lines, which do not relax when the patient is not frowning and demonstrate significant visual muscle hypertrophy (Table). The average corrugator supercilii muscle strength pretreatment was 4.7, ranging from 4 to 5. Injection of BTXA into the corrugator supercilii muscles rendered these muscles immobile, producing a score of 0 and defining the toxin's duration of action (period during which the corrugator supercilii muscles were rendered inactive).

Through a single injection, using a 1-inch, 30-gauge needle, 25 units of BTXA (Allergan, Inc, Irvine, Calif.) in 0.5 mL of saline was infiltrated into the corrugator supercilii muscle on each side, for a total of 50 units (Figure). All of the injections were performed by one of the authors (B.G.) to assure consistency. Patients were asked to frown to identify the cutaneous attachments of the muscle by observing the dimpling in the skin. The infiltration began at the most lateral aspect of the skin dimpling. The entire course of the muscle was infiltrated with BTXA as the needle was directed deeper and more caudally toward the root of the nose.

Patients maintained a daily diary of the symptoms including location, frequency, and intensity of headaches following the injections and were seen for return visits at 1 and 2 months postinjection. Patients were asked to refrain from using any new or additional prophylactic migraine medications. Patients were instructed, however, to use their migraine medications if they experienced an acute attack and to record this in their diaries.

Following BTXA injection, a minimum 50% reduction in intensity or frequency of migraine was considered an improvement. The results were then statistically analyzed using binomial distribution z statistics with continuity correction. The P values were calculated by comparing the observed proportion based on 29 patients undergoing BTXA injection against 1% improvement. When comparing the preinjection and postinjection frequency and intensity data, the 2-tailed Wilcoxon signed rank test was used.

RESULTS

Following injection of BTXA, 24 (83%) of 29 patients noted improvement in headache ($P < .001$). The frequency fell from 5.21 to 0.70, and the intensity reduced from 8.92 to 2.04. During the 6-week follow-up period, 16 patients (55%, $P < .001$) had complete disappearance of headache, while 8 patients (28%, $P < .04$) observed significant improvement. The average frequency decreased from 6.4 to 2.1 per month, and the intensity fell from 8.6 to 6.1. Five patients (17%)

Patient Demographics and Pretreatment and Posttreatment Results of Single-Site Botulinum Toxin Type A (BTXA) Injection for Elimination of Migraine Trigger Points*

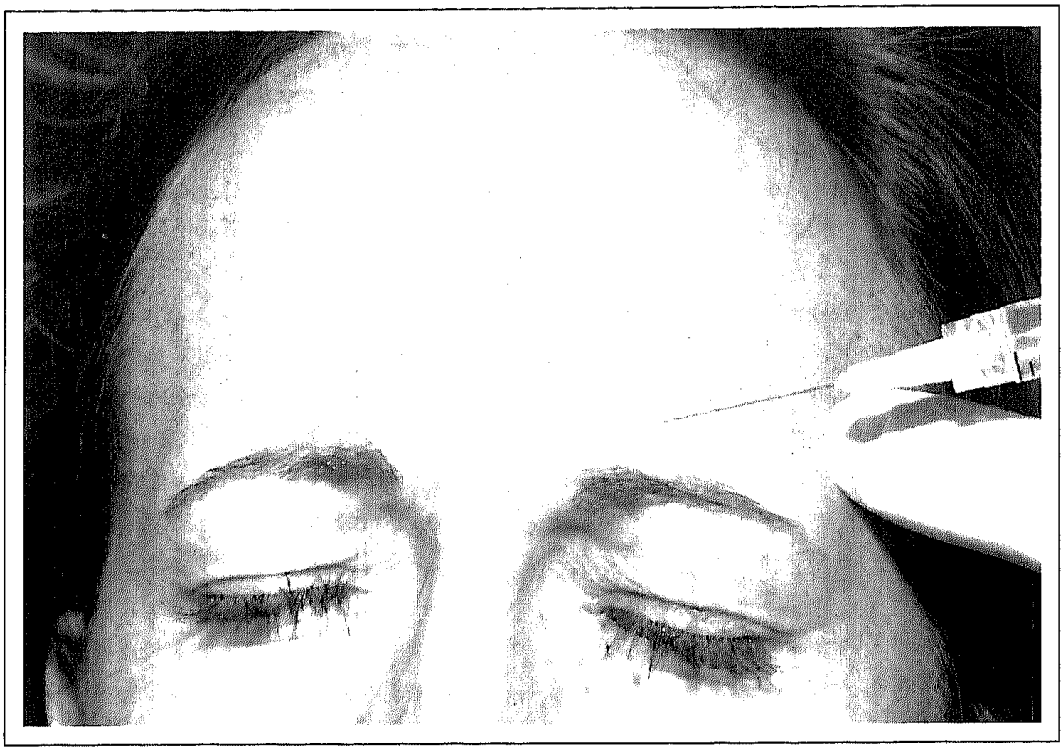
				Pretreatment			Posttreatment		
Patient	Age, y	Sex	Aura (A) Nonaura (N)	CSM Hyper-trophy	Headache Frequency per Month	Headache Intensity per Month	Headache Frequency per Month	Headache Intensity per Month	BTXA Outcome
1	47	F	A	4	6	9	2	8	SD
2	40	F	A/N	5	8	9	0	0	E
3	49	M	N	5	8	9	2	6	SD
4	40	F	A	5	3	10	0	0	E
5	42	F	N	5	4	9	0	0	E
6	35	F	N	5	8	9	12	7	NR
7	38	F	A	5	—	10	2	9	SD
8	44	M	A	4	4	10	0	0	E
9	47	M	A	4	5	8	2	7	SD
10	53	F	A	5	3	10	0	0	E
11	41	F	N	5	6	7	0	0	E
12	49	F	A	4	6	8	0	0	E
13	48	F	A	5	4	8	0	0	E
14	63	M	N	4	6	9	15	9	NR
15	58	M	N	5	9	7	2	8	SD
16	53	F	A	4	3	9	0	0	E
17	47	F	N	5	4	8	1	4	SD
18	34	F	A		5	9	0	0	E
19	53	F	N	5	4	9	5	7	NR
20	45	F	N	5	5	8	5	4	SD
21	30	F	A	5	3	8	0	0	E
22	29	F	A	4	5	9	0	0	E
23	49	F	N	5	9	10	0	0	E
24	24	F	A	5	5	9	0	0	E
25	63	F	N	4	19	7	10	7	NR
26	62	F	A	5	8	9	11	9	NR
27	44	F	A	5	3	10	0	0	E
28	38	F	N	4	8	10	1	3	SD
29	38	F	N	5	3	10	0	0	E
Mean/ Total	45	F 24 M 5	A 14 N 14 A/N 1	4.7	5.9	8.7	2.4	3.0	E 16 SD 8 NR 5

*CSM indicates corrugator supercilii muscle; SD, significant decrease; E, elimination; NR, no response. Corrugator supercilii muscle hypertrophy was graded from 1 to 5: 1, inability to frown; 2, minor skin tension lines formed in response to frowning, but vertical frown lines not seen; 3, formation of small vertical frown lines without obvious muscle hypertrophy; 4, multiple deep vertical frown lines with increased muscle size; and 5, deep vertical frown lines which do not relax when patient is not frowning and demonstrate significant visual muscle hypertrophy. Frequency was recorded as number of migraines per month. Intensity was measured on an analog scale of 1 to 10 with 10 being the most severe.

reported no change. Two patients (7%) noted transient unilateral upper eyelid ptosis that lasted 2 weeks for one patient and 3 weeks for the other patient. Both patients were among the group with an improvement in headache. The duration of action of BTXA ranged from 6 to 12 weeks, with an average of 8 weeks' duration. In all patients, discernible muscle function recovery was noted 3 to 4 weeks after recurrence of migraine. Paralysis of the frontalis muscle was not observed in any of these patients.

COMMENTS

Researchers have studied the role of the trigeminal nerve in the pathogenesis of migraine for over



Injection of botulinum toxin type A (BTXA) into the corrugator supercilii muscle. Patient is asked to frown, thus identifying the lateral cutaneous attachments of the muscle into the overlying skin. Injection begins at this site and the needle is advanced medially to the root of the nose. The BTXA is evenly infiltrated along this injection path.

30 years. The predominant theory is that the activation of this nerve results in release of neuropeptides such as substance P, calcitonin gene-related peptide, and neurokinin A.[7,8] These peptides cause neurogenic inflammation.[9-14] What activates the terminal branches of the trigeminal nerve, however, remains unknown. Central sensitization remains the dominant theory.[15] We propose that in a significant proportion of migraineurs, these nerves may be stimulated by the strong contraction of facial animation muscles such as the corrugator supercilii. The supratrochlear and supraorbital nerves pierce the corrugator muscle to reach the cutaneous level. While the main trunk of the supratrochlear nerve passes through the corrugator supercilii muscle, only branches of the supraorbital nerve, rather than the main nerve, traverse in between muscle fibers.

The mechanism of action of BTXA in relieving headaches is not yet fully understood. Botulinum toxin type A inhibits release of acetylcholine at the neuromuscular junction, thereby decreasing muscle tone. Relief of head pain may be due to this mechanism or to the inhibition of exocytosis of neurotransmitters and neurally active substances that play an inflammatory role in the pathogenesis of migraine.[16] Botulinum toxin type A may also have a direct effect on peripheral sensory nerves, although this is unlikely. If central sensitization were the only "trigger" for the initiation of the complex cascade of events that comprise the pathophysiology of migraine, BTXA should not be an effective therapy for migraine, since it is unlikely to act centrally. Aoki and Guyer have reported that only small quantities of inactive BTXA amino acid fragments travel retrograde into the central nervous system.[17,18] Many primary headaches involve activation of the trigeminal nerve branches, resulting in inflammation and release of neuropeptides. This "neurogenic inflammation" comprises part of the migraine pathophysiology along with vasodilatation and neuronal spreading depression as seen on positron emission tomography and single photon emission computed tomography scans.[19] When neurogenic inflammation affects the meninges, it may result in a response producing headache, nausea, photophobia, phonophobia, and other central nervous system symptoms characteristic of migraine. It has been the authors' observation that migraine is provoked by stress or protracted sun exposure, and many patients exhibit significant hypertrophy of corrugator muscles. Also, considering the fact

that many of these patients have tender and nodular muscles, the influence of muscle as a "migraine trigger" by impinged trigeminal sensory nerve branches becomes more compelling. We believe that BTXA, by virtue of paralyzing the offending muscle, eliminates a significant trigger point, hence forestalling migraine. Perhaps the strongest support of this theory is the elimination or reduction of migraine following surgical removal of the forehead muscles.[5,20-22]

These results support the hypothesis that focal injection of BTXA may serve to temporarily eliminate or significantly reduce the pain of migraine. While a large proportion of this group of patients had improvement or complete elimination of headache, other trigger points must exist and may have contributed to some patients not having a complete response. In our study, the practical benefit of injecting only one muscle, bilaterally, with a total of 50 units of BTXA is the reduced expense of the procedure. Other nerves that can be compressed or irritated by a neighboring muscle include the zygomaticotemporal branch of the trigeminal nerve, compressed by the temporalis muscle; and the greater occipital nerve, compressed by the occipitalis muscle. Currently, we are evaluating the efficacy of BTXA in eliminating these additional potential trigger points in patients with migraine.

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