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# The Use of Botulinum Toxin for the Treatment of Chronic Facial Pain

Gary E. Borodic* and Martin A. Acquadro†

**Abstract:** **An open label pilot study was conducted to evaluate efficacy of botulinum toxin injections for the treatment of patients with chronic facial pain seeking tertiary care at a pain clinic. Diagnoses included temporomandibular joint syndrome, postsurgical pain syndromes, essential headache, and idiopathic trigeminal neuralgia. Thirty-three (75%) of 44 patients favorably responded, including 8 of 11 patients with trigeminal neuralgia. The duration of beneficial effect ranged from 2 to 4 months, and all responding patients desired further injections. Complications were mild and included temporary facial asymmetry and weakness secondary to neuromuscular effects of botulinum toxin. Doses ranged from 25 to 75 LD 50 units with Hall strain–derived botulinum toxin type A. A small degree of facial edema during pain or erythema seemed to have predictive value when categorically evaluated against response.**



***Key words:*** *Botulinum type A , BOTOX (Allergan Inc, Irvine, CA), DYSPORT (Ipsen Inc, Milford, MA), NEUROBLOK (Elan Pharmaceuticals, Dublin, Ireland), temporal mandibular joint disease, trigeminal neuralgia, surgical pain.*

Chronic facial pain often presents difficult management problems requiring interdisciplinary consultations and multiple attempts at different therapy modalities. In this report a series of patients with chronic facial pain deemed to be ineffectively controlled with conventional medical and surgical procedures were treated with transcutaneous injection of botulinum type A toxin. The cases were classified into the following categories: (1) idiopathic trigeminal neuralgia, (2) postsurgical chronic pain syndromes, (3) temporomandibular joint syndrome, and (4) chronic essential headaches. Essential headache patients included patients with tension headache or combined episodic tension–migraine headaches. The trigeminal neuralgia patients included those individuals whose medical therapy failed and who did not go on to have a surgical procedure, and those whose medical therapy failed but who later had temporary relief for a variable duration after a surgical procedure, only to have their pain return. Postsurgical pain syndromes included patients with various forms of head and neck surgery with pain persisting for 24 months, and temporomandibular joint syndrome included patients with facial pain, decrease jaw excursions, and trigger points over the temporal mandibular muscle.

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From the *Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, and the †Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Address reprint requests to Gary E. Borodic, MD, 100 Charles River Plaza, 3rd Floor, Boston, MA 02114. E-mail: borodic@aol.com



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Botulinum toxin has been used extensively to treat regional dystonias that are often associated with pain or some form of sensory disturbance. Botulinum toxin injections for the treatment of spasmodic torticollis repeatedly showed efficacy mitigating pain at rates substantially greater than other components of this syndrome.[1,4,10,18] Such observations led to the study of nondystonic pain syndromes, such as myofascial pain and tension headache, which initially produced beneficial results[1] and is currently being studied in larger controlled trials.[15,19] Furthermore, trial injections after skull base surgery further indicated potential efficacy in a small series of patients. Recently, botulinum toxin has been investigated for the treatment of migraine headache,[22] and initial blinded controlled studies have produced some evidence of efficacy.

The long duration of action and general lack of serious systemic effects associated with the use of type A botulinum toxin prompted us to initiate a trial pilot open-labeled study. The described trial targeted the treatment of patients with chronic facial pain for whom conventional therapeutic modalities failed and who were seeking care from a tertiary pain clinic. This open label single site trial involved dosing units conventionally applied for other facial applications, such as essential blepharospasm, hemifacial spasm, and the treatment of myofacial pain.[2,5,8,16,17]

## Material and Methods

Forty-four patients treated at the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary for chronic facial pain were evaluated for possi-

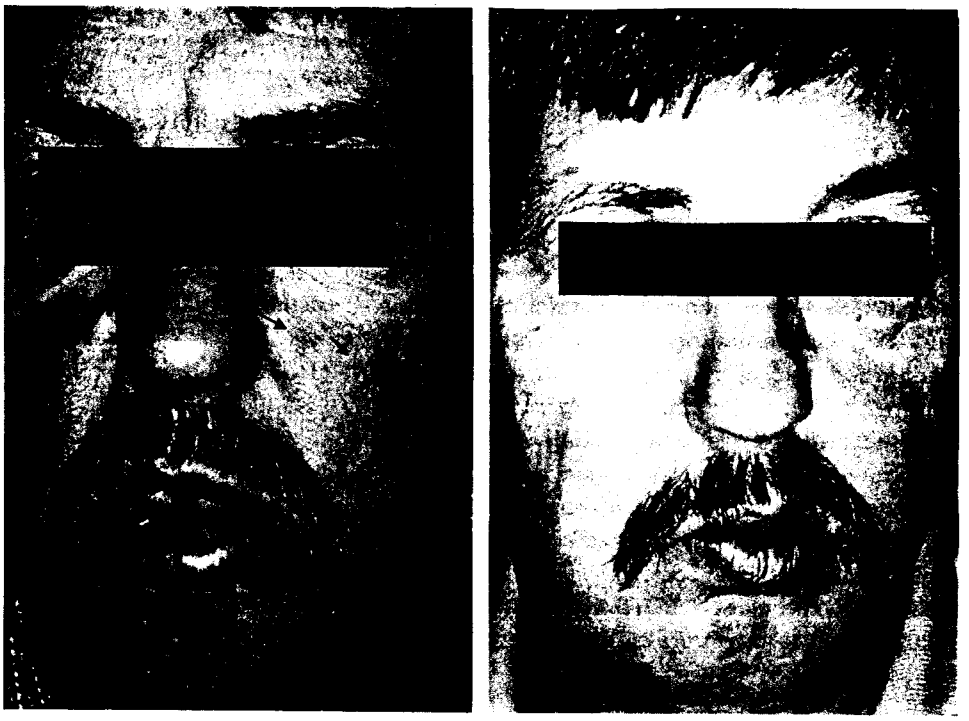

**Figure 1.** Patient with 5-year history of trigeminal neuralgia with pain experienced within the left second division of the trigeminal nerve. During episodes of pain edema and erythema would be noted over the left side of the lower malar face associated with lip edema. These findings would often be present between periods of severe pain. (Right) Note the improvement in lip and malar edema seen 2 weeks after successful injection of botulinum type A toxin for primary pain control.

ble botulinum toxin injections. Each patient was questioned for any past history of neuromuscular disease that would potentially contraindicate the use of botulinum toxin, such as myasthenia gravis.[6] Informed consent was obtained with emphasis on transient attendant risk of weakness and disfigurement produced by localized injections. The study was initiated after institutional internal review board approval.

Criteria for entry into the study were failure of at least 3 medicinal therapies, description of high severity and intensity of pain, ability of the patient to describe a distinct anatomic area over which the pain was experienced, presence of the problem for at least 2 years, and understanding of the informed consent with emphasis on transient facial weakness complication.

Botulinum type A toxin was obtained in a lyophilized form and reconstituted with preservative-free normal saline for injection at a concentration of 5 LD 50 units per 0.1 mL. One LD 50 unit is the dose necessary to kill 50% of the population of 20- to 30-g Swiss–Webster mice. Effort was made to limit initial exposure to a total dose of less than 50 units to avoid weakness.

Injection sites were chosen according to the patient's descriptive and demonstrative anatomic localization of the pain and the avoidance of brow and upper or lower eyelid injections to avoid diffusion of toxin into the orbit, because ptosis and diplopia may result. Sample injection strategy is outlined in Fig 1.

Injections were tailored to the location of the pain and can be generally summarized as follows:

1. Temporomandibular joint pain: temporalis muscle injected in at least 2 locations above the zygomatic arch. No patients were given intraoral injections.
2. Essential headache: injections from glabellar lines over the mid forehead to the temporalis and masseter muscles. The area within 2 cm of the superior orbital rim is important to avoid because ptosis may result from diffusion of the botulinum toxin into the levator palpebrae superioris muscle.
3. Postsurgical pain: botulinum is injected to the region where pain is localized, usually close to the surgical incision sites.
4. Trigeminal neuralgia: multifocal injections are given over the dermatome where pain was experienced.

Injections were given generally 10 mm apart so as to cover the anatomic region in which the facial pain was experienced. The injection depth varied between 1 and 3 mm, except for patients with temporomandibular myofascial muscle pain, in whom a depth of 5 to 10 mm was used to ensure the toxin was injected into the masseter and temporalis muscle on the involved side. Each patient was assessed with computed tomography or magnetic resonance imaging to rule out the presence of structural pathology. Care was taken to examine for the presence of any subtle cutaneous erythematous patches or evidence of facial edema associated with

**Table 1. Stratification of Patient Population by Primary Diagnosis and Response**

| | No. of Patients | No. Responding | Fisher Test |
|---|---|---|---|
| Total treated | 44 | 33 | |
| Temporomandibular joint syndrome | 8 | 6 | NS |
| Essential headache | 12 | 8 | NS |
| Neuralgia-trigeminal | 11 | 8 | NS |
| Postsurgical | 13 | 11 | NS |

Abbreviation: NS, not significant.

**Table 2. Characterization of Facial Pain Based on History**

| | No. of Patients | No. Responding | Fisher Test |
|---|---|---|---|
| Total treated | 44 | 33 (75%) | |
| Neurogenic | 12 | 8 | NS |
| Myofascial pain | 15 | 13 | NS |
| Neurogenic/myofascial | 16 | 12 | NS |
| Inflammatory signs | 33 | 28 | $P < .01$ |
| No inflammatory signs | 12 | 4 | $P < .01$ |

Abbreviation: NS, not significant.

severe pain, because we have noted such a phenomenon is often associated with the aggravation of pain in early cases. Any red discoloration would qualify as an erythematous patch.

Diagnosis was confirmed by at least 2 physicians. An effort was made to characterize each patient's pain as neuropathic, myofascial, or combined neuropathic-myofascial in quality. For the purposes of this study, neuropathic pain was defined as localized over a division of the trigeminal nerve, having a sharp stabbing quality, and an "on-off" temporal quality precipitated or made worse by touch. Such a description would be characteristic of typical trigeminal neuralgia. The term myopathic was used in lieu of nociceptive because the patients in the study had experienced their pain for more than 2 years, the pain involved muscle by careful history and examination, often improved with tactile stimulation, often radiated to other neck, head, and facial areas with or without palpation, was out of proportion to observed or known pathologic condition, and did not fit other descriptions for neuropathic pain. Combined neuropathic and myofascial pain had qualities consistent with both processes.

Patients with temporomandibular joint syndrome presented with localized pain of the muscles of mastication, aggravated with mandibular movement and palpation of muscles.

Chronic essential headache was found in a variety of locations of the head, forehead, periorbital, retroorbital, and zygomatic facial areas. Patients having an evolution of a syndrome type during a period of years received classification and diagnosis at the time of treatment rather than on the basis of symptomatology at the onset of pain.

Patients were followed at 2 and 6 weeks to assess the outcome. Improvement was categorically defined as a perception by the patient of at least 50% reduction in frequency and/or intensity of pain, reduction in use of any analgesic medication, or expressed desire for further injections, with the patient acknowledging definite benefit after the first injection cycle. A cycle was defined as the total dose given within a 2-week period, with dose not to exceed 100 IU. The patients were directly questioned several weeks after injection, and responses were categorically assigned into either responder or nonresponder status by the treating physician.

Data were also treated categorically with respect to outcome and syndrome-outcome predictors and analyzed with a 2-tailed chi-square test.

## Results

The nosological diagnoses for the 44 patients studied are given in Table 1.

The 12 men and 32 women had an average age of 54.2 years (range, 34 to 89 years). The average duration of the chronic facial pain was 7.5 years (range, 1 to 37 years). The average duration of follow-up was 7.65 months (range, 4 to 20 months), and the average number of injection cycles was 2.12 injections (range, 1 to 4 injections). One patient was lost to follow-up. Eleven nonresponding patients never received more than 2 injection cycles.

Total dose received per injection cycle ranged between 25 and 75 IU (average, 48.3 units), with a maximum of 7.5 units per percutaneous puncture. In each diagnostic category there was a substantial number of responders, including patients with trigeminal neuralgia (8 of 11). The responses varied from partial relief of pain (>50% improvement of pain as stated by the patient) to complete pain relief. No patient wished further therapy if he/she believed there was not at least a greater than 50% improvement in pain and discomfort. Reduction in other medication use was noted in 16 of the 33 responding patients. No patient reduced medication unless there was a 50% improvement in pain. The duration of effect varied from 5 to 12 weeks, consistent with the known duration of action of botulinum toxin for other indications. No diagnostic category showed any significant difference in response rates. In characterizing the patients as neuropathic, myopathic, and combined, there were no significant differences in response rates (Table 2).

**Table 3. Migraine History in Remote or Recent Past**

| | No. of Patients | No. Responding | Fisher Test |
|---|---|---|---|
| Total treated | 44 | 33 | |
| Migraine history | 11 | 8 | NS |
| No migraine history | 33 | 25 | NS |

Note. Migraine is defined as severe throbbing headaches with nausea or vomiting associated with photophobia or worsening with physical activity.

In patients diagnosed with trigeminal neuralgia, the average duration of disease was 10 years (range, 3 to 37 years), and all patients failed conventional medical therapy with carbamazepine and phenytoin. Three patients underwent radiofrequency ablation of the trigeminal nerve, 4 patients underwent chemical ablation (phenol, glycerol, or alcohol), and 1 patient underwent craniotomy with microvascular decompression. Each patient, except 1 patient with a chronic history of trigeminal neuralgia, on careful questioning and physical examination had episodes of facial discomfort associated with mild edema (Fig 1). No patient with multiple sclerosis was included in this study. One nonresponding patient suffered a brainstem stroke, which was thought to cause the syndrome. Doses of botulinum toxin A ranged from 30 to 50 U in this subpopulation.

Postoperative pain occurred after the following surgical procedures: enucleation, orbitectomy, endoscopic and traditional sinus procedures, temporomandibular joint reconstruction, large facial plastic reconstruction after cancerous tongue resections, parotid tumor resection, transoccipital craniotomy for the resection of acoustic neuroma or other skull base tumors, and dental extraction. No patient was treated within 6 months of a procedure, and all patients experienced sustained pain for at least 6 months.

The historical incidence of migraine headache was not significantly different comparing responding and nonresponding patients (Table 3). Among the 12 patients with chronic essential headache, 5 stated they had 1 to 3 monthly episodes of migraine. All 5 patients were among the 8 patients responding to botulinum injections. All the patients with essential headaches described some form of chronic daily headache pain characterized as continuous with frequent variation in intensity during the day. All essential headache patients, including migraine headache patients, on careful history and physical examination were found to have some degree of myofascial pain of at least 1 of the locations involving the shoulder, neck, head, facial, or masticatory muscles. No headache patients had a current known dental problem, except for some instances of masticatory muscle tenderness. No patients had cluster headache or other type of secondary headache.

Eight patients had temporomandibular joint syndrome, and 6 responded. One patient was in the early postoperative period after temporomandibular joint surgery.

Complications included transient facial asymmetry during dynamic movements, which was found troublesome in 5 of 29 patients. No dysphagia or ptosis occurred during treatment, and no patient experienced systemic side effects.

Slight erythematous discoloration or edema of the painful areas of skin were seen in 32 (72%) of 44 patients and were predictive of clinical response (Table 2).

## Discussion

Chronic facial pain can be a difficult management problem. In this study 4 types of chronic facial pain were identified and effectively treated with injection of botulinum toxin into involved areas, achieving total or partial relief of symptoms without the use of further systemic medications carrying notable side effects. The long duration of action of botulinum toxin and highly limited systemic complications associated with its use are attractive pharmacologic attributes of this therapy for the management of these chronic pain syndromes. Complications are limited to possible temporary regional weakness over the injection sites and asymmetry of facial expression during dynamic facial movements. Although occasionally annoying, patients generally found these complications tolerable, considering the gravity of the affliction for which treatment was being sought, particularly for trigeminal neuralgia.

Facial pains result from a variety of common etiologies or are associated with a diversity of disease states; however, all the precise mechanisms responsible for the pains are more often not completely understood or even known. Interestingly, we have noted facial pains to be frequently associated with varying degrees and manifestations of inflammatory responses. Indeed, the inflammatory response, subtle or overt, may be a significant mechanistic component of pain or discomfort and may even become the principal perpetuating factor.

The sensory innervation of the face is predominantly supplied by the trigeminal nerve. The trigeminal sensory complex describes the multiple connections and communications between the trigeminal nucleus and other cranial nerve nuclei, reticular activating system, autonomic nervous system, thalamus, and multiple other ascending and descending nervous system tracts that facilitate or suppress excitatory and inhibitory pathways from above and below the brainstem area.[20] Furthermore, the trigeminal sensory complex dips down into the dorsal horn of the spinal cord to a level of approximately C4 as a continuum. This helps to explain the convergence and referral patterns so often seen in facial pain.

The basic science and clinical pain literature has established the great importance of discovery and

recognition of the mechanisms causing pain. Indeed, a number of disease etiologies can share common mechanisms of pain. It is this fundamental importance of understanding the mechanisms of pain that should dictate future pain treatments. Knowing the etiology may often help prevent, alter, or cure a disease process, but the mechanisms of the pain may be independent of the etiology, known or unknown, or whether the etiology can be corrected.[13,25,26]

Another fundamental consideration in the complexities of facial, head, neck, and oral pains is the degree that neurogenic inflammation may play. Peripheral neurogenic inflammation may well be involved in fundamental alterations of the sensory nervous system, in the periphery as well as centrally, and an understanding of the mediators, receptors, transduction, conduction, transmission, and phosphorylative and transcriptional changes of the nervous system may require accounting.[13,25,26] Indeed, the goal of pain treatment frequently involves pharmacologic intervention somewhere in the sensory system. Botulinum toxin may well be a safe regional, nonsystemic, long-acting agent altering the chemical environment of peripheral neurogenic inflammation. Diminishing peripheral sensory nerve chemical stimuli may contribute to a decreased peripheral and/or central nervous system responsiveness and peripheral and/or central nervous system change.[25]

In the context of this study the classification of facial pain into essential headaches deserves explanation. The patients admitted to the group were categorized and referred as patients with chronic pain. Virtually all patients in the essential headache group had some form of combination type headache syndrome when analyzed during an extended period (eg, migraine-tension headache, migraine-myofascial pain). Patients with episodic migraine headaches were not included in this study. Because of multiple symptom components at different times, a more global term, essential headache, was applied to this group.

We have applied botulinum toxin to a number of patients with a variety of facial pains involving a number of divergent etiologies. However, the common presentation correlating with the greatest likelihood for a positive response in diminishing pain and discomfort was swelling, edema, and/or the sensation of fullness overlying the area of facial discomfort; redness, erythema, and/or feeling of increased warmth; and some comfort with tactile facial stimulation by hand placement, with or without a cool or warm face cloth. Systematic medications have produced variable responses for these syndromes, and such responses did not seem to occur with the botulinum toxin result. No evidence of adverse interactions between systemic analgesic medication and botulinum toxin injections has been established.

Botulinum toxin has been noted to effectively reduce or eliminate pain or aberrations in sensory experience associated with a number of diseases including adult onset spasmodic torticollis, bruxism, tension headache, myofascial pain, migraine, dystonic limb spasms, hemifacial contracture after seventh cranial nerve injury, and cervical spasms after skull base surgery. Furthermore, improvement in photophobia[5] has been consistently noted in patients with essential blepharospasm and Meige syndrome. Such observations suggest that there is an intrinsic effect on the sensory nervous system, either through direct binding on receptors or indirectly on modulating tissues such as endothelium or mast cells.

A most remarkable clinical category in this series included patients with trigeminal neuralgia. This syndrome is difficult to treat and has enormous negative impact on quality of life. The literature is deficient of double-blind placebo control trials involving the use of many of the accepted first line systemic medications, such as carbamazepine (Tegretol; Geighy Chemical Corp, Ardsley, NY), phenytoin (Dilantin; Parke, Davis & Co Corp, Detroit, MI), gabapentin (Neurontin; Warner-Lambert Co, Morris Plains, NJ), tricyclic antidepressants, and baclofen.[14] The sustained efficacy of phenol, glycerol, or alcohol injections[14] and thermocoagulation[14,24,27] are not well documented. Dysesthesia and corneal numbness represent problematic eye complications associated with both thermocoagulation and injections. Microvascular decompression has been widely used for treatment of refractory cases, with benefit reported at high percentages in a recently reported series.[3] However, attendant serious complications associated with intracranial surgery limits the application of this technique.

Aberrant blood vessels providing an irritating and scarring nidus for the intracranial portion of the trigeminal nerve have been the proposed cause leading to pain and the surgical lesion for therapeutic microvascular decompression.[3] Observations in primates have shown that antidromic stimulation of the trigeminal nerve has been associated with mast cell degranulation and possible attendant release of inflammatory autocoids.[11,12] Perhaps an orthodromic-antidromic nexus could be playing a distinct role in trigeminal nerve dysfunction. The presence of edema and erythema may be the physical signs of such a process. Findings of cutaneous erythema have been well known to occur in myofascial pain syndromes inclusive of tension headache, temporomandibular muscle and joint disease, and postsurgical incisional pain syndromes.

Botulinum toxin injections would offer some distinct advantages over existing therapies with respect to safety and efficacy. Weakness induced by botulinum toxin is transient, usually resolving within several weeks. Dosing levels per injection reported in this study are below levels used for conditions in which immunologic resistance has been commonly reported. The dose range varied from 25 to 75 U injected in 1 to 4 locations, whereas doses ranging from 100 to 300 U have been used for spasmodic torticollis, the indication most

commonly associated with antibody formation[9] by using Hall strain–derived type A botulinum toxin preparations. The increase in specific activity in recent toxin preparations has also appeared to mitigate this complication in animal studies.

The results in temporomandibular joint syndromes have been consistent with those of other investigators,[15] indicating a consistent usefulness for this indication at different centers. However, application for tension headache has been less consistent,[19] considering lack of efficacy in 1 controlled trial. Patient selection and syndrome component stratification with outcome concordance analysis in clinical studies may be useful in qualifying appropriate patients for treatment. With respect to outcome predictors, the presence of facial erythema and/or edema appeared to have positive concordance to outcome.

Despite efficacy in the short term, there have been no long-term studies or reports on the use of botulinum toxin for chronic pain disorders. The closest long-term experience comes from patients with adult onset spasmodic torticollis, a condition that has been effectively treated for more than 16 years. Over time, reduction in analgesic effect for this condition has been associated with the development of immunologic resistance, and there are patients who seem to derive little benefit without exhibiting neutralizing antibodies to the neuromuscular effect of botulinum toxin. The sustainable effect of botulinum toxin for any primary pain syndrome still needs further analysis both in quality of efficacy studies and in full scientific analysis of dose response relationships. In a double-blinded study evaluating the treatment of migraine, lower doses (25 IU) were effective for the treatment of migraine whereas higher doses (75 IU) showed less efficacy.[22] Relative to our past experience, botulinum dose response often achieves a plateau as dosing increases but efficacy reversals are not seen. Botulinum toxin generally is efficacious at lower doses to treat pain associated with spasmodic torticollis over other syndrome components. In the application for facial pain, lower doses are preferred initially so that facial weakness may be avoided. If a negative response is encountered, dosing is increased to a point of inducing facial weakness, which defines the dosing endpoint.

Pain relief associated with botulinum toxin injections involves nonneuromuscular bioeffects over a diffusion area, altering afferent sensory innervation.

The generic mechanism of action by which botulinum toxin reduces pain in the syndromes under discussion seems to relate to sensory nerve adaptation, possibly resulting from impaired secretion of neuro-effectors from mast cells, sensory nerve tissue, or blood vessel endothelium.[7] We have repeatedly observed blockage of sympathetically mediated urticaria (exertional cholinergic urticaria) within the diffusion-denervation field of botulinum toxin on the human face in patients with this syndrome. Given this reproducible response to botulinum toxin on multiple patients, it appears that a nonneuromuscular effect is operational, which blocks edema (urticaria), erythema, sensory discomfort, and even heat release. The syndrome of cholinergic urticaria is thought to involve mast cell degranulation with release of neuro-effecting substances such as histamine and possibly other sensory neuro-effectors important in the generation of sensory disturbances and neurogenic inflammation.[21,23] Reduction of photophobia in patients with benign essential blepharospasm after botulinum toxin injection further supports the neurosensory effect of injectable botulinum toxin. Such observations support anti-inflammatory properties of botulinum toxin. Myofascial pain, temporomandibular joint syndrome, migraine, tension headache, and postoperative pain have pathogenesis involving inflammatory phenomena. The patients with trigeminal neuralgia responding also showed signs of inflammatory phenomena (erythema and edema). Collectively, there is mounting evidence that an inflammatory mechanism is operative.

This study must be viewed as a pilot experience, because an open-labeled, non-controlled design was implemented. Clearly, controlled study designs will be needed to confirm findings. A linear evaluation of response of subjective endpoints in varied domains could add to the statistical data. Here, the categorical analysis is made by the clinician and does incorporate physician impression into the outcome. This study design, although limited in scientific dependability, is reasonable for initial analysis.

In summary, patients with severe chronic facial pain can respond to botulinum type A injections, which may provide a useful nonsurgical tool for management of difficult cases. However, temporary facial weakness and temporarily impaired facial expression are the most common side effects. Facial weakness was most noticeable when the inner malar region of the face was targeted. Clearly, further study of efficacy by using double-blinded design will be needed to advance these observations.

## References

1. Acquadro M, Borodic GE: Treatment of myofascial pain with botulinum toxin. Anesthesiology 80:705-706, 1994

2. Anderson RL, Patel BC, Holds JB, Jordan DR: Blepharospasm past, present and future. Ophthal Plast Reconstr Surg 14:305–317, 1998

3. Barker F, Jennetta P, Bissonette P, Larkins MV, Jho HD: The long term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 334:1077-1083, 1996

4. Boghen D, Flanders M: Effectiveness of botulinum toxin in the treatment of spasmodic torticollis. Eur Neurol 33: 199-203, 1993

5. Borodic GE: Photophobia, an unrecognized component of the essential blepharospasm syndrome. Association of Ophthalmic Plastic and Reconstructive Surgery, Chicago, IL, November 7, 1996

6. Borodic GE: Myasthenia gravis after botulinum toxin. Lancet 352:1832, 1998

7. Borodic GE, Acquadro M, Johnson EA: Botulinum toxin therapy for pain and inflammatory disorders: Mechanisms and therapeutic effects. Expert Opin Investig Drugs 10:1531-1544, 2001

8. Borodic GE, Cozzolino D: Blepharospasm and its treatment with emphasis on the use of botulinum A toxin. Plast Reconstr Surg 83:546-553, 1989

9. Borodic GE, Johnson EA, Goodnough M, Schantz E: Botulinum toxin, immunologic resistance, and problems with available materials. Neurology 46:26-29, 1996

10. Borodic GE, Mills L, Joseph M: Botulinum A toxin for adult onset spasmodic torticollis. Plast Reconstr Surg 87: 285-289, 1991

11. Buzzi MG, Bonamini M, Moskowitz MA: Neurogenic model for migraine. Cephalalgia 15:277-289, 1995

12. Buzzi MG, Dimitriadou V, Theoharides TC, Moskowitz MA: 5-Hydroxytrytamine receptor agonists for the abortive treatment of vascular headaches block mast cell, endothelial and platelet activiation within the rat dura mater after trigeminal stimulation. Brain Res 528:127, 1992

13. Costigan M, Woolf CJ: Pain: Molecular mechanisms. J Pain 1(suppl 1):35–44, 2000

14. Fields HL: Treatment of trigeminal neuralgia. N Engl J Med 334:1125-1126, 1996

15. Freund B, Schwartz M, Symington JM: Botulinum toxin: New treatment for temporomandibular disorders. Br J Oral Maxillofac Surg 38:466-471, 2000

16. Johnson EA: Clostridial toxins as therapeutic agents: Benefits of nature's most toxic proteins. Annu Rev Microbiol 53:551-575, 1999

17. Mauriello JA, Keswani R, Franklin M: Long term enhancement of botulinum toxin injections by upper eyelid surgery in 14 patients with facial dyskinesia. Arch Otolaryngol Head Neck Surg 125:627-631, 1999

18. Poewe W, Wissel J: Use of botulinum toxin in the treatment of cervical dystonia. Bailleres Clin Neurol 2:179-185, 1993

19. Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R: Treatment of tension-type headache with botulinum toxin type A: A double-blind, placebo-controlled study. Headache 40:300-305, 2000

20. Sessle BJ: Neural mechanisms of oral and facial pain. Otolaryngol Clin North Am 22:1059-1072, 1989

21. Sheffer AL, Soter NA, McFadden ER Jr, Austen KF: Exercise-induced anaphylaxis: A distinct form of physical allergy. J Allergy Clin Immunol 71:311-316, 1983

22. Silberstein S, Mathew N, Saper J, Jenkins S: Botulinum toxin type A as a migraine preventive treatment. Headache 40:445-450, 2000

23. Soter NA, Wasserman SI, Austen KF, McFadden ER Jr: Release of mast-cell mediators and alterations in lung function in patients with cholinergic urticaria. N Engl J Med 302:604-608, 1980

24. Wilkinson HA: Trigeminal nerve peripheral branch phenol/glycerol injections for tic douloureux. J Neurosurg 90:828-832, 1999

25. Woolf CJ, Costigan M: Transcriptional and posttranslational plasticity and the generation of inflammatory pain. Proc Natl Acad Sci 96:7723-7730, 1999

26. Woolf CJ, Mannion RJ: Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet 353: 1959-1964, 1999

27. Yoon KB, Wiles JR, Miles JB, Nurmikko TJ: Long term outcome of percutaneous thermocoagulation for trigeminal neuralgia. Anesthesia 54:803-808, 1999