Essential Tremor (ET)

# Botulinum toxin treatment in tremors

**Joseph Jankovic, MD**

Since its introduction in the 1980s, botulinum toxin (BTX) has revolutionized the treatment of various disorders associated with muscular spasms and involuntary movements, including tremors [Jankovic, 2004a]. Long-term followup of patients treated with repeat BTX injections for more than a dozen years show this treatment is effective and safe.[Mejia and Jankovic, 2005].

Almost all types of tremor have been reported to benefit from BTX injections. Initially used in the treatment of dystonia (involuntary muscle contractions), BTX was observed to improve not only the abnormal movement and posturing but also the accompanying dystonic tremor. This observation stimulated interest in BTX as a treatment modality for different types of tremors.

## BTX treatment of limb tremor

In their initial pilot study, Jankovic and Schwartz [1991] found 67% of patients with disabling head-neck (42 patients) and hand (10 patients) tremor had moderate to marked functional improvement and a reduction in the amplitude of their tremor. In a subsequent study, Trosch and Pullman [1994] treated 12 patients with Parkinson's disease (PD) and 14 with ET for their hand tremor. Six weeks after the injection, five patients each with PD and ET reported improvement of 3 or greater on a 4-point scale. The only adverse reaction was weakness of digit extension, noted on examination in all patients, but this did not result in functional impairment.

Jankovic et al [1996] conducted the first double-blinded, placebo-controlled study in patients with ET hand tremor. Twenty-five patients with 2+ to 4+ tremor severity score were randomized to receive placebo (12 patients) or 50 U of BTX (13 patients) injections into the wrist flexors and extensors. In addition to a statistically significant improvement in a tremor score in the BTX-treated group as compared to the group treated with a placebo, 75% of BTX-treated patients vs. 27% of placebo-treated patients reported significant improvement. This was also confirmed by postural accelerometry, amplitude of tremor. Adverse reaction was mild finger weakness in about half of the BTX patients at week four and persisted in some to week 16, but no patient reported interference with daily functions or activities.

Brin et al [2001] conducted a similar placebo-controlled trial involving 133 patients with hand ET recruited from 10 centers in North America. The patients were randomized to one of three treatment groups: low dose BTX, high dose BTX, and placebo. They were then followed up for 16 weeks. The postural tremor was rated 2 on a 0–4 scale. For the low-dose group, 15 U were injected into flexor carpi radialis and ulnaris and 10 U into extensor carpi radialis and ulnaris. For the high-dose group, 30 U were injected into the flexors and 20 U into the extensors. Members of the control group were injected with the comparable volume containing albumin and sodium chloride solution.

Based on tremor rating, both low and high BTX dose groups improved significantly by physician and subjective ratings, with peak effect at six to 16 weeks. Hand weakness was the most common side effect; 30 percent of the low-dose group and 70 percent of the high-dose group complained of decreased grip strength. Other adverse reactions included rash, pain, stiffness, cramping, hematoma (blood clot), and paresthesias (burning or prickling sensations). Since these initial studies, we have significantly modified our technique to focus chiefly on the flexor rather than extensor forearm muscles. As a result, hand weakness is now a rare adverse effect, and even if it does occur, it usually is not troublesome and resolves spontaneously within days or weeks.

Based on our long-term experience, for refractory tremor, we can conclude that BTX treatment is usually effective in reducing the tremor amplitude and improving function and this treatment strategy should be considered before any surgical intervention.

## BTX treatment in head tremor

Head tremor, usually due to essential tremor, generally does not respond well to medications such as propranolol and primidone [Jankovic, 2002].

Intractable head tremor, therefore, is particularly suited for treatment with BTX injections. Besides ET, head-neck tremor also presents in up to 68% of patients with cervical dystonia (CD) [Pal et al, 2000]. Many studies

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have shown that BTX treatment not only improves CD, but also ameliorates associated head tremor in the majority of CD patients [Jankovic, 2004b].

Pahwa et al [1995] conducted a double-blind, placebo-controlled study of BTX-A treatment in 10 ET patients with intractable head tremor. Each subject received normal saline as placebo or BTX injection three months apart. BTX was injected into each ternocleidomastoid muscle at 40 U and splenius capitis at 60 U under EMG guidance. Rating by "blinded" examiners showed that 50% had moderate to marked improvement with BTX as compared to only 10% improvement in patients who received placebo. Subjective moderate to marked improvement also occurred in 50% of patients treated with BTX as compared to 30% in those who received placebo.

There was no statistically significant difference between the two groups, however, when the tremor was measured by accelerometry. Side effects were again transient and mild, mainly neck weakness, swallowing difficulty, and headache.

Wissel et al [1997] assessed 43 patients with head tremor: 29 suffered from tremulous CD and 14 had ET head tremor without dystonia. Average BTX-A (Dysport®) dosages were 500 U (range 320 to 720 U) in CD and 400 U (range 160 to 560 U) in ET. After two to three weeks, subjective improvements occurred in 100% of ET and 90% of CD patients. Side effects were mild and transient, including local pain, neck weakness, and dysphagia (difficulty swallowing) in 40% of ET and 39% of CD patients.

In summary, essentially all patients with head tremor of various etiologies (ET, CD, or cerebellar-rubral lesions) seem to benefit from BTX injections. According to different studies, at least half of the patients improve on objective examinations or measurements, while subjective improvement percentages can be even more robust.

Response typically occurs a week after the injection and may last for eight to 12 weeks. Common side effects are mostly mild and transient, including neck weakness, swallowing problems, and local pain.

## BTX treatment in voice tremor

Spasmodic dysphonia (SD) had long been successfully treated with EMG-guided injections of BTX [Jankovic, 2004a]. The response of BTX injection on essential voice tremor (EVT), however, has not been thoroughly studied until recently. EVT is caused by oscillation of the vocalis muscle complex or posterior pharyngeal muscles with frequency about 5 to 7 Hz, most noticeable during sustained vowels. EMG recordings have shown that the intrinsic laryngeal muscles, specifically thyroarytenoid, are the most frequently involved. While the voice of SD is characterized by a strained, choked, strangled, and abrupt character (adductor type) or breathy, whispering voice (abductor type), EVT is characterized by pitch breaks and vocal arrests with excessive or interrupted glottal airflow. Approximately 25% of patients with ET have EVT. The mechanism by which EVT is reduced with BTX injections is not completely clear.

Hertegard et al [200] studied BTX injections in 15 patients with EVT. All patients were injected into thyroarytenoid muscles with additional cricothyroid or thyrohyoid muscles in some patients. Ten patients reported subjective improvement one month after the injection. There were also significant improvements when the voice was tested by perceptual evaluations of recordings of patients' connected speech and sustained vowels on the digital audiotapes rated by two phoniatricians.

This evaluation showed a significant decrease in voice tremor during connected speech. Twelve of 15 patients had a temporarily breathy and weak voice for one to two weeks. Three patients had hoarseness lasting up to four weeks. The authors concluded that the treatment was successful in 50% to 65% of patients depending on the method of evaluation. These results were confirmed by other investigators [Warrick et al, 2000].

In summary, about 30% to 50% of EVT patients improve based on objective acoustic analysis, and 65% to 80% of patients improved by subjective assessments. The objective response rates in patients with EVT are not as robust as those in SD. This is probably due to the fact that different factors in laryngeal, respiratory, and orofacial systems contribute to the generation of EVT. The beneficial effect of BTX injection is limited to the effect on the thyroarytenoid muscle, the most frequently injected muscle. The side effects are mostly mild and temporarily include hoarseness, breathiness, and weak voice. The various studies suggest that BTX injection is an ideal therapeutic option for patients with EVT who usually fail to obtain satisfactory response to oral medical treatment.

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