

Long-Term Botulinum Toxin Treatment of Cranial Dystonia

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Abstract

We report the results of an open trial of botulinum toxin (Botox) in the treatment of 46 patients with cranial dystonia (38 patients with blepharospasm and 8 patients with Meige syndrome). The average age of the patients was 55,8 years, and duration of symptoms was 10,6 years. The blepharospasm involuntary movement (BIM) scale was used to assess clinical severity at baseline before BoNT/A injections and at two follow up visits after 6 and 12 weeks covering one BoNT/A treatment period with maximum effect size at the first follow up. The average latency from injection to response was 6,8 days, and the average duration of maximum improvement was 10,5 weeks. Local complications, lasting an average of 20,6 days noted in three patients, consisting of ptosis. Botulinum toxin treatment led to a significant improvement of clinical scale assessed with the blepharospasm involuntary scale (BIM). The results of this study indicate, that botulinum toxin injection is safe and effective for the long-term management of focal cranial dystonia.

Keywords: *blepharospasm, Meige syndrome, botulinum toxin, blepharospasm involuntary movement scale*

Blepharospasm, repetitive involuntary sustained contraction of orbicular oculi, is one of the most frequent types of idiopathic adult onset focal dystonia. As a result of increased publicity and general awareness of this disabling condition, more and more patients are being recognised throughout the world. Several open label and double blind studies have shown the efficacy of botulinum toxin treatment on this condition. In placebo controlled studies, BoNT/A provided efficient reduction of the increased muscle tone in dystonia. (1-2). Jankovic et al also showed long term clinical efficacy of BoNT/A injections over at least five treatment sessions in patients with blepharospasm and cervical dystonia. (3). This study was performed to assess the effects of botulinum toxin treatment on cranial dystonia with the blepharospasm involuntary movement (BIM) scale, and define which subgroups of patients (blepharospasm and Meige syndrome) are likely to gain the greatest benefit.

Patients and Methods

As clinical experience had shown that patients just starting on BoNT/A often report an initial dramatic treatment effect compared with follow up injection, only

patients with long term BoNT/A treatment were selected to avoid possible confounding of our results.

46 patients (31 women and 15 men) with cranial dystonia (38 patients with blepharospasm and 8 patients with Meige syndrome) were studied after we obtained informed consent. Their diagnosis had been established in accordance with common diagnostic criteria. (4). Their mean age at onset was 55,8 (range 26-84) years and the mean duration of symptoms was 10,6 years. . Dosage and injection sites of BoNT/A were individualized according to the distribution and degree of dystonic muscle activity. Botox (Allergan Inc, Irvine, CA, USA) was applied in 34 patients and 12 patients received Dysport (Speywood Biopharm Ltd, Wrexham, UK;)

In each patients, the disease severity was assessed by the blepharospasm involuntary movement (BIM) scale at three time point covering one BoNT/A treatment period: first at the baseline assessment before the BoNT/A injection and at two follow up visits reflecting the presumed time of the maximal BoNT/A effect in the first (interval from baseline to first follow up visit 5,9weeks) and the end of the BoNT/A treatment period in the second visit (interval from first to second follow up visit 6,2 weeks). As additional sociodemographic data, after

age and sex, the individual marital (unmarried, married, divorce) and employment status (employed, unemployed/ retired) were surveyed at the baseline examination. All patients were examined by the same neurologist (M.S). We used the following scale according to the scale used by Fahn to rate cranial dystonia. (Score 1 point for each positive answer unless directed otherwise).

Location of involuntary movements

Upper face: 1.Frontalis or corrugator, 2.Orbicularis oculi, 3.Nasal muscles, 4.Zygomatic muscles.

Lower face: 5.Pursing of lips, 6.Retraction of lips, 7.Corner of mouth pulled sideways (risoris), 8.Buccinator (sucking in of cheeks), 9.Puffing out cheeks, 10.Mentalis, 11.Platysm.

When present: 12.At rest, 13.Only with action (e.g. speaking)

Influencing factors: (worse=+1, no change=0, better=-1; if no information NI), 14.In sulight, 15.At movies, 16.Watching television, 17.Walking, 18.Talking, 19.Writing, 20.Reading, 21.Sewing, 22.Card playing, 23.Working, 24.Listening, 25.Singing, 26.Yawning, 27.Wearing regular eyeglasses, 28.Wearing sunglasses, 29. Anger.

Frequency of Involuntary movement 30 (at baseline).
Movement constantly present at rest >75% of the time (+5)
Movement present at rest 51-75% of waking time (+4)
Movements present at rest 26-50% of waking time (+3)
Movement present at rest 10-25% of waking time (+2)
Movement present at rest <10% of walking time (+1)

Severity of Involuntary Movements (select the maximum point from among the chooses) 31.Upper face: increased blinking of eyelids (+1) Closure of eyelids (+2) Forceful closure of eyelids (+3) Severe, forceful closure of eyelids (+4) 32. Mouth (excluding jaw): Mild forcefulness (+1) Moderate forcefulness (+2) Severe forcefulness (+3)

All analyses were performed with the superior performance software SPSS version 10,0 for Windows (SPSS Inc, UK Ltd, Surrey, England)

Patients with blepharospasm had a significantly higher mean age than those with Meige syndrome, $p<0,01$; ANOVA, whereas there were no inter-group differences for disease duration and duration of BoNT/A treatment before the study. In the blepharospasm group, the disease severity assessed with the involuntary movement scale was significantly higher in patients with Meige syndrome ($p<0,01$, unpaired t test). BoNT/A treatment led to a significant improvement of clinical severity scale assessed at the first follow up visit in both

groups, whereas no differences between the baseline and the second follow up assessment could be found (Tab.1, paired t test). Also no differences between improvements of clinical severity could be found. The blepharospasm group had a significantly higher number of employed than unemployed or retired subjects than the Meige syndrome cohort ($p<0,05$). However, no differences were found for sex and marital status.

Many patients were severely disabled before treatment. Approximately two-thirds of patients were rendered functionally blind to the extent that they were judged to require surgery or botulinum toxin injections to restore vision. Many had to give up work, or could not leave the house alone because they were "blind". Improvement appeared from 4 days to 2 week after injection, and reached its peak from 10 days to 3 weeks. The duration of improvement measured from its onset until the first evidence of deterioration ranged from 8 to 15 weeks. Doses for a single treatment of both eyes ranged from 0,4-2ng of neurotoxin. Side effects are described on Tab.2.

Discussion

Blepharospasm is a focal dystonia, which appears mainly in women, usually in six decade (5). Blepharospasm very often was associated with dystonia elsewhere, principally involving the cranial -cervical area (6). Oromandibular dystonia is the commonest association (Meige syndrome)(7). Most cases of cranial dystonia have no other identifiable disease.

Many drugs have been claimed to relieve muscle spasm, but there is not consistent pharmacological response (8-10). Anticholinergic drugs give probably the best chance of benefit, (11-12), but side effects are common and the response is inconsistent. Different surgical approaches were tried to relive blepharospasm. Bilateral avulsion of facial nerves was the most successful, (13) producing initial improvement in more than 90% of the patients. Unfortunately recurrences were frequent (75%), occurring on average one year after surgery, although then not as disabling as the original illness. Muscle stripping of orbicularis oculi was initially successful in only 25% of patients so treated (14). Other surgical approaches such as alcohol injections or thermolytic lesions of facial nerves (15) produced only temporary benefit.

Injection of botulinum toxin type A into orbicularis oculi and lower face muscles, for cranial dystonia is the most effective treatment. Botulinum neurotoxin binds to peripheral motor nerve terminals and inhibits the release of acetylcholine. (16). Side effects are not common and usually local and transient.

In this open labelled prospective study, we assessed changes in two cohorts of patients with either blepharospasm or Meige syndrome over a 12week

BoNT/A treatment cycle. In both of over study groups limitations of physical and social functions was found. Meige syndrome cohort seemed to experience a higher degree of disability, than patients with blepharospasm, which was expressed by blepharospasm disability scale. However, the higher mean age of patients with blepharospasm has to keep in mind while interpreting these results.

Our data demonstrate a significant temporary improvement in clinical scale (BIM) in both types of focal dystonia after BoNT/A treatment. Side effects in our trial including partial ptosis, facial weakness, were most likely the result of using a relatively high dose of toxin. Nevertheless botulinum toxin injections are so far the best therapeutic measure that can be offered to patients with disabling cranial dystonia.

cranial dystonia (n=46)	age (y)	sex	disease duration (y)	BoNT/A duration (y)	Baseline	First follow up	Second follow up
					BIM scale	BIM scale	BIM scale
blefarospasm (n=38)	68,7*	10M/28F	6,8	3,6	7,4**	4,7**†	6,1**
Meige syndrome (n=8)	61,4	5M/3F	10,6	3,9	12,6**	9,4**††	10,8**

Tab.1 % of Georgian Pharmaceutical market

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Длительное лечение краниальной дистонии ботулиновым ТОКСИНОМ

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Р Е З Ю М Е

Приводятся результаты проспективного исследования лечения ботулиновым токсином 46 больных краниальной дистонией (38 пациентов с блефароспазмом и 8 - "Meige" синдромом). Средний возраст пациентов составлял 55,8 лет, продолжительность симптомов болезни -10,6 лет. Для оценки клинической тяжести использована шкала произвольных движений блефароспазма (ВМ) до инъекции ботулинового токсина и затем 2 раза: через 6 и 12 недель после лечения с учетом максимальной эффективности на 6 неделе после инъекций. Средний период первых положительных клинических проявлений составлял 6-8 дней, а средний период максимальной клинической эффективности - 10,5 недель. Выявленные локальные побочные явления в виде птоза отмечались у трех пациентов в течение 20 дней. На фоне лечения ботулиновым токсином типа А, улучшились показатели клинической шкалы. Результаты исследования указывают, что инъекции ботулинового токсина являются максимально безопасными и эффективными для длительного лечения фокальных краниальных дистоний.

Ключевые слова: *краниальная дистония, ботулиновый токсин типа А, шкала произвольных движений блефароспазма (ВМ)*