

Quantitative Assessment of Efficacy of Dysport (Botulinum Toxin Type A) in the Treatment of Idiopathic Blepharospasm and Hemifacial Spasm

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Abstract- This study was a Phase IV, prospective, one arm, non-comparative open trial, to investigate the efficacy and safety of Dysport (Botulinum toxin type A) in patients with idiopathic blepharospasm or hemifacial spasm. During the treatment period, patients were evaluated at baseline (week 0), week 6, and week 8, 10, or 12. Thirty two women and 16 men completed the whole course of the study. The therapeutic efficacy of Dysport became evident from 1.5 to 15 days (mean \pm SD, 6.1 \pm 2.9 days). The maximal effect appeared 12.2 \pm 5.0 days later. Injection of Dysport achieved 72.9 (13.0% amelioration in the spasm symptom. Dysport significantly improved the following functions, such as reading, watching TV, house work, working, driving and outing alone. At the twelfth week after Dysport injection, it was still effective in relieving blepharospasm or hemifacial spasm. The most frequent adverse event was ptosis, which was noted in 9 cases and represented 18.7% of total patients. Other adverse events were very mild, although lagophthalmos and dry eyes occurred in some patients, but none manifested any corneal complications. In conclusion, Dysport injection appears to be a safe, and effective procedure - accompanied only by minor, and transit adverse events.

Key Words: Dysport, Efficacy, Blepharospasm, Hemifacial spasm

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INTRODUCTION

Blepharospasm or hemifacial spasm is characterized by forceful, and involuntary contractions of the orbicularis oculi, and sometimes spreading to other parts of the

face. It is a chronic disease, usually occurring in 50-60 years, and it affects women more often than men. The prevalence data are limited, but the estimated figure is 5 per 100,000 of the population⁽¹⁾. Blepharospasm or hemifacial spasm may be unilateral and asymmetric at

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onset. However, the early symptoms, such as excessive blinking and discomfort, are often misdiagnosed and ascribed to ocular disorders. Therefore, the actual prevalence may be much higher. This involuntary, spasmodic and repetitive eyelid closure, in severe cases, can lead to functional blindness. In a few severe cases, driving, reading and unaccompanied walking may be compromised. The disease makes the work difficult or impossible. Anxiety and depression are also associated with this condition due to its disfiguring nature.

The treatment options for blepharospasm and hemifacial spasm include surgery, such as microsurgical decompression, and a variety of drug treatments such as anticholinergic agents, L-dopa and bromocriptine. In the majority of cases, these treatments are unsuccessful⁽¹⁾. Although there is a strong evidence for an organic aetiology⁽²⁻⁴⁾, some doctors believe the conditions to be primarily psychiatric or hysterical and treat the patients accordingly⁽⁵⁾. Hence, treatment with botulinum toxin becomes an effective method for blepharospasm or hemifacial spasm.

A number of studies have investigated Dysport (Botulinum toxin type A) in the treatment of blepharospasm and hemifacial spasm, and most of which were open long-term experiences⁽⁶⁻¹⁷⁾. Three studies were performed versus Botox dosage⁽¹⁸⁻²⁰⁾, two studies were performed with a low dose administration^(21,22) and one post marketing study was performed⁽²³⁾. The largest series of patients is reported by Elston⁽⁶⁻⁹⁾ who treated 234 blepharospasm or hemifacial spasm patients from 1983 and 1990.

The aim of this study is to investigate the therapeutic effect of the Dysport (Botulinum toxin type A) in patients with blepharospasm or hemifacial spasm. The secondary aim of the study is to investigate the safety of the Dysport.

MATERIALS AND METHODS

Study design

This study was a Phase IV, prospective, one arm, non-comparative open study, to investigate the efficacy and safety of Dysport in patients with idiopathic ble-

pharospasm or hemifacial spasm. The study lasted 3 months for each patient. During the treatment period, patients were evaluated at baseline (week 0), week 6, and week 8, 10, or 12.

Inclusion criteria

Patients fulfil all the following criteria, prior to entry into the study: 1. Patients between 18 and 70 years old, 2. Patients with blepharospasm or hemifacial spasm defined by a typical history and clinical signs, 3. Blepharospasm or hemifacial spasm for at least 6 months, 4. Blepharospasm or hemifacial spasm with a severity score > 1, 5. Patients who have been informed of the study's conditions and given their informed consent.

Exclusion criteria

Patients fulfil all the following exclusion criteria, prior to entry into the study: 1. Patients with known hypersensitivity to any of the test materials or related compounds, 2. Patients treated with aminoglycoside antibiotics, 3. Patients suffering from a known disease, which may affect the ophthalmic evaluation, 4. Patients suffering from cerebropontine angle tumors, aneurysm or strokes, 5. Patients with a severe progressive disease, requiring heavy and protracted treatment, overt hepatic, renal or cardiac diseases, 6. Patients with myasthenia gravis, 7. Patients already taking part in another study, 8. Expected non compliance to the study protocol, for whatever reasons (e.g. patients suffering from a mental disorder, with only limited understanding, illiterate, or alcoholic), 9. Pregnant or breast feeding women, 10. Women of child bearing potential without using an effective contraceptive method, during the study and 3 months following the withdrawal of treatment. 11. Patient treated with drugs that have neuromuscular blocking activities, including lincosamides, polymyxins, tetracyclines and muscle relaxants. 12. Patients treated with botulinum toxin or withdrew stopped receiving botulinum toxin less than 4 months.

Method of assigning patients to treatment groups

The study was last 2 to 3 months. Each patient was

seen at least 3 times (3-5 times): at baseline for the inclusion visit, after 6 weeks and during the final visit.

Selection of doses in the study

The recommended initial dose for bilateral blepharospasm or hemifacial spasm was 90 units per eye. For blepharospasm, 90 units were divided into 4 doses and injection was performed in the internal part and the external part in the junction between the preceptal and orbital part of the upper and lower orbicularis oculi muscles of each eye (Fig. 1A). For hemifacial spasm 90 units were divided into 6 doses and injection was done in the internal part and the external part in the junction between the preceptal and orbital part of the upper and lower orbicularis oculi muscles of each eye and lower face (Fig. 1B).

Efficacy measurements

The primary efficacy were evaluated by the difference between the baseline values and values measured at the sixth week of the disease severity score. There are six response variables in the disease severity score; they are reading, watching TV, house work, working, driving and outing alone. Further, for each response variable of the disease severity score, there are five levels of discrete values, namely, 0, 1, 2, 3, and 4 to represent severity of symptom from mild to severe. To integrate these six response variables, the sum or average of these variables would be treated as the overall disease severity score.

The secondary efficacy were the evaluation of the

sensory symptoms (i.e., photophobia), corneal erosion (or ulcer), Elston score and global assessment of the blepharospasm or hemifacial spasm.

Safety measurements

For all included patients, the occurrence of at least one adverse event, the total number of adverse events and the severity of adverse events will be described.

Statistics and variables analyzed

The demographic characteristics included age, height, weight, Week 0 (the length of time between the date of first symptom and the date of Dysport injection), Diagnosis~Week 0 (the length of time between the date of diagnosis and the date of Dysport injection) and Sympt~Week 0 (the length of time between the date of first symptom and the date of diagnosis). The following organ systems would also be examined at the baseline visit; they are skin, eyes (other than blepharospasm or hemifacial spasm), ear/nose/throat, lungs, heart, lymph nodes, gastro-intestinal, liver, uro-genital, neurological, extremities and locomotive system, and others.

The study method of this clinical trial was a non-comparative repeated measurement design. The baseline values were obtained from the values of various response variables of each subject before the Dysport injection. After one time treatment, these response variables of each subject would be repeatedly measured at the sixth, and the eighth, tenth or twelfth week (abbreviated as Week 6, and Week 8, 10 or 12).

The efficacy score were analyzed using the nonpara-

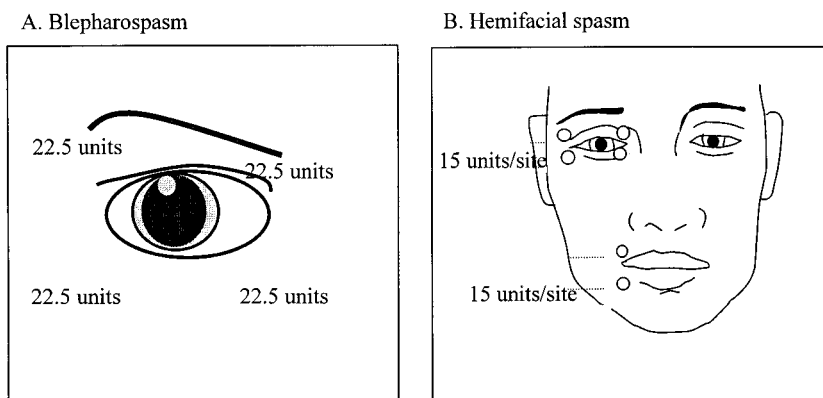


Figure 1. Injection sites of the blepharospasm and the hemifacial spasm.

metric statistics analysis method of Wilcoxon Signed Ranks Test and using Friedman nonparametric data analysis for dependent sample. Subsequently, the Student-Newman-Keuls test were adopted for the multiple pair wise comparisons.

The data, which include 'effect appearance time' and 'maximum effect appearance time' were analyzed using survival data analysis of Kaplan-Meier method.

RESULTS

Patients

There were 53 subjects enrolled in this study. Five patients were not included in the intent-to-treat population analyses due to loss in follow-up (3 cases) or ineligibility of subjects (one case of systemic lupus erythematosus and another case of pituitary tumor). Therefore, the valid sample size was 48 patients.

Demographic and clinical characteristics

There were 32 women and 16 men that completed the whole course of study. The mean age of these patients was 54.7 ± 9.6 years (mean \pm SD), with a range of 29.8 to 69.8 years. Among these patients, only six did not have previous treatment experience (neither botulinum toxin type A nor other muscle relaxant medications). None of them had a significant medical history. Several minor medical conditions were recorded in the

physical examination. There were 28 patients that had concurrent medications during the trial. Only two subjects suffered from other facial dystonia. One patient had minor corneal erosion.

Efficacy evaluation

The mean (M) and standard deviation (SD) of each subject's average of the disease severity score were 1.84 and 0.47 at the baseline, respectively. At the sixth week the mean of each subject's average of the disease severity score was decreased to 0.71 with a standard deviation of 0.45. The data indicated a statistically significant improvement in blepharospasm or hemifacial spasm. The value of each response variable in the disease severity score at the sixth week was significantly lower than baseline values ($p < 0.001$).

With respect to the secondary efficacy, the mean of baseline value for photophobia was 1.96, which was decreased to 0.79 at the sixth week ($p < 0.001$). This result suggested that Dysport significantly improved the sensory symptoms of patients. Regarding the Elston Score, the mean was changed from 4.5 to 5.35 ($p < 0.001$). For the 'global assessment of blepharospasm or hemifacial spasm', the mean quotation was reduced from 1.90 to 0.79 ($p < 0.001$) indicating that the overall spasm condition was significantly relieved by Dysport.

The mean of the 'effect appearance time' was $6.10 \pm$

Table 1. Global efficacy assessment

Response variable	Baseline (Week 0)			Visit 2 (Week 6)			Visit 3 (Week 8)			Visit 3a (Week 10)			Visit 3b (Week 12)			p value*
	N	M	SE	N	M	SE	N	M	SE	N	M	SE	N	M	SE	
Sum of scores	48	9.67	0.38	48	3.77	0.33	48	2.60	0.28	43	2.74	0.36	36	3.39	0.43	<0.001
Average of scores	48	1.84	0.07	48	0.71	0.07	48	0.50	0.06	43	0.54	0.08	36	0.67	0.10	<0.001
(1) Reading	47	2.09	0.11	47	0.70	0.10	47	0.51	0.09	42	0.52	0.12	35	0.74	0.13	<0.001
(2) Watching TV	48	2.00	0.09	48	0.75	0.09	48	0.52	0.09	43	0.58	0.11	36	0.83	0.11	<0.001
(3) House work	48	1.73	0.08	48	0.77	0.07	48	0.60	0.08	43	0.67	0.09	36	0.78	0.10	<0.001
(4) Working	44	1.70	0.10	44	0.66	0.07	44	0.43	0.08	39	0.46	0.08	32	0.50	0.09	<0.001
(5) Driving	18	2.33	0.16	18	0.78	0.24	18	0.22	0.15	16	0.13	0.13	12	0.33	0.22	<0.001
(6) Outing alone	48	1.46	0.08	48	0.67	0.09	48	0.50	0.08	43	0.51	0.10	36	0.50	0.11	<0.001
Photophobia	48	1.96	0.10	48	0.79	0.08	48	0.67	0.07	43	0.65	0.07	36	0.81	0.07	<0.001
Elston	48	4.50	0.15	48	5.35	0.08	48	5.48	0.08	43	5.51	0.10	36	5.47	0.11	<0.001
Global assessment	48	1.90	0.09	48	0.79	0.07	48	0.79	0.07	43	0.77	0.07	36	0.75	0.08	<0.001

N: number of patient; M: Mean, SE: standard error; *: Statistics test method: Friedman test; Null hypothesis: The population's mean rank is the same between week 0, 6,8,10 and 12.



2.86 days and the mean of the maximum effect was 12.21 ± 5.01 days. Whereas, the 'percentages of maximal amelioration' was $72.92 \pm 13.00\%$.

Table 1 shows the omnibus testing results of the baseline, the sixth, eighth, tenth and twelfth week. There was a statistical significance among the five different time points for all of the response variables within the primary and secondary efficacies ($p < 0.001$).

The disease severity scores at the sixth, eighth, tenth and twelfth week showed a significant improvement when compared scores at the baseline ($p < 0.01$). To all of the response variables, the maximal improvement occurred at the eighth week. In addition, the results showed that there was a statistical significance for each

response variable between the twelfth week and baseline.

The mean of survival time of 'effect appearance time' was 6.10 days and the 95% confidence interval was 5.29 to 6.91 days (Fig. 2). Whereas, the median survival time was 7.00 days and the 95% confidence interval was 6.71 to 7.29 days. Approximately 37.5% of all subjects had the 'effect appearance time' on the seventh day after the Dysport injection. On the tenth day after Dysport treatment, 46 subjects (96%) had an efficacy. Before the fifteenth day inclusive, all 48 subjects experienced an efficacy.

The mean survival time of 'maximum effect appearance time' was 12.21 days and the 95% confidence inter-

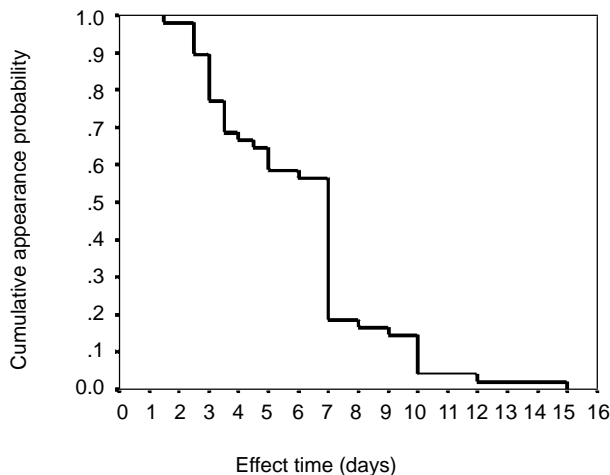


Figure 2. Effect time's survival curve with baseline as initial time.

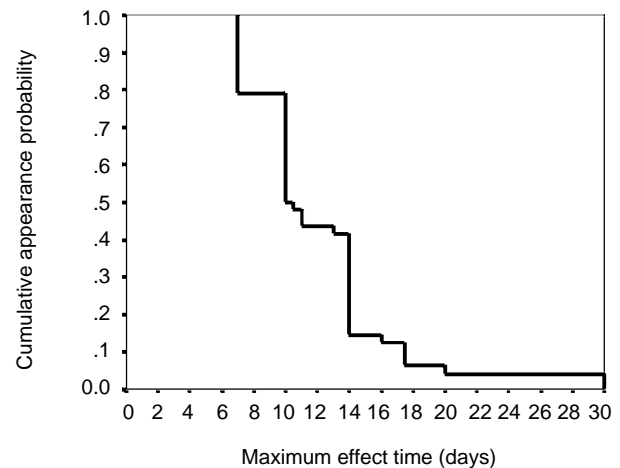


Figure 3. Maximum effect time's survival curve with the baseline as initial time.

Table 2. Summary of the adverse events

Adverse events	Frequency (%)	Intensity	Duration (days)	Recovery
Ptosis	9 (18.7%)	severe	18, 58, 79	Completely
		moderate	14, 19	Completely
		mild	14, 14, 14, 30	Completely
Eye closing weakness	2 (4.1%)	mild	11, 34	Completely
Mouth angle drooping	2 (4.1%)	severe	77	Partially
		mild	31	Completely
Dry eye	2 (4.1%)	mild	14, 17	Completely
Tearing	2 (4.1%)	mild	8, 10	Completely
Tightness of face	1 (2.1%)	mild	8	Completely
Lagophthalmos	1 (2.1%)	mild	14	Completely

val was 10.79 to 13.63 days (Fig. 3). The median survival time was 10.00 days and the 95% confidence interval was 8.40 to 13.63 days. On the twentieth day after Dysport treatment, 46 subjects (96%) had a maximal efficacy. Before the thirtieth day after Dysport treatment, all 48 subjects had 'maximum effect appearance time'.

The mean survival time of 'maximum effect appearance time' was 6.10 days and the 95% confidence interval was 4.85 to 7.36 days (Fig. 4). The median survival time was 4.00 days and the 95% confidence interval was 3.52 to 4.48 days. The maximal efficacy appeared in 47 subjects (98%) on the fifteenth day after the 'effect appearance time'. Before the twenty-third day inclusive after 'effect appearance time', all 48 subjects had 'maximum effect appearance time'.

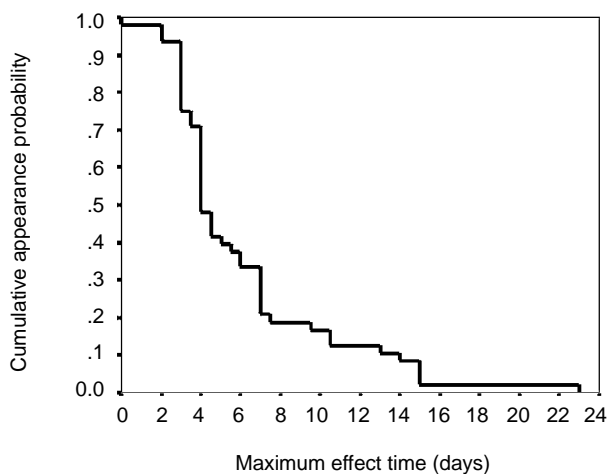


Figure 4. Maximum effect time's survival curve with effect appearance time as initial time.

Safety evaluation

Table 2 shows the summary of the adverse events. Eighteen events were completely recovered except one event recovered partially at the end of study. The most frequent adverse event was ptosis in 9 cases (18.7%). The ptosis was temporary with returning to normal eyelid position within 79 days. The other adverse event was mouth angle drooping in two cases with complete recovery in one, and partial recovery in one at the end of the

study. Although lagophthalmos and dry eye occurred in some patients, none of them manifested any corneal complications.

DISCUSSION

Blepharospasm or hemifacial spasm is a chronic disorder and may cause social embarrassment. In a few cases, the disorders may jeopardize their marriage or employment and mostly, they may interfere with the daily activities. In severe cases, functional blindness is noted because of eye closure⁽²⁴⁾. Therapy includes benzodiazepines (clonazepam) or anticholinergics (trihexyphenidyl HCl), but these drugs do not provide a long term relief. Also, patients who take these drugs are likely to experience side-effects eventually. Surgery offers the possibility of cure if vascular structures impinging on the facial nerve root entry zone. Microvascular decompression for hemifacial spasm have been successful in offering permanent relief^(25,26), but a recurrence may be up to 60%⁽²⁷⁾. The extirpation of the offending muscles by botulinum toxin injection is, therefore, becoming a successful alternative treatment to these disorders.

Botulinum toxin is a potent neuroparalyzing agent. The bacterium *Clostridium botulinum* produces 7 antigenically distinct toxins designated types A, B, C, D, E, F and G. Botulinum toxin type A is the most studied botulinum toxin and the most potent biological poison. This toxin acts as a presynaptic blocking agent at cholinergic terminal nerve endings and then inhibits acetylcholine release at the neuromuscular junction. Botulinum toxin type A blocks neuromuscular transmission through a three-step process: 1) toxin binding to nerve terminals, 2) internalisation, and 3) inhibition of neurotransmitter release. It is believed that the three-step process is to be followed by the sprouting of new axon terminals, which results in re-establishment of neuromuscular transmission.

Following years of experience with Dysport, Elston⁽⁹⁾ demonstrated the effectiveness of botulinum toxin treatment for a period from 6 months to 7 years. There was a 78.6% reduction in abnormal movements in ble-

pharospasm or hemifacial spasm with the effect lasting for 12-15 weeks. Doses administered in other long-term studies varied from 30 units to 200 units per eye⁽¹⁰⁻¹⁷⁾. All noted similar efficacy with a 60%-100% improvement. Higher doses (100-200 units per eye) were associated with a greater efficacy (up to 100%), a greater incidence of ptosis and diplopia and a long duration of action of 3-5 months⁽¹⁵⁻¹⁷⁾. Elston⁽⁹⁾ determined that by setting the injection further away from the eyelid margin, a highly efficacious dose could be used with a reduced number of side effects. Aramideh et al.⁽²²⁾ compared the response to Dysport after two injections technique in 45 patients with blepharospasm or hemifacial spasm. Initially, patients were treated according to the triple injections technique - two injections medially and laterally at the preseptal crease of the upper lid and one laterally in the lower lid. A mean dose of 37 units (8-87 units) was injected in each eye. Subsequently, the same patients received two injections (10-15 units) into the pretarsal portion, in addition to the triple injections. The total dosage was the same. The initial injection technique gave successful results in 81% of treatments, with a mean duration of benefit of 8.5 weeks. Using additional pretarsal injections significantly increased the number of successful treatments to 95% and the duration of benefit to 12.5 weeks. Van den Bergh et al.⁽²¹⁾ treated 57 blepharospasm or hemifacial spasm patients with a low dose Dysport. They observed a peak improvement in 12/17 blepharospasm or hemifacial spasm patients following administration of a total dose of ≤ 55 units per eye, as well as a 90% improvement in the hemifacial spasm group.

The responses of hemifacial spasm or blepharospasm patients following injection were compared between two commercially available preparations on botulinum toxin, Dysport and Botox⁽¹⁸⁻²⁰⁾. All patients in these studies responded favorably to Dysport, with a duration of effect reported as lasting 8.03 weeks⁽²⁰⁾ and 13.3 weeks⁽¹⁹⁾. A one-year post-marketing surveillance study (DYSP/007) was carried out in Germany from 1993 to 1994⁽²³⁾. Of the periocular/facial injections with a mean dose of 146 units and 110 units respectively, the efficacy of the periocular injections was considered good

in 77% and 74% of periocular/facial injections.

The present study confirms that patients with blepharospasm or hemifacial spasm can benefit from local injection of botulinum toxin type A. The onset of beneficial effects, peak effects and clinical improvement in daily functions are comparable with other clinical studies. Few patients had adverse events, which disappeared spontaneously within weeks. In this study, the most frequent adverse event was ptosis, due to the spread of toxin to the levator palpebrae muscle. Direct spread of toxin may also determine weakness of the lower facial muscles in patients with hemifacial spasm.

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