The Difference of Treatment Results between Botulinum Toxin A Split Injection Sites and Botulinum Toxin A Non-Split Injection Sites for Hemifacial Spasm

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Objective: *To compare hemifacial spasm treatment results between Botulinum toxin A split injection sites and Botulinum toxin A non-split injection sites.*

Material and Method: *Thirty-one hemifacial spasm patients were randomly assigned into the non-split injection sites group (injecting Botulinum toxin A to the zygomaticus major and risorius each) or split injection sites group with the same amount of Botulinum toxin A as the first method (injection Botulinum toxin A to the zygomaticus major and minor and risorius two injections each) The main outcomes are onset of improvement and effective duration of treatment.*

Results: *Fifteen patients were assigned to non-split injection sites group and 16 patients were assigned to split injection sites group. The median onset of improvement in non-split injection sites group and split injection sites group was 4.0 and 4.5 days, respectively (p = 0.984). The effective duration of treatment in the non-split injection sites group was 60.0 days and in the split injection sites group was 54.5 days (p = 0.582).*

Conclusion: *The splitting of injection sites did not significantly improve the efficacy of Botulinum toxin A in the treatment of hemifacial spasm.*

Keywords: *Botulinum toxin, Hemifacial spasm, Dysport®*

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Hemifacial spasm (HFS) is clinically marked by involuntary unilateral contraction of the muscular system innervated by the facial nerve[1]. The most common cause is believed to be the result from the compression of the 7th cranial nerve at its root exit zone[2] by a blood vessel in the area that includes the basilar artery, anterior and posterior inferior cerebellar arteries and vertebral artery[3-5]. Other causes include compression by cholesteatoma, acoustic neuroma, facial nerve neuroma, and adenoid cystic tumors[6].

Symptoms may vary substantially. Some patients present with orbicularis muscle spasm. In other patients, the entire musculature innervated by the facial nerve: corrugators, frontalis, zygomaticus, buccinators, depressor angulioris, and platysma may be involved[8]. The abnormalities occur ipsilaterally[1,7]. HFS is more common in females than in males, in age range of 40 to 79-years-old[6]. Mild progression of the disease is seen in many cases[1]. Even though this disorder is a benign condition, it can cause functional disability and cosmetically disturb for the patient[8].

Medical treatment by carbamazepine may be useful in some cases but it has many side effects[9]. Surgical treatment for vascular decompression is effective (84%)[10] but it also has severe potential complications, such as facial palsy (4.2%), permanent deafness (3.2%), cerebellar infarction (0.3%), cerebro-spinal fluid (CSF) leakage (2.4%), and intraoperative death (0.1%)[10].

Many studies reveal the effectiveness of Botulinum toxin A injection at the affected areas[11-16]. Although there are some side effects, such as ptosis, dry eye, tearing, facial palsy, and diplopia, they are temporary occurrences with no systemic side effects[1]. Botulinum toxin A is a neurotoxin produced by *Clostridium botulinum*, which is an anaerobic organism. Botulinum toxin A causes muscle paralysis by blocking acetylcholinergic neurotransmitters at the neuromuscular junction[17]. Dysport® is a formulation of Botulinum toxin A that has wide uses and is effective in many studies for HFS treatments[8,18-22]. An average dose is between 53 and 160 units per session[8,18-22].

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The injection method depends on the affected region. However, the number of injected locations of each muscle is inconclusive. The present study compared the split injection sites and non-split injection sites for HFS. A clinical five-point scale widely used in many clinical studies[23] was used to discriminate the results between these two methods.

Material and Method

Thirty-one patients with HFS were enrolled in the present prospective, double-blind study between February and May 2009. Informed consent was obtained from each subject using a consent form approved by the Ethics Committee of Prince of Songkla University, Thailand and was run in accordance with the principles of Good Clinical Practice (Helsinki Declaration).

The inclusion criteria were patients with spasm on the zygomaticus muscle and risorius muscle. The exclusion criteria included Botulinum toxin resistance, any previous surgical treatment, pregnancy, and breast-feeding women.

Dysport® was prepared (2.5 unit/0.01 ml) by an assistant nurse for use in the present study. Patients were randomly assigned into the split injection sites group or non-split injection sites group treatment regimen. Injection was done at 4 points namely A, B, C, and D in both groups (Fig. 1). Point A was the point of intersection between an imaginary line joining the lateral canthus of the eye and the angle of the mouth with a horizontal line drawn at the level of the lower end of the ala of the nose. Injection at point A delivered the drug to the zygomaticus major muscle. Point B was 1 cm vertically above point A. Injection at point B was meant for the zygomaticus minor muscle. Injection at point C was given at the nasolabial fold at the level of the angle of the mouth. Injection at point C was meant for the risorius muscle. Point D was 1 cm lateral to point C. Injection at site D was meant for the risorius muscle.

In all patients the dosage of Dysport® was calculated by the examining physician depending on the severity of the spasm and allotted for the zygomaticus muscle group (injected at point A and B) and the risorius muscle (injected at point C and D) (Fig. 2).

The treatment regimen for the non-split group was as follows:

1. At point A, the whole dose of Dysport® meant for the zygomaticus muscle group was injected.

2. At point B, 0.02 cc of normal saline solution was injected.

3. At point C, the whole dose of drug meant for the risorius muscle was injected.

4. At point D, 0.02 cc of normal saline solution was injected.

The treatment regimen for the split group was as follows:

1. At point A, two-thirds of the dosage of Dysport® meant for the zygomaticus muscle group was injected.

2. At point B, one-third of the total dosage of Dysport® meant for the zygomaticus muscle group was injected.

3. At point C, one-half of the dosage of Dysport® meant for the risorius muscle was injected.

4. At point D, the remaining half of the dosage of Dysport® meant for the risorius muscle was injected.

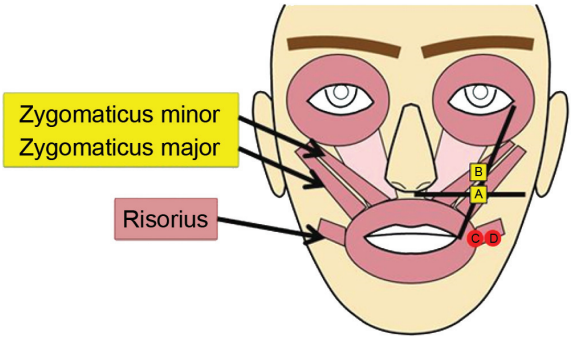

Fig. 1 A) The point of intersection between an imaginary line joining the lateral canthus of the eye and the angle of the mouth with a horizontal line drawn at the level of the lower end of the ala of the nose. B) The point 1 cm vertically above the point A. C) The point at the nasolabial fold at the level of the angle of the mouth. D) the point 1 cm lateral to point C.

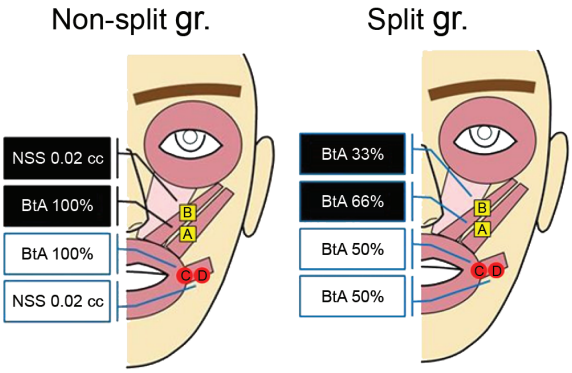

Fig. 2 Percentage of Botulinum toxin A given to each point in each group (BtA = Botulinum toxin A, NSS = normal saline).

The injector and the participants were both blinded to the treatment regimen. All syringes were prepared by a separate health assistant and covered with a plastic tape before being injected by the injector.

At 12 weeks post-treatment follow-up, the primary treatment outcomes studied in both groups were as follows:

1. Time of onset of drug action, which was described as the first noticeable improvement in symptoms since injection.

2. Duration of effectiveness of treatment described as the time from the first noticeable improvement to return of symptoms.

Frequency of spasm, severity of spasm, disturbance of daily activities (eating, talking, and socializing) and complications of treatment were also recorded.

Statistical analysis

Analysis was performed in Excel and SPSS software version 16. All variables in this study were evaluated with Mann-Whitney U test because of non-normal distribution. A *p*-value of less than 0.05 was considered statistically significant.

Results

Thirty-one patients were recruited into the study. Fifteen patients were randomized into the non-split group and 16 into the split group. The median age of the patients was 57.0 years (range, 25-82 years). Twenty-seven (87.1%) patients were female and four were male. Median duration of the disease was 36.0 weeks (range, 6-240 weeks). All the baseline characteristics between the two groups were similar in terms of age, gender, frequency of spasm, severity of spasm, and underlying disease. The mean dose of Dysport® was 9.07 units in the non-split group and 8.00 units in the split group.

The median time of onset of drug action was 4.0 days (range, 1-20 days) in the non-split group compared with 4.5 days (range, 1-20 days) in the split group. There was no statistically significant difference ($p = 0.984$) (Table 1).

Median duration of effectiveness of treatment was 60.0 days (range, 25-79 days) in the non-split group, compared with 54.5 days (range, 23-83 days) in the split group. There was no statistically significant difference ($p = 0.572$) (Table 1).

The severity of spasm after treatment was similar in both groups. Twelve (80.0%) of the 15 patients in the non-split group had no spasm at all (score 0), compared with 13 (81.2%) of 16 patients in the split group after treatment. There was no statistically significant difference ($p = 0.546$) (Table 2).

The frequency of spasm was not different in the two groups. Twelve (80.0%) of the 15 patients in the non-split group barely had spasm (score 0), compared with 14 (87.5%) of the 16 patients in the split group. There was no statistically significant difference ($p = 0.570$) (Table 3).

Disturbance of daily activities and complications were reported in only a minority of patients and there were no differences between the groups.

Discussion

Even though the results of the treatment of HFS with Botulinum toxin were excellent, the duration of drug action was not long and patients needed repetitive treatment. The present study was designed to examine different techniques of Botulinum toxin injection. The authors found no differences between the treatment results in the two groups in terms of onset of drug action, mean duration of effectiveness of treatment, severity of spasm, frequency of spasm, disturbance of daily activities, and complications.

Botulinum toxin with a single point injection may diffuse into the non-injected area in the non-split injection technique, which gives the same results of treatment as the 2-point split injection technique. Further, injection into the larger zygomaticus major muscle may adequately suppress the spasm without the need to inject in the smaller zygomaticus minor muscle.

Due to limited number of sample size, the authors might conclude preliminary outcome of the

Table 1. Onset of improvement, peak, and effective duration of treatment comparison of the non-split group with the split group

	Non-split group (days), median (min-max)	Split group (days), median (min-max)	*p*-value
Onset of improvement	4.0 (1-20)	4.5 (1-20)	0.984
Peak of effect	14.0 (2-41)	15.0 (4-45)	0.379
Effective duration of treatment	60.0 (25-79)	54.5 (23-83)	0.572

Table 2. Severity score comparison of the non-split group with the split group

Severity score	Non-split group (n = 15)	Split group (n = 16)	*p*-value
0	12 (80.0%)	13 (81.2%)	0.546
1	2 (13.3%)	3 (18.8%)	
2	1 (6.7%)	0 (0%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	

Score: 0 = no symptom, 1 = barely noticeable, 2 = mild, daily activities not disturbed, 3 = moderate, disturbed daily activities, 4 = severe, unacceptable

Table 3. Frequency score comparison of the non-split group with the split group

Frequency score	Non-split group (n = 15)	Split group (n = 16)	*p*-value
0	12 (80.0%)	14 (87.5%)	0.570
1	2 (13.3%)	2 (12.5%)	
2	1 (6.7%)	0 (0%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	

Score: 0 = no spasm, 1 = less than 25% of waking hours, 2 = between 25-50% of waking hours, 3 = between 50-75% of waking hours, 4 = more than 75% of waking hours

present study as the non-split injection technique is enough to reach a good treatment outcome without separate injections into two points and without inducing more pain. However, the further research is recommended to yield more validated result.

The limitations of the present study were the small number of patients and some patients did not use the provided calendar form to record their symptoms but tried to recall the symptoms when asked on the follow-up date. This may have resulted in data errors. Finally, since the present study only inspected three muscles, the results cannot be implied to other muscles.

What is already known on this topic?

The treatment of HFS usually injects Botulinum toxin A subcutaneous along the areas of the symptoms. The dose and number of the injection depends on the physicians' decision, which will adjust the dosage for the injection to the areas of the symptoms according to the severity of symptoms and muscle size.

What this study adds?

The present study found that the divided of the injected points of Botulinum toxin A from two to four points for the treatment of HFS in the muscles of zygomaticus and risorius did not make the treatment better even using the same dose.

Potential conflicts of interest

None.

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ความแตกต่างของผลการรักษาโรคกล้ามเนื้อใบหน้ากระตุกครึ่งซีก ด้วยการฉีดยาโบทูลินัมทอกซินแบบแบ่งจุดฉีดกับไม่แบ่งจุดฉีด

อนุวัชร์ พฤทธิพงศ์สิทธิ์, นิพัฒน์ เอื้ออารี

วัตถุประสงค์: *เพื่อเปรียบเทียบผลการรักษาโรคใบหน้ากระตุกครึ่งซีกด้วยการฉีดโบทูลินัมทอกซิน (Botulinum toxin) ด้วยวิธีการแบ่งตำแหน่งฉีดกับไม่แบ่งตำแหน่งฉีด*

วัสดุและวิธีการ: *ผู้ป่วยโรคใบหน้ากระตุกครึ่งซีกทั้งหมด 31 ราย แบ่งออกเป็นสองกลุ่มด้วยวิธีการสุ่ม กลุ่มแรกคือกลุ่มแบ่งตำแหน่งฉีด ได้รับการรักษาโดยการฉีดโบทูลินัมทอกซินเข้ากล้ามเนื้อ zygomaticus major, zygomaticus minor และ risorius ซึ่งแบ่งการฉีดที่ risorius เป็นสองตำแหน่ง กลุ่มที่สองคือกลุ่มไม่แบ่งตำแหน่งฉีด ได้รับการรักษาโดยการฉีดโบทูลินัมทอกซินเข้ากล้ามเนื้อ zygomaticus major และ risorius โดย risorius ได้รับการฉีดที่ตำแหน่งเดียว และได้รับยาหลอกคือ normal saline ที่กล้ามเนื้อ zygo maticus minor และ risorius อีกตำแหน่งที่เหลือ ตัวแปรหลักที่นำมาวิเคราะห์ผลของการศึกษานี้คือ วันเริ่มออกฤทธิ์ของยา และระยะเวลาออกฤทธิ์ของยา*

ผลการศึกษา: *แบ่งผู้ป่วย 16 ราย อยู่ในกลุ่มแบ่งตำแหน่งฉีด และ 15 ราย อยู่ในกลุ่มไม่แบ่งตำแหน่งฉีด มีอายุอยู่ที่ 57.0 ปี (25-82 ปี) มีอาการของโรคเป็นมา 36.0 สัปดาห์ ได้รับปริมาณยาเฉลี่ย 6.72 ยูนิต และ 5.67 ยูนิต ในกลุ่มแบ่งตำแหน่งฉีดและไม่แบ่งตำแหน่งฉีด ตามลำดับ ติดตามผลของการรักษาที่ 12 สัปดาห์ วันเริ่มออกฤทธ์ของยาอยู่ที่ 4.0 วัน และ 4.5 วัน ตามลำดับ ($p = 0.984$) ระยะเวลาออกฤทธิ์ของยาอยู่ที่ 60.0 วัน และ 54.5 วัน ตามลำดับ ($p = 0.572$)*

สรุป: *การรักษาโรคใบหน้ากระตุกครึ่งซีกด้วยวิธีการแบ่งตำแหน่งฉีดกับไม่แบ่งตำแหน่งฉีด ไม่มีความแตกต่างในผลการรักษา และผลข้างเคียง*