การศึกษา เปรียบเทียบประสิทธิภาพการรักษาโรคใบหน้ากระตุกครึ่งซีก ของยาโบทูลินั่มท็อกซินขนาดยาปกติ กับขนาดยา 75% ของขนาดปกติ

พิชัย โรจนพิทยากร พบ.

Hemifacial spasm: comparative study efficacy of treatment with 75% dose and normal dose botulinum toxin injection

Abstract

Objective: To explore the efficacy of low 75 % dose botulinum toxin A (BTA) comparison to normal dose treatment for hemifacial spasm (HFS).

Method: A randomized single-blinded prospective trial with BTA injection at the botulinum Clinic in Suratthani Hospital, Thailand. The patients who were attended in January 2019 and were evaluated in April 2019. The single-blind patients were random by alternative patients 1:1 to assess outcome. Low dose BTA diluted to get the same volume of normal dose.

Result: A total of 69 patients with HFS include 34 patients in normal dose group and 35 patients in low dose group. There were female more than male in both groups. The mean ages were 59 years and 60 years. The left side was more affected the same. The mean number of injection were 12.5 times in normal group and 11 times in low dose group. The mean dose of treatment was 65.3 units in normal dose and 46.1 in 75% dose. The mean duration between treatments were 2.9 months and 3 months. The outcome of treatment was assessed at appointment after injection for 3 months by the patients. The outcome of treatment was not significantly difference in both groups. Most patients had fair improvement in 17 patients (50%) in normal dose and 15 patients (43%) in low dose. Most treatments had no complication in 97-100 %.We reduce the cost by 2,648 bath per person per year.

Conclusion: 75% dose BTA injection was an effective treatment for hemifacial spasm patients none inferiority than normal dose. There was maintain duration response as same as normal dose and low complication rate in this study.

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บทคัดย่อ

วัตถุประสงค์การวิจัย

เพื่อศึกษาประสิทธิภาพของยาโบทูลินั่มท็อกซิน ขนาด 75% ของขนาดยาปกติ ในการรักษาโรคใบหน้ากระตุกครึ่งซีกเทียบกับขนาดยาปกติที่ใช้

วิธีการวิจัย

การศึกษานี้เป็นการศึกษาแบบสุ่มไปข้างหน้า โดยที่ผู้ป่วยไม่รู้ถึงขนาดยาที่ใช้ในการรักษาที่ได้รับในโรงพยาบาลสุราษฎร์ธานีที่โบทูลินั่มคลินิก ผู้ป่วยที่เข้าร่วมได้รับการรักษาในเดือนมกราคม ปี พ.ศ. 2562 และได้รับการประเมินผลการรักษาในเดือนเมษายน ปี พ.ศ. 2562 การสุ่มเลือกผู้ป่วย โดยจะเลือกฉีดยาโบทูลินั่มท็อกซินขนาดปกติและขนาด 75% ของขนาดปกติ สลับกันไปทีละคนก่อนโดยที่ผู้ป่วยจะไม่รู้ขนาดยาที่ได้รับ โดยจะเตรียมยาทั้งสองกลุ่มให้ปริมาตรเท่ากัน โดยวิธีเจือจางด้วยน้ำเกลือที่ฉีดยา

ผลการวิจัย

กลุ่มประชากรที่ทำการศึกษาทั้งหมด 69 คน โดยที่ 34 คนเป็นกลุ่มที่ได้ยาขนาดปกติ และ 35 คนเป็นที่ยา 75% ของขนาดปกติ พบว่ากลุ่มประชากรส่วนใหญ่เป็นผู้หญิงทั้ง 2 กลุ่ม อายุเฉลี่ยใกล้เคียงกันทั้ง 2 กลุ่ม คือ 59 ปี และ 60 ปี ส่วนใหญ่มักจะเป็นด้านซ้ายทั้ง 2 กลุ่ม ค่าเฉลี่ยจำนวนครั้งที่ฉีดยาใกล้เคียงกัน คือ 12.5 ครั้ง ในกลุ่มขนาดยาปกติ และ 11 ครั้งในกลุ่มที่ลดขนาดยา ค่าเฉลี่ยขนาดยาที่ใช้ ในกลุ่มขนาดยาปกติ คือ 65.3 ยูนิต และ 46.1 ยูนิต ในกลุ่มที่ลดขนาดยา การประเมินผลจะประเมิน โดยผู้ป่วยทุก 3 เดือน ตามนัด ผู้ป่วยส่วนใหญ่จะให้ความเห็นอยู่ในกลุ่มดีขึ้นปานกลางทั้ง 2 กลุ่ม คือ 50% ในกลุ่มขนาดยาปกติ และ 43% ในกลุ่มลดขนาดยา ไม่พบภาวะแทรกซ้อนจากการรักษาทั้ง 2 กลุ่ม อยู่ที่ 97 - 100 % ไม่ต่างกัน และสามารถลดค่าใช้จ่ายได้ 2,648 บาท ต่อคน ต่อปี

บทสรุป

การลดขนาดยาโบทูลินั่มท็อกซินลง 75% ให้ประสิทธิผลการรักษาไม่ด้อยกว่าขนาดยาที่ใช้ปกติ ให้ผลการรักษาในระยะเวลาที่ไม่ต่างกันกับขยาดยาปกติ และมีภาวะแทรกซ้อนต่ำ

คำหัส : ยาโบทูลินั่ม ท็อกซินขนาดต่ำ, โรคใบหน้ากระตุกครึ่งซีก

Background

Hemifacial spasm (HFS) is an abnormal craniofacial movement that produces involuntary eyelid twitching and closure.[1] HFS is characterized by repetitive synchronous contraction of facial nerve innervated muscles on one side of the face[2]. HFS is often triggered by fatigue, anxiety, stress[3], reading, and driving and it may persist during sleep.[4] The usual cause is a vessel touching the facial nerve near its origin from the brain stem. Although it is a benign condition it can cause significant cosmetic and functional disability.[5] The efficacy and safety of botulinum toxin type A (BTA) injections have been accepted and widely used for the treatment of HFS.[5-7] However, different doses of injection may influence the effectiveness and side effects. The mean duration of action of each injection ranged between 2.6 and 4 months.[8, 9] The most common side effects were ptosis 2.8% to 7 %[10, 11] and facial weakness 17.6%.[10]

Two studies have shown the efficacy and safety of low dose botulinum toxin A (BTA) injection in HFS.[12, 13] In these two studies were case series report study and open-label, prospective case-series study. The objective of this study was to randomized prospective study the demographic data as well as efficacy and safety of low dose BTA injection in HFS patients.

Methods

The study design was a randomized single-blinded prospective trial with BTA injection at the botulinum Clinic in Suratthani Hospital, Thailand. The patients who were attended in January 2019 and were evaluated in April 2019. The study was approved by the Suratthani Hospital Institutional Review Board. This study includes adult-onset patients and receiving continuous treatment more than 2 times in this clinic. That included 34 patients in the normal dose group and 35 patients in 75% dose group. The study case was chosen randomly by alternative patients 1:1 and everyone signed the informed consent before treatment. We analyzed demographic data such as sex, age, side of hemifacial spasm, underlying diseases (hypertension, diabetes mellitus, stroke, others neurological or medical disease), sites of BTA injection, dose of each BTA treatment, duration of response, side effect and efficacy. The severity was defined by severity of spasm (SMC grade) : grade I - localized spasm around the periocular area; grade II - involuntary movement spreads to other parts of the ipsilateral face and it affects other muscle groups, i.e. the orbicularis oris, zygomaticus, frontalis or platysma muscle; grade III - interference with vision because of frequent tonic spasms, and grade IV - disfiguring asymmetry.[14] The outcomes of the treatment were assessed by the patients at appointment after injection. We classified as excellent (> 81% improvement), good (61-80% improvement), fair (21-60% improvement), mild (1-20% improvement) and no improvement. We appointment was made every three months for each treatment. The complications and duration of response were assessed by the patients and investigator.

The drug study was Botulinum toxin type A (Dysport®, 500 unit per vial, IPSEN, Boulogne Bilancourt, France) was reconstituted for injection to yield 200 unit/ml by 0.9% sterile saline solution and diluted the 75% BTA to get the same volume of normal dose by the author. The technique injection was the patient in a lying position, the injection sites were chosen by the clinical assessment of spasm. The injection sites were cleaned with 70% alcohol and BTA was approximately injected intramuscularly 10-20 unit each site.

Statistical analysis

Stata program was used for analysis. To compare the baseline clinical characteristics between normal dose and 75% dose, Categorical variables were presented as percentages and were compared using Fisher's exact test. Continuous variables data were present as the mean, standard deviation (SD) and were compared using the two-sample t-test. Shapiro-Wilk test access the distributed platform. Non-parametric continuous variables were presented interquartile ranges (IQRs) and were compared using the Wilcoxon rank-sum test. All proportions and P values were

calculated based on variables with no missing data. The logistic regression analysis was carried out to determine the severity grading factor associated outcome of both groups.

Result

The study included a total of 69 patients, 34 patients were normal dose BTA and 35 patients in 75% dose BTA group. The demographic data of all patients were shown in Table 1.

There were more common in women 29 patients (85%) in normal dose group and 28 patients (80%) in 75% dose group. The mean age of both patients groups were 58.7 years (range 52.5-68 years) and 60.4 years (range 53-69 years). The affected side of HFS patients mostly affected in the left side were 22 patients in normal group (65%) and 18 patients in 75% dose group (51%). The underlying disease of FHS was not significantly different in both groups but the severity of HFS in the normal dose group was slightly more severity.

The number of times BTA injection were 12.5 times (range 7-18 times) in normal group and 11 times (range 5-21) in 75% group. The number point of injections were 3.5 points in normal dose group and 3.3 points in 75% group. Both numbers and points of injection were not significantly different. The mean dose of BTA in normal dose was 65.3 unit and 46.1 unit in 75% group, all data shown in table 2.

The mean duration response of injections was 2.9 months in normal dose group and 3 months in 75% dose group. The outcomes of treatments were not significantly different. Most patients were fair improvement in both group and no one was no an improvement. There was no complication in most treatments, as shown in table 3

Discussion

HFS usually mean age was 50 - 61 years and that was common in women.[7, 10, 15] BTA was effective and less complication of treatment. In the others series shown high response rate in long term treatment of the patients about 90-98%.[8, 10, 13, 16] This study showed most patients were women may be the women was more concern in cosmetic. The mean age was not different in other studies. The underlying diseases were not differenced in both group, most patients do not have underlying diseases. The outcome response of treatment was different between two groups but in normal dose group had mild response in 5 patients (15%) and 9 patient in 75% dose group (26%). Most patients had been treatment for long time, the median number of injection was 11-12 times. The times usually injections every 3 months, therefore the average time of patients who received treatment for at least 3 years. The evaluation of treatment in patients who have continued to treat may not see the difference clearly but the difference may be obvious if compared with before treatment. The good response was a similar response in both group, the duration of response and complications of treatment were no different. The severity of HFS defined by SMC grade. The normal dose group may be more severity but both groups were not significantly different. We used logistic regression analysis calculated the relationship between severity and outcome that showed no relation, p=0.205, 95% CI -0.65-0.13.

The mean total dose of Dysport® for HFS range from 54 to 213 unit in other studies.[17] The mean dose of treatment in this study was 65.3 units per injection in normal dose group and 46.1 unit per injection in 75% dose group. The cost of BTA treatment in Suratthani hospital was 34.5 baht per unit. If we reduce the dose by 19.2 unit, it will reduce the drug price by 662 baht per person or 2,648 baht per person per year. The treatment efficiency remains the same. The possible reason may be the biological availability of Dysport ® could be enhanced by increasing the injection volume[18], we dilute the 75% BTA to get the same volume of normal dose. The low-dose treatment was as effective as the treatment with the recommended normal doses. The benefits include a low risk of antibody formation and substantial cost savings.

Summary

Botulinum toxin A treatment for hemifacial spasm is effective, sustainable, safe and had minimal, well-tolerated side effects. Low dose BTA injection is an effective treatment for hemifacial spasm and sustainable response as high dose. Therefore low dose BTA is non-inferiority than high dose BTA.

The author was suggested there was a longer duration trial of response in low dose BTA. This study is an ongoing trial to study in efficacy, minimal doses response, sustainable response and complication of treatment in the next research.

Table 1 baseline characteristic of all hemifacial spasm patients

	Normal dose n = 34 (%)	75 % dose n = 35 (%)	p-value
Sex			
Female	29 (85)	28 (80)	0.750
Male	5 (15)	7 (20)	
Age, mean (SD)	58.7 (13.0)	60.4 (11.9)	0.570
range	(52.5, 68)	(53.0, 69)	
โรคประจำตัว			0.750
No underlying disease	21 (62)	23 (66)	
Hypertension (HT)	4 (12)	3 (9)	
Diabetic mellitus (DM)	2 (6)	0	
HT + DM	1 (3)	2 (6)	
Old CVD	1 (3)	3 (9)	
Others neuro-disease	1 (3)	0	
Others medical disease	4 (12)	4 (11)	

	Normal dose n = 34 (%)	75 % dose n = 35 (%)	p-value
Grade, mean (SD)	3.4 (0.7)	3.1 (0.7)	0.073
2	5 (15)	8 (23)	
3	10 (29)	16 (46)	
4	19 (56)	11 (31)	
Side			0.530
Left	22 (65)	18 (51)	
Right	11 (32)	15 (43)	
Bilateral	1 (3)	2 (6)	

SD=Standard Deviation, HT=hypertension, DM=diabetes mellitus, CVD=cerebrovascular disease

Table 2 Dose of botulinum toxin and duration of response

	Normal dose n = 34	75 % dose n = 35	p-value
Dose of botulinum toxin, mean (SD), unit	65.3 (15.6)	46.1 (10.8)	<0.001
Point of injection, mean (SD)	3.5 (1.1)	3.3 (1.0)	0.300
Number of injections, median (IQR), times	12.5 (7.0, 18.0)	11.0 (5.0, 21.0)	0.540

IQR= interquartile range

Table 3 Outcome and complications of treatments

	Normal dose n (%)	75 % dose n (%)	p-value
Outcome of treatment			0.280
Excellent (>81%)	1 (3)	0	
Good (61-80%)	11 (32)	11 (31)	
Fair (21-60%)	17 (50)	15 (43)	
Mild (1-20 %)	5 (15)	9 (26)	
Not improvement	0	0	
Duration of response, mean (SD), month	2.9 (0.2)	3.0 (0.2)	0.140
Complication			1.000
No complication	34 (100)	34 (97)	
Mild ptosis	0	0	
Mild facial paresis	0	1 (3)	

เอกสารอ้างอิง

1. Lolekha P, Choolam A, Kulkantrakorn K. A comparative crossover study on the treatment of hemifacial spasm and blepharospasm: preseptal and pretarsal botulinum toxin injection techniques. Neurol Sci. 2017 ;38(11):2031-6.
2. Karp BI, Alter K. Botulinum Toxin Treatment of Blepharospasm, Orofacial /Oromandibular Dystonia, and Hemifacial Spasm. Semin Neurol. 2016 ;36(1):84-91.
3. Dong H, Fan S, Luo Y, Peng B. Botulinum toxin relieves anxiety and depression in patients with hemifacial spasm and blepharospasm. Neuropsychiatr Dis Treat. 2019;15:33-6.
4. Elston J S MP, ed., editors. Indiopathic blepharospasm, hemifacial spasm and therapeutic ptosis induction.1995.
5. Costa J, Espirito-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, et al. Botulinum toxin type A therapy for hemifacial spasm. Cochrane Database Syst Rev. 2005 Jan 25(1):CD004899.
6. Batisti JP, Kleinfelder AD, Galli NB, Moro A, Munhoz RP, Teive HA. Treatment of hemifacial spasm with botulinum toxin type a: effective, long lasting and well tolerated. Arq Neuropsiquiatr. 2017 ;75(2):87-91.
7. Schellini SA, Matai O, Igami TZ, Padovani CR, Padovani CP. [Essential blepharo spasm and hemifacial spasm: characteristic of the patient, botulinum toxin A treatment and literature review]. Arq Bras Oftalmol. 2006 ;69(1):23-6.
8. Jitpimolmard S, Tiamkao S, Laopaiboon M. Long term results of botulinum toxin type A (Dysport) in the treatment of hemifacial spasm: a report of 175 cases. J Neurol Neurosurg Psychiatry. 1998 ;64(6):751-7.
9. Astarloa R, Morales B, Sanchez V, Penafiel N, Rabano J, Olivan J, et al. [Focal dystonias and facial hemispasm: treatment with botulinum A toxin]. Arch Neurobiol (Madr). 1991;54(5):210-7.
10. Poungvarin N, Viriyavejakul A. Two hundred and fifty patients with hemi facial spasm treated with botulinum toxin injection. J Med Assoc Thai. 1992;75(4):199-203.
11. Yoshimura DM, Aminoff MJ, Tami TA, Scott AB. Treatment of hemifacial spasm with botulinum toxin. Muscle Nerve. 1992 ;15(9):1045-9.
12. Suputtitada A, Phanthumchinda K, Locharernkul C, Suwanwela NC. Hemifacial spasm: results of treatment with low dose botulinum toxin injection. J Med Assoc Thai. 2004 ;87(10):1205-11.
13. Van den Bergh P, Francart J, Mourin S, Kollmann P, Laterre EC. Five-year experience in the treatment of focal movement disorders with low-dose Dysport botulinum toxin. Muscle Nerve. 1995 ;18(7):720-9.
14. Lee JA, Jo KW, Kong DS, Park K. Using the new clinical grading scale for quantification of the severity of hemifacial spasm: correlations with a quality of life scale. Stereotact Funct Neurosurg. 2012;90(1):16-9.

15. Shah A, Horowitz M. Persistent hemifacial spasm after microvascular decompression: a risk assessment model. Br J Neurosurg. 2017;31(3):327-35.
16. Dutton JJ, Buckley EG. Long-term results and complications of botulinum A toxin in the treatment of blepharospasm. Ophthalmology. 1988 ;95(11):1529-34.
17. Hubble J, Schwab J, Hubert C, Abbott CC. Dysport (botulinum toxin type A) in routine therapeutic usage: a telephone needs assessment survey of European physicians to evaluate current awareness and adherence to product labeling changes. Clin Neuropharmacol. 2013 ;36(4):122-7.
18. Bigalke H, Wohlfarth K, Irmer A, Dengler R. Botulinum A toxin: Dysport improvement of biological availability. Exp Neurol. 2001 ;168(1):162-70.