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A. Suputtitada

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Treatment of spastic adult patients with low dose of botulinum toxin type A at King Chulalongkorn Memorial Hospital

Areerat Suputtitada*

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- Objective** : *To assess efficacy and safety of low dose botulinum toxin type A(BTA) in spastic adult patients.*
- Design** : *An open-label, uncontrolled , before-after treatment comparison clinical study*
- Setting** : *Spastic and Dystonia Clinic, Department of Rehabilitation Medicine, King Chulalongkorn Memorial Hospital*
- Patients** : *84 adult patients with spasticity (45 males, 39 females) were recruited when their medical and neurological conditions were stable: no outstanding cognitive deficit, capable of independent activities in daily livings (ADL) , ambulation, and had received at least 6 months of rehabilitation therapy.*
- Study drug** : *Low dose of BTA(1/2-2/3 of recommended dose) were studied.*
- Main outcome measures** : *(1) modified Ashworth scale (MAS), (2) an observational gait and motion of the upper limbs were recorded and assessed by video, (3) global pain scale, and (4) the patient or caregiver evaluation of overall response by continuous scale.*

- Results** : *Low dose of BTA reduced spasticity, spasm frequency, pain, and functional disability in all patients. Often, improvements were seen in the first 3 - 5 days post-treatment. Mean modified Ashworth scores (MAS) dropped within 4 weeks of treatment, approached the lowest at week 8 (3.1 ± 0.2 before injection to 0.21 ± 0.11 at week 8 after injection; $p < 0.01$) The durations of no spasticity were 3 - 6 months. 25 patients (29.76 %) had no return of spasticity after 2 - year follow up. All patients had no adverse event.*
- Conclusion** : *The low dose of BTA had significant efficacy and safety in the treatment of spastic adult patients.*
- Key words** : *Spastic adult patients, Low dose of botulinum toxin type A (BTA).*

Reprint request : Suputtitada A. Department of Rehabilitation Medicine, Faculty of Medicine,
Chulalongkorn University, Bangkok 10330, Thailand.

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อารีรัตน์ สุพุทธิธาดา. การรักษาภาวะกล้ามเนื้อหดเกร็งในผู้ใหญ่ด้วยยาฉีดโบทูลินุมชนิดเอปริมาณน้อยที่โรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2545 เม.ย; 46(4): 315 - 25

- วัตถุประสงค์** : เพื่อศึกษาประสิทธิภาพและความปลอดภัยในการรักษาภาวะกล้ามเนื้อหดเกร็งในผู้ใหญ่ด้วยยาฉีดโบทูลินุมชนิดเอปริมาณน้อย
- รูปแบบ** : การทดลองชนิดเปิดและไม่มีกลุ่มควบคุม เปรียบเทียบผลก่อนและหลังการรักษา
- สถานที่** : คลินิกลดเกร็ง ฝ่ายเวชศาสตร์ฟื้นฟู โรงพยาบาลจุฬาลงกรณ์
- ผู้ป่วยที่ทำการศึกษา** : ผู้ป่วยผู้ใหญ่ที่มีภาวะกล้ามเนื้อหดเกร็ง (ชาย 45 ราย หญิง 39 ราย) รับผิดชอบเข้ามาทำการศึกษานานกว่า 6 เดือน ไม่มีการเปลี่ยนแปลงทางด้านอายุรกรรมและระบบประสาทแล้ว ไม่มีความผิดปกติของการรับรู้ มีแนวโน้มที่จะทำกิจวัตรประจำวันและเดินได้เอง และเคยได้รับการรักษาทางเวชศาสตร์ฟื้นฟูมาแล้วไม่น้อยกว่า 6 เดือน ก่อนนำมาศึกษา
- ยาที่ศึกษา** : ยาฉีดโบทูลินุมชนิดเอปริมาณน้อย (1/2-2/3 ของปริมาณยาที่ใช้ในต่างประเทศ)
- การวัดผล** : (1) ความรุนแรงของการเกร็งโดย modified ashworth scale (MAS) (2) วิเคราะห์การเดินและการเคลื่อนไหว การใช้แขนและมือโดยบันทึกวิดีโอ (3) ระดับอาการปวดโดยรวม (4) ความรู้สึกของผู้ป่วยและญาติต่อการตอบสนองต่อการรักษาโดยรวม
- ผลการศึกษา** : การรักษาด้วยยาฉีดโบทูลินุมชนิดเอปริมาณน้อยสามารถลดความรุนแรงของการเกร็ง อาการปวด ความสามารถในการทำงาน ในผู้ป่วยทุกราย เริ่มเห็นผล 3 - 5 วัน หลังฉีดยา ค่าเฉลี่ยของ MAS ลดลงภายใน 4 สัปดาห์และลดลงมากที่สุดเมื่อสัปดาห์ที่ 8 (3.1 ± 0.2 ก่อนฉีดยา เหลือ 0.21 ± 0.11 อย่างมีนัยสำคัญทางสถิติที่ $P < 0.01$) ระยะเวลาที่ไม่มีอาการเกร็งประมาณ 3 - 6 เดือน ผู้ป่วย 25 ราย (29.76 %) ไม่พบอาการเกร็งอีกเมื่อติดตามนาน 2 ปี ทุกรายไม่พบอาการข้างเคียงใด ๆ
- สรุป** : ยาฉีดโบทูลินุมชนิดเอปริมาณน้อยมีประสิทธิภาพและปลอดภัยในการรักษาภาวะกล้ามเนื้อหดเกร็งในผู้ใหญ่
- คำสำคัญ** : ผู้ป่วยผู้ใหญ่ที่มีภาวะกล้ามเนื้อหดเกร็ง, ยาฉีดโบทูลินุมชนิดเอปริมาณน้อย

Spasticity is a significant functional problem in the physiatric management of patients with upper motor neuron lesions. Most of the current treatments for spasticity have side effects and limitations. There is a need for an easily administered treatment that will control spasticity without producing generalized weakness or other systemic effects. Existing treatments for spasticity may be categorized as systemic or locally acting. The latter has the advantage of reducing harmful spasticity in one area while preserving useful spasticity in other areas. The treatments include nerve and motor point blocks and surgical procedures.

Botulinum toxin type A (BTA) is effective for the treatment of focal dystonia. The potentiality of BTA in the treatment of spasticity has been more recently recognized; it may offer several advantages over nerve and motor point block such as pain-free paresthesia, no thrombophlebitis, simple and quickly to be administered by an experienced physician.

The first paper on the use of BTA for spastic adult patients was published in 1989.⁽¹⁾ In the meantime a few hundred respective publications were released. The majority of which, however, were experience reports, case records or reports on open-label studies.⁽²⁾ Some were randomized placebo-controlled, double blind studies.⁽²⁾ Since BTA treatment is an expensive intervention, I propose to evaluate the lowest effective dose of BTA in the treatment of spastic adult patients.

This is an open-label, uncontrolled clinical study to assess the efficacy and safety of low dose BTA in the treatment of spastic adult patients.

Materials and Methods

Study design

This was a prospective open-labeled, uncontrolled clinical trial, before-after treatment comparison clinical study.

Study subjects

Adult patients, males and females, with spasticity who were consulted for treatments of spasticity at the Spastic and Dystonia Clinic, Department of Rehabilitation Medicine, King Chulalongkorn Memorial Hospital from December 1995 until November 2001. (6 Years) were recruited into the study with the following criteria: (1) over 15 years old; (2) having spasticity from all causes; stroke, brain injury, spinal cord lesion, multiple sclerosis, degenerative disease, etc; (3) have spasticity in any limb; (4) being medically and neurologically stable, (5) having no notable cognitive deficits, with potential independent activities of daily livings (ADL) and ambulation, (6) having received at least 6 months of rehabilitation therapy.

Criteria for exclusion were: (1) complete plegia (strength grade < 2 in target segments); (2) known hypersensitivity to any ingredient in the BTA preparation; (3) diagnosis of myasthenia gravis, Eaton Lambert syndrome, or amyotrophic lateral sclerosis; (4) uncontrolled systemic disease; (5) evidence of a fixed contracture in the target limb; (6) pregnancy, planned pregnancy, lactation; (7) current/previous surgery or phenol injections into target muscles, (8) concurrent use of aminoglycoside antibiotics; (9) obvious atrophy of the muscles of target limb.

The study is complied with the Declaration of Helsinki recommendations regarding biomedical research involving human patients. The study design,

purpose, and potential risks of participation were discussed with each patient prior to enrollment.

Study medication

Botulinum toxin type A (Botox 100 unit vial; Allergan, Inc, Irvine, CA) was reconstituted for injection with 50 unit/ml of 0.9 % sterile unpreserved saline.

Interventions

At the initial visit, the degree of spasticity, activities of daily living (eating, grooming, bathing, dressing, transfer), ambulation, goals of treatment in each patient were evaluated. Because of the high cost of BTA and general safety concerns, it was desirable to use the lowest dose that would provide the desired clinical benefit. The starting doses used in this study were about 1/2-2/3 of recommendation dose based on the Spasticity Study Group recommendations.⁽³⁾ The doses of Botox were adjusted according to modified Ashworth scale (MAS) and, the size of the muscles to be injected.

A 27- gauge Teflon-coated combination electromyography electrode/injection needle (Botox injection needle; Allergan) was used both to locate the optimum injection site within each muscle, and to inject the toxin. The choice of injection site was guided by anatomical knowledge of the location of the motor end plate for each muscle, established by standard guidelines.⁽⁴⁾

After injection, all patients were instructed to do stretching exercises by the author. They needed to do the exercises at home everyday.

Outcome measures

The effects of the treatment were assessed

by (1) a modified Ashworth scale (MAS) for passive and active muscle tone and degree of spasticity,(2) an observational gait and motion of the upper limbs assessment by recorded video-tape, (3) global pain scale,⁽⁵⁾ (4) spasm frequency scale,⁽⁵⁾ and (5) the patient or caregiver evaluation of overall response by continuous scale.⁽⁵⁾

All patients were evaluated at baseline and 2,4 and 8 weeks after injections. The patients were then evaluated every 2 months until spasticity returned to the observed level before the BTA injection.

The author participated in all measurements. For most patients, a third-year resident in the clinic also took all measurements, and the result determined by the two observers were the same, However no formal interobserver reliability testing was performed. Adverse events were evaluated based on spontaneous patient reports.

Statistical analysis

Descriptive statistics were used to report patient demographics and student's t-tests were used to detect significant change between pre-and postinjection outcome measures of global pain scale and the patient or caregiver evaluation of overall response by continuous scale. Wilcoxon non-parametric analysis was used to analyse changes in spasticity as graded by the MAS. The changes between pre-and postinjection was statistical significant at $p < 0.01$.

Results

Patients population

84 spastic adult patients (45 males, 39 females) were enrolled in the study. Their mean age

at the time of study entry was 45 ± 6 years old. 52 (61.9 %) adult patients had stroke, 19 (22.6 %) had brain injury, 8 (9.5 %) had spinal cord injury, 3 (3.5 %) had multiple sclerosis, 2 (2.3 %) had spinocerebellar degeneration. 22 (26.19 %) patients had both upper and lower limbs spasticity. 21 (25 %) had upper limbs spasticity, 39 (46.42 %) had lower limbs spasticity, 4 (4.76 %) had truncal spasticity, 2 (2.3 %) had lower limbs and truncal spasticity.

The clinical patterns were as the followings; 9 patients were abducted/internally rotated shoulder, 26 patients were flexed elbow, 3 patients were pronated forearm, 18 patients were flexed wrist, 6 patients were thumb-in-palm, 11 patients were clenched fist, 4 patients were intrinsic plus hand. 5 patients were flexed hip, 4 patients were flexed knee, 4 patients were adducted thigh, 2 patients were extended knee, 19 patients were equinovarus foot, 7 patients were equinus foot, 28 patients were spastic toes.

Dosage findings

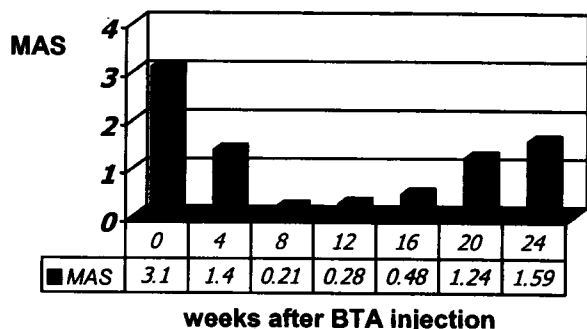
The potential muscles involved and range of dosage findings were as the followings; pectoralis complex 50 - 75 units, subscapularis 20 - 40 units, brachioradialis 15 - 25 units, biceps 30 - 75 units, pronator teres 15 - 20 units, FCR 25 - 50 units, FCU 15 - 20 units, FPL 5 - 10 units, adductor pollicis 5 - 10 units, FDP 15 - 30 units, FDS 15 - 30 units, lumbricals interossei 10 - 20 units/hand, iliopsoas 30 - 75 units, medial and lateral hamstrings 50 - 100 units, adductor magnus/longus/brevis 50 - 100 units/leg, quadriceps 50 - 100 units, gastrocnemius 25 - 125 units, soleus 25 - 50 units, tibialis posterior 25 - 75 units, EHL 50 - 95 units, FHL 50 - 95 units, FD 25 - 85 units.

Efficacy findings

Treatment with BTA reduced spasticity, spasm frequency, pain, and functional disability in all patients. Often, improvements were seen during range-of-motion exercises in the first 3 to 5 days posttreatment.

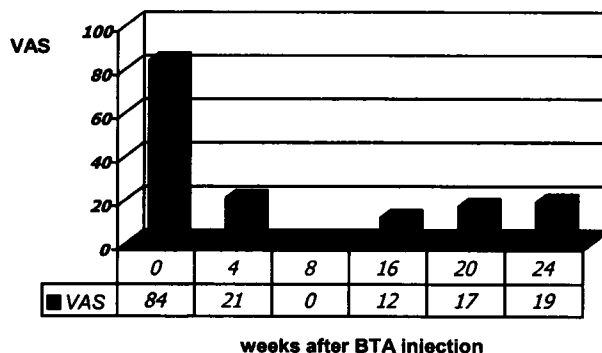
Mean modified Ashworth scale (MAS) dropped within 4 weeks of treatment (3.1 ± 0.22 preinjection and 1.4 ± 0.08 at week 4; $p < 0.01$), approached the lowest at week 8 (3.1 ± 0.22 preinjection and 0.21 ± 0.005 at week 8; $p < 0.01$) and then gradually increased throughout the 6-month studied period (1.59 ± 0.02 at week 24) (Graph 1). Twenty-five of these patients (29.76 %) still exhibited beneficial effects more than 2 years after the treatment. Eleven patients (13.09 %) returned to baseline spasticity levels at month 3. Nineteen patients (22.6 %) returned to baseline at month 4. Eleven patients (13.09 %) returned to baseline at month 5. Eighteen patients (21.42 %) returned to baseline at month 6. Mean global pain score (visual analogue pain scores; VAS) also decreased during the first 4 weeks following treatment (84 ± 5 preinjection and 21 ± 3 at week 4; $p < 0.01$), approached zero at week 8 (84 ± 5 preinjection and 0 ± 2 at week 8; $p < 0.01$) and remained below 20 (out of 100) through week 20. At the end of the 6-month studied period, the mean pain score was still less than half what it was at baseline (19 ± 5) (Graph 2).

Mean percentage of normal functional ability mirrored the ashworth and pain scores, increased during the first 4 weeks posttreatment (15 ± 4 preinjection and 64 ± 5 at week 4; $p < 0.01$), reached the peak at week 8 (15 ± 4 preinjection and 89 ± 7 at week 8; $p < 0.01$) and remained above 60 % throughout the 6-month studied period (Graph 3).



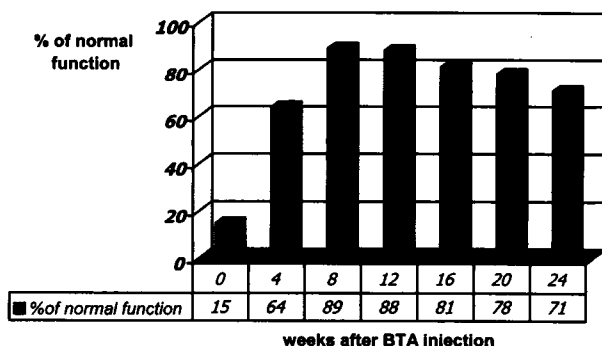
Graph 1. Effect of BTA on mean modified Ashworth scale (MAS).

Mean MAS dropped within 4 weeks after BTA injection, approached the lowest score at week 8 and then gradually increased throughout the 6 months studied period.



Graph 2. Effect of BTA on global pain scale (VAS).

Mean global pain score decreased during the first 4 weeks following BTA injection, approached the zero score at week 8 and then gradually increased. At the end of 6-month studied period, the pain score still less than half what it was at baseline.



Graph 3. Effect of BTA on functional ability.

Mean percentage of normal function increased during the first 4 weeks after BTA injection, reached the peak at week 8 and remain

Safety findings

No adverse events were reported.

Discussion

This preliminary study suggests that treatment of spastic adult patients with low dose BTA is safe; the treatment provides a long-lasting improvements of spasticity, global pain, and functional ability for most patients. However, a further study is needed to determine whether the dosing paradigm employed in the study should be slightly for higher or lower.

Members of the Spasticity Study Group have arrived at a consensus on recommended initial doses and dose ranges for the treatment of spasticity, based on their collective clinical experience.⁽³⁾ However, additional considerations must be addressed to determine whether to adjust the initial dose within the range given. The present study used an initial BTA dose based on baseline spasticity severity as measured by the modified Ashworth scale. Because of the high cost of BTA and general safety precaution,

it is always desirable to use the lowest dose that will give the desired clinical benefit. The starting doses used in the study were chosen based on the Spasticity Study Group recommendations and investigator's clinical experience. This open-label study showed that many patients were effectively treated with doses that were slightly lower than the Spasticity Study Group recommendations. However, a larger, double blind, randomized clinical trial is needed to explore further issues.

This study showed significant improvement with low complication. The hypotheses were (1) the low effective doses to be given (2) the EMG guidance for efficacy and precise localization (3) the strengthening and stretching exercise that were prescribed after injection (4) the potential of patients to independent ADL and ambulation and had no impair cognitive function were included, so that they all use the target limbs after injection. Several papers focus on the methods to improve the result of treatment with BTA in spastic disorders: electrical stimulation improves the action of BTA in patients with leg spasticity, hemiparesis and in those presenting with arm flexor spasticity following stroke.⁽⁶⁻⁸⁾ Muscle stretching may improve the therapeutic effect of BTA.⁽⁹⁾ Automatic EMG guidance may improve the result of treatment with BTA.⁽¹⁰⁾

The majority of patients experienced reductions in spasticity, pain, and functional disability within a few weeks of treatment. No patients returned to baseline spasticity scores before 3 months posttreatment and most experienced benefits for 5 to 6 months or longer. The duration of the effect reported in this study is at the high end of the 2 - 6 month range commonly reported for BTA therapy.^(1,11-37)

Twenty-five of the patients (29.76 %) still exhibited beneficial effects more than 2 years after their treatment. This might be a combined effects with the rehabilitation therapy after injection and the spontaneous improvement that can be experienced by brain injury patients and stroke patients over a long period of time.

There were also placebo-controlled, double-blind studies, regarding adductor spasticity and hemispasticity that revealed BTA alleviated pain and lacerated spasms.^(38,39) Moreover, there are clinical experience reports about its effect on arm/hand/finger flexor spasticity and spasticity of every kind.^(18,21,27)

The success of low doses of BTA treatment in relieving signs and symptoms of spasticity in adults adds further support to the expanding literature on the usefulness of BTA in the treatment of many further types of spasticity. It is also my personal observation that patients also seem benefit more from their physical therapeutic regimen when their spasticity was reduced by BTA. The lack of any significant adverse effects is also typical of BTA treatment for a number of reasons. Even when significantly larger doses were prescribed to children, most adverse effects were mild to moderate and transient.⁽³³⁻³⁷⁾

Intramuscular BTA injection benefits the treatment of local spasticity without providing the same disadvantages of phenol injections which may cause dysesthesia and local tissue necrosis in the treated limb.. It is an established standard treatment for strabismus, blepharospasm, hemifacial spasm, torticollis, and focal dystonias (AAN Consensus statement). Recently, it has been used to treat limb spasticity. Unlike phenol nerve blocks, it has a selective action on motor nerves without affecting

sensory nerve conduction. Preserved perception is an integral part of maximizing motor recovery after stroke, brain injury, incomplete spinal cord injury, etc and therefore treatments that do not cause sensory disturbance have an advantage over those that cause sensory deficits.^(40,41)

Conclusion

In conclusion, the study shows that low dose BTA (1/2-2/3 of Spasticity Study Group's recommended dose) safe and effective a treatment for spasticity in adults.

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