

Effect of Botulinum Toxin Injection for Achalasia in Thai Patients

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Background: Achalasia is a disorder of the esophagus. The lower esophageal sphincter fails to relax and increases the loss of body peristalsis. It is an uncommon disease worldwide. Data regarding its treatment are derived mostly from North America and European countries. Few data regarding this treatment were available in Asia and no data about using botulinum toxin injection for this disease was available in Thailand.

Objective: To evaluate the efficacy of botulinum toxin in achalasia in Thai patients.

Material and Method: Eleven achalasia adult Thai patients with a mean age of 56.5 ± 16.9 were studied. There are nine females and two males. The duration of symptom before treatment was 27.5 ± 34.5 months. All patients receiving botulinum toxin injection at Siriraj hospital between 2001 and 2006 were retrospectively reviewed. Pretreatment of baseline lower esophageal sphincter, symptom score and body weight were compared. Time to second botulinum toxin injection or the need to receive treatment for recurrence was recorded to evaluate the time of recurrence. Adverse events from this procedure were collected.

Results: Eleven patients were involved in this study. One patient that received 40 units of botulinum toxin showed no response after a six months follow up. The other ten patients received botulinum toxin 80 units for each session and were enrolled in this study. All ten patients demonstrated good response to the first botulinum toxin injection and subsequent injections. Four patients received only one session of botulinum toxin injection during study period. Meanwhile, five patients received two sessions and only one patient required four sessions. Symptom score of all ten patients improved significantly compared with pretreatment score (7.3 ± 1.3 for pretreatment and 0.4 ± 0.5 , 0.9 ± 0.7 and 1.6 ± 1.3 after 2 weeks, 3 months and 6 months, respectively). Body weight increased significantly when compared with pretreatment (47.7 ± 6.5 Kg for pretreatment and 49.2 ± 5.8 , 50.5 ± 6.4 , and 50.7 ± 5.8 Kg after 2 weeks, 3 months, and 6 months, respectively). Previous treatments prior botulinum toxin injection do not seem to influence the effect of this treatment. Mean time of recurrence is 444 ± 132 days (270 – 718 days). Minor adverse events such as chest pain and reflux symptoms were seen in this therapy.

Conclusion: Botulinum toxin injection in Thai achalasia patients is an effective, simple, and safe treatment. These results showed the similar outcomes as in Caucasian patients.

Keywords: Botulinum toxin, Botox, Achalasia, Thais

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Achalasia is a disorder of lower esophageal sphincter (LES) characterized by the absence of peristalsis, an elevated pressure of the LES, and failure of the LES to relax during swallowing⁽¹⁾. This phenome-

non is characterized by an imbalance of excitatory and inhibitory neurons in LES. The hypertonic LES fails to relax because of the selective loss of the inhibitory nerves. Locally injected botulinum toxin (Botox) blocks the release of acetylcholine and may restore the LES to a more normal resting tone^(2,3). At present, conventional treatments for this disease includes Botox injection,

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esophageal pneumatic dilatation, and surgical myotomy.

Botox injection for achalasia has first been employed in human by Pasricha PJ⁽⁴⁾. Many studies of this treatment has shown good initial response however, its effect is not as long lasting as the esophageal pneumatic dilatation or the surgical myotomy. More serious complications such as esophageal perforation and esophageal stricture were seen in a patient treated by pneumatic dilatation and subsequently, myotomy. On the other hand, Botox injection is less expensive, risk-free, easily performed by any endoscopist, and the result of the treatment seem to be reproducible. Up to now, most of the data regarding the efficacy of Botox injection came from North America and Europe. Few data were from Asia and no data was available in Thailand. Our objective in this study is to clarify the efficacy of Botox injection in adults Thai achalasia patients.

Material and Method

Patients

Eleven adult patients with clinical and esophagogastroduodenoscopy (EGD), esophageal manometry or barium swallowing, compatible with achalasia were enrolled in this study. We excluded patients younger than 18 years old.

Study design

A retrospective study of achalasia patients treated by Botox injection in Siriraj hospital, a tertiary care medical school, between 2001 and 2006 was performed.

Esophageal manometry

Esophageal manometry was performed with Mui system No 9043H03 11 (MUI Scientific Company, Ontario, Canada). It is comprised of eight capillary tubes around a larger central tube with an overall diameter of 4.5 mm. One orifice locates at the distal margin to monitor intragastric pressure and six at 0, 3, 8, 13, 18 and 23 or 28 cm respectively from the upper margin of the sleeve sensor (Dent sleeve, Arndorfer Medical system, Greendale, WI, USA). The lumen of each tube was constantly perfused with distilled water at a rate of 0.3 mL/min. A pressure transducer was incorporated to each perfusion line and connected to a polygraph device. During the study, the manometric recordings were displayed on the screen of an online computer and were stored for later analysis with the use of a software of Polygram program. Esophageal manometry

was assessed baseline LES and relaxation. The presence of peristalsis and esophageal amplitude in distal esophagus were analyzed during 5 wet swallows. An average of esophageal amplitudes greater than 37 mmHg⁽⁵⁾ was diagnosed as vigorous achalasia.

Endoscopic Botulinum toxin injection

Botox (Oculinum, Allergan, Irvine, California, USA) was injected through a 5-mm sclerotherapy needle into the region of the LES. Aliquots of 1 ml each (20 units of Botox per milliliter of saline) were injected into quadrants, for 80 units. The injection locations were estimated endoscopically to within one centimeter above the squamocolumnar junction by one endoscopist in Siriraj hospital. The procedure was performed on an outpatient basis in most cases, and the patients were allowed to eat later the same day. As we mentioned above, this technique has not been started in Thailand until 2001. At that time, we decided to use 40 units of Botox in one patient as the recommended lowest dosage was 50 units⁽⁶⁾.

Clinical assessment

We assessed the baseline pretreatment LES pressure, symptom response before and after treatment by modified symptom score⁽⁷⁾, which was the sum of the individual scores for three symptoms of achalasia: dysphagia, regurgitation, and chest pain. The frequency of each of these symptoms was graded on a scale of 0 to 3 (0, none; 1, occasional; 2, daily; 3, with each meal). Thus, the maximal total score was 9 points. Clinical remission was defined as a score of 3 or less during follow-up, and failure of treatment (or relapse) as a score of 4 or more. Body weight before and after treatments were used to assess the efficacy of Botox therapy. Comparing before and after treatment at 2 weeks, 3 months, 6 months and 12 months of Botox injection regarded as LES pressure, symptom score and body weight were performed for evaluation of efficacy of Botox therapy. When the data obtained was more than 80%, it was eligible for analysis.

Statistical analysis

Wilcoxon signed-rank test with multiple comparison were used for paired nonparametric data. Data is expressed as means SD and any $p < 0.05$ was considered statistically significant. Time of recurrence was determined by using Kaplan-Meier curves.

Results

Eleven patients were involved in this study.

One patient who received 40 units of Botox showed no response after 6-month period of follow up. Ten out of the eleven patients who received Botox 80 units were enrolled in this study. The mean age of the ten patients was relatively old (58.9 ± 15.8). Nine of ten patients were female. This might be from the patients' selection of the modality of treatment. Botox seems to have fewer complications compared with pneumatic dilatation and surgery. The diagnosis of achalasia was confirmed by EGD and esophageal manometry 40%, EGD, manometry and barium swallowing 30%, EGD and barium swallowing 20%, and only EGD 10%. Two patients were diagnosed as vigorous achalasia. We excluded one patient who received Botox 40 units and failed to respond in both symptom score and body weight. This patient subsequently received esophageal balloon dilatation. All the patient characteristics are summarized in Table 1.

Clinical Outcome of Botulinum toxin injection

Eleven patients were involved in this study. One patient received 40 units of Botox and showed no response after follow up for six months. The other ten patients who received Botox 80 units for each session were enrolled in this study. All ten patients demonstrated good response to the first Botox injection and subsequent injections. Four patients received only one session of Botox injection during study period. Meanwhile, five patients received two sessions and only one required four sessions. Symptom score of all ten

patients improved significantly compared with pretreatment score (7.3 ± 1.3 for pretreatment and 0.4 ± 0.5 , 0.9 ± 0.7 and 1.6 ± 1.3 after 2 weeks, 3 months and 6 months, respectively). Body weight increased significantly when compared with pretreatment (47.7 ± 6.5 for pretreatment and 49.2 ± 5.8 , 50.5 ± 6.4 , and 50.7 ± 5.8 after 2 weeks, 3 months and 6 months, respectively). Previous treatments prior to the Botox injection do not seem to influence the effect of this treatment. Mean time of recurrence is 444 ± 132 days (270-718 days). Three out of ten patients received Botox therapy for first treatment and esophageal pneumatic dilatation subsequently after relapsing from their symptoms at 9, 12, and 16 months, respectively. Only one from ten patients received four sessions of botulinum toxin therapy after 12, 25, 11 and 2.9 months of each Botox therapy, subsequently. This patient was initially treated by surgery 43 years before the first Botox treatment and end up with esophageal pneumatic dilatation after the fourth Botox therapy. Moreover, one patient initially treated by dilatation had recurrence of symptoms 9 months after and was crossed over to Botox therapy. Sixteen months after first Botox therapy, he remained in remission until loss to follow up. This patient was the only one patient that was loss from follow up. Interestingly, one patient has been in remission for 4 years and 3 months after the first session of Botox therapy.

Initial response

Two weeks after Botox therapy, symptom score showed a significant improvement, which decreased from 7.3 ± 1.3 to 0.4 ± 0.5 ($p < 0.05$) (Table 2). Similarly, the mean of body weight also demonstrated significant improvement as well. The mean body weight increased from 47.7 ± 6.5 to 49.2 ± 5.8 ($p < 0.05$) (Table 2). Unfortunately, there was not enough data to analyze the LES pressure after treatment at 2 weeks.

Long-term follow-up

The results of symptom score and body weight at 3 months and 6 months after Botox injection therapy shows a significant improvement compared with pretreatment. The symptom score was 7.3 ± 1.3 vs 0.9 ± 0.7 ($p < 0.05$), and 1.6 ± 1.3 ($p < 0.05$ vs pretreatment) while the mean of body weight was 50.5 ± 6.4 , $p < 0.05$ vs pretreatment) at 3 months and significant improvement at 6 months (50.7 ± 5.8 vs pretreatment 47.7 ± 6.5 ($p < 0.05$) (Table 2). Data regarding baseline LES pressure after Botox injection at 3 and 6 months were not available to analysis as at 2 weeks after treatment either.

Table 1. Patients' characteristics

	Botulinum toxin injection
No. of patients	11
Age (years, mean \pm SD)	56.5 ± 16.9 (33-81)
No. of patients using Botox 40 units	1
No. of patients using Botox 80 units	10
Male/Female	2/9
Duration of symptoms (months)	27.5 ± 34.5
Body weight, Kg	47.7 ± 6.5
Initial symptom score (0-9)	7.3 ± 1.3
Initial LES pressure (mmHg)	29.5 ± 24.9
No. of patients undergoing (N = 11)	
1 procedure	5
2 procedures	5
3 procedures	0
4 procedures	1

LES = Lower esophageal sphincter

Table 2. Clinical parameters at baseline and after therapy from Botulinum toxin injection

Clinical parameter	Pretreatment	2 wk	3 mo	6 mo
Symptom score (0-9)	7.3 ± 1.3	0.4 ± 0.5*	0.9 ± 0.7*	1.6 ± 1.3*
Body weight (Kg)	47.7 ± 6.5	49.2 ± 5.8*	50.5 ± 6.4*	50.7 ± 5.8*

data were expressed as mean values ± SD, N = 10

* p < 0.05 vs pretreatment

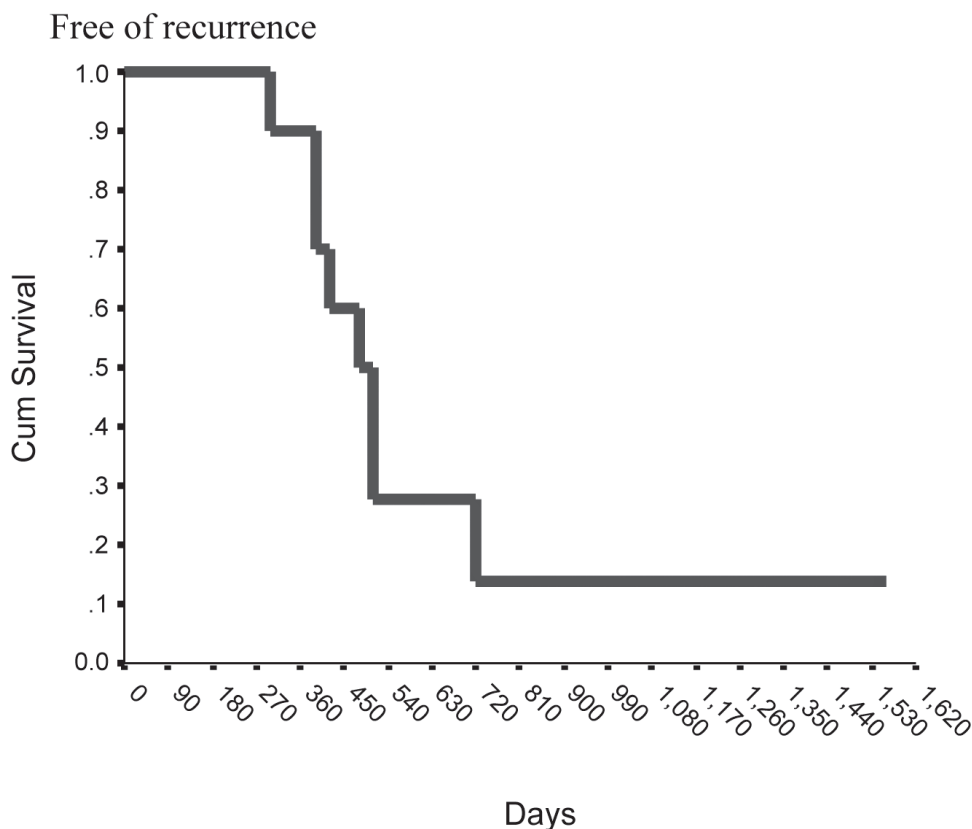


Fig. 1 Remission rate after a single botulinum toxin injection, Median survival time is 480 days (270-718 days). Mean time of recurrence = 444 ± 132 days

Previous treatments prior to Botox injection do not seem to influence the effect of this treatment. Mean time of recurrence is 444 ± 132 days (270-718 days). Median time of these data is 480 days (16 months). Surprisingly, good response of Botox therapy was seen in both naïve achalasia and prior treated by esophageal pneumatic dilatation or surgery.

Side effect

There were no serious adverse events of any injections. Two patients reported transient mild chest

pain and three had mild heartburn that could be controlled by proton pump inhibitor.

Discussion

It has been shown that Botox injection is good for the treatment of achalasia, improving the clinical symptoms and objective parameters⁽⁸⁾. This study was the first study in Thai patients to show the efficacy of Botox in management of achalasia. Botox is relatively expensive compared with pneumatic dilatation however, it is quite safe and simple for any experienced

upper endoscopist to practice. The dosage of 40 units for each session does not seem to show any benefit for Thai patient. As we had only one patient in this group, we were not able to analyze the outcome. More data need to confirm that result. 80 units of Botox injection showed similar good effect in Thai compared with Caucasian patients. It has been shown that doses of 200 units are not substantially more effective than the usual dose of 80-100 units. Previous pneumatic dilatation and surgery does not seem to influence the effects of Botox treatment. This observation is the same as in the previous study done by Pasricha⁽⁹⁾. However, recent studies have shown that previous treatment with Botox injection may increase the difficulty level of the surgical procedure.

Our data have a relative small number of patients, however, the results are reproducible. The difficult technique for measure the baseline LES pressure by using manometry before and after treatment is one of our weak aspects of the data to confirm the results of Botox injection in this study. Anyway, by comparing the body weight and symptom score pre- and post-treatment at each particular time are reasonable parameters to conclude the outcomes of this injection. Our duration of patient symptom, age and number of vigorous achalasia that demonstrates a good response of symptom improvement of Botox injection might be the factors causing this study to have the same outcome as previous studies⁽¹⁰⁻¹²⁾. Botox injection also showed a good response last more than one year after the first session of injection. This should be the first line of recommendation treatment for any elderly achalasia patient who suffers from many underlying diseases. It has been suggested that low-risk patients can choose between pneumatic dilatation or surgical myotomy, however, in case of failure, Botox injection can be performed.

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ผลของการใช้ botulinum toxin ในผู้ป่วย achalasia คนไทย

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สถาพร มานัสสถิตย์

ที่มา: Achalasia เป็นโรคที่เกิดจากความผิดปกติในการทำงานของหูรูดของหลอดอาหารส่วนปลาย ซึ่งไม่สามารถคลายตัวได้ร่วมกับ ตัวหลอดอาหารที่ไม่มีการบีบตัว โรคนี้พบได้ไม่บ่อยในทั่วโลก ข้อมูลส่วนใหญ่เกี่ยวกับการรักษาของโรคนี้จะได้รับมาจากผู้ป่วยในประเทศแถบอเมริกาเหนือ และยุโรป มีเพียงข้อมูลส่วนน้อยจากทวีปเอเชีย และไม่มีข้อมูลเลยสำหรับการรักษาโดยการใช้ Botulinum toxin (Botox) สำหรับโรคนี้ในเมืองไทย

วัตถุประสงค์: เพื่อเป็นการประเมินผลของการใช้ยา Botulinum toxin ในผู้ป่วยไทยที่เป็นโรค achalasia

วัสดุและวิธีการ: เป็นการศึกษาผลการรักษาย้อนหลังจากเพิ่มผู้ป่วย ในผู้ป่วยไทยที่เป็น achalasia จำนวน 11 ราย ในโรงพยาบาลศิริราช ที่ได้รับการฉีดด้วย Botulinum toxin ระหว่างปี พ.ศ. 2544 - พ.ศ. 2549 ทำการเปรียบเทียบผลของความดันของหูรูดหลอดอาหารส่วนปลาย คະแนนของอาการของผู้ป่วย และน้ำหนัก ก่อนและหลังการฉีด Botulinum toxin ศึกษาระยะเวลาที่มีความจำเป็นต้องฉีดยาล้ำซ้ำ เมื่อมีอาการเกิดขึ้นอีก นอกจากนี้ดูผลข้างเคียงของการรักษาในผู้ป่วยทั้งหมด

ผลของการศึกษา: มีผู้ป่วยจำนวน 11 ราย อายุเฉลี่ย 56.5 ± 16.9 ปี เป็นเพศหญิง 9 ราย ชาย 2 ราย เฉลี่ยผู้ป่วยมีอาการของโรค 27.5 ± 34.5 เดือนก่อนการรักษา ผู้ป่วยทั้งหมดได้รับการฉีดด้วย Botulinum toxin โดยมี 1 ราย ได้รับการฉีดจำนวน 40 unit ซึ่งพบว่าผู้ป่วยไม่ตอบสนองต่อการรักษา หลังจากติดตามไปได้ 6 เดือน ในผู้ป่วย 10 รายที่เหลือ ทั้งหมดได้รับการฉีด Botulinum toxin จำนวน 80 unit สำหรับแต่ละครั้งของการฉีด โดยทั้งหมดมีการตอบสนองที่ดีต่อการรักษาไม่ว่าจะเป็นการฉีดครั้งแรกหรือการฉีดซ้ำก็ตาม มีผู้ป่วย 4 ราย ได้รับการฉีด Botulinum toxin เพียง 1 ครั้งระหว่างการศึกษา ขณะที่ 5 ราย ได้รับการฉีด 2 ครั้ง และมี 1 รายที่ต้องฉีดจำนวน 4 ครั้ง คະแนนของอาการในผู้ป่วยทั้ง 10 ราย มีการลดลง เมื่อเทียบกับก่อนการรักษาอย่างมีนัยสำคัญทางสถิติ ณ ที่ 2 สัปดาห์, 3 เดือน และ 6 เดือนหลังการรักษา (7.3 ± 1.3 สำหรับก่อนการรักษา และ 0.4 ± 0.5 , 0.9 ± 0.7 และ 1.6 ± 1.3 หลังจาก 2 สัปดาห์, 3 เดือน และ 6 เดือน ตามลำดับ) พบว่าน้ำหนักผู้ป่วยเพิ่มขึ้น หลังการรักษาเมื่อเทียบกับก่อนการรักษา อย่างมีนัยสำคัญทางสถิติ (47.7 ± 6.5 กิโลกรัม สำหรับก่อนการรักษา และ 49.2 ± 5.8 , 50.5 ± 6.4 , และ 50.7 ± 5.8 กิโลกรัมหลังจาก 2 สัปดาห์, 3 เดือน และ 6 เดือนตามลำดับ) การรักษาด้วยวิธีอื่นก่อนการฉีดด้วย Botulinum toxin ไม่พบว่าทำให้เปลี่ยนแปลงผลของการรักษาในแต่ละการฉีด พบว่าระยะเวลาของค่าเฉลี่ยของโอกาสที่จะมีอาการเกิดเป็นซ้ำเท่ากับ 444 ± 132 วัน (270 - 718 วัน) ผลข้างเคียงของการรักษาไม่พบน้อยมาก ส่วนใหญ่เป็นแบบไม่อันตราย

สรุป: การรักษาโรค achalasia ในผู้ป่วยไทยด้วยการฉีด Botulinum toxin นั้น พบว่าให้ผลดี ง่ายและปลอดภัย การศึกษานี้ให้ผลลัพธ์ของการรักษาเหมือนกับการศึกษาในต่างประเทศ