การศึกษาเปรียบเทียบประสิทธิภาพของการรักษาริ้วรอยตีนกา ด้วยการฉีดสาร โอนาโบทูลินั่มท็อกซินเอ และผลิตภัณฑ์โบทูลินั่มท็อกซินเอชนิดใหม่

Comparison of Onabotulinumtoxin A and New botulinum toxin type A product, in the treatment of Crow's feet

SONGPON MANVONGVIROT

นพ.ทรงพล มั่นวงค์วิโรจน์[1], นพ.ไพศาล รัมณีย์ธร[2]

[1]นิสิตระดับปริญญาโท, [2]อาจารย์

นิสิตระดับปริญญาโท สาขาวิชาตจวิทยา มหาวิทยาลัยแม่ฟ้าหลวง

บทคัดย่อ

โบทูแล๊กซ์ เป็นผลิตภัณฑ์โบทูลินั่มท็อกซินเอชนิดใหม่ มีการนำมาใช้เพื่อการรักษาริ้วรอยบนใบหน้าอย่างแพร่หลายในทวีปเอเชีย ซึ่งผลิตภัณฑ์นี้ผลิตจากแบคทีเรียคลอสติเดียม โบทูลินั่ม สายพันธุ์เดียวกับผลิตภัณฑ์โอนาโบทูลินั่มท็อกซินเอ (โบท็อกซ์)

วัตถุประสงค์ เพื่อศึกษาเปรียบเทียบประสิทธิภาพของผลิตภัณฑ์โบทูลินั่มท็อกซินเอชนิดใหม่ (โบทูแล๊กซ์) และผลิตภัณฑ์โอนาโบทูลินั่มท็อกซินเอ (โบท็อกซ์) ในการรักษาริ้วรอยตีนกา

วิธีการศึกษา ผู้เข้าร่วมโครงการ 20 คน เป็นอาสาสมัครที่มีริ้วรอยตีนกาขณะยิ้มเต็มที่เท่ากันทั้งสองข้าง โดยมีระดับความรุนแรงปานกลางถึงมาก ได้รับการรักษาด้วยการฉีดสารโบทูลินั่มท็อกซินเอบริเวณริ้วรอยตีนกาโดยการสุ่ม หางตาข้างหนึ่งฉีดโบท็อกซ์ปริมาณ 12 ยูนิต และหางตาอีกข้างฉีดโบทูแล๊กซ์ปริมาณ 12 ยูนิต ประเมินผลการรักษาจากภาพถ่าย และประเมินผลภาวะแทรกซ้อนจากแบบสอบถาม เปรียบเทียบผลก่อนและหลังการรักษา ในวันที่ 7, 14, 21, 30, 60, 90, 120, 150 และ 180

ผลการทดลอง กลุ่มตัวอย่างที่รับการรักษาทั้งสองกลุ่มมีอัตราการตอบสนอง 100 เปอร์เซ็นต์ ตั้งแต่วันที่ 7 หลังการรักษา และค่อย ๆ ตอบสนองลดลงจนเป็น 0 เปอร์เซ็นต์ ที่ 180 วันหลังการรักษา โดยไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในเรื่องของประสิทธิภาพการรักษา ซึ่งประเมินโดยการวัดอัตราการตอบสนอง, คะแนนเฉลี่ยความเปลี่ยนแปลงริ้วรอยก่อนและหลังรักษา ระยะเวลาของการออกฤทธิ์ และความพึงพอใจของคนไข้ เรื่องของผลข้างเคียงจากการรักษาทั้งสองวิธี พบว่าเป็นผลข้างเคียงที่ไม่รุนแรง และไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุปผล โบทูแล๊กซ์ ซึ่งเป็นผลิตภัณฑ์โบทูลินั่มท็อกซินเอชนิดใหม่ มีประสิทธิภาพเทียบเท่ากับผลิตภัณฑ์โอนาโบทูลินั่มท็อกซินเอ (โบท็อกซ์) ในการรักษาริ้วรอยตีนกาที่มีความรุนแรงปานกลางถึงมาก โดยผลิตภัณฑ์ทั้งสองชนิดมีความปลอดภัยสูง

คำสำคัญ โบทูลินั่มท็อกซินเอ, โอนาโบทูลินั่มท็อกซินเอ (โบท็อกซ์), โบทูแล๊กซ์, ริ้วรอยตีนกา

ABSTRACT

A new botulinum toxin type A (Botulax®) produced from the same strain of Clostridium botulinum as OnabotulinumtoxinA (Botox®) is widely used in Asia.
Objective: To compare the efficacy and safety of new botulinum toxin type A (Botulax®) and OnabotulinumtoxinA (Botox®) in treatment of Crow's feet.
Materials and Methods: Spilt-fact, Randomized, Double-blind Clinical Trial was performed. Twenty Thai participants with bilaterally symmetric moderate or severe crow's feet at maximum smile were randomly assigned to treatment with the Botox® 12 units and the Botulax® 12 units injected on each of periorbital areas (dose ratios of 1:1).
The primary efficacy outcome was the responder rate according to investigator assessment at days 7, 14, 21, 30, 60, 90, 120, 150, and 180 after treatment.

Mean of Facial Wrinkle Scale (FWS) change from baseline**,** duration of action**,** Subject satisfaction after injection were analyzed for secondary efficacy outcomes, and adverse effects were demonstrated for the safety evaluation.
Results: The peak of responder rates of both agents were seen in all subjects (100%) since day 7 after treatment and returned to baseline (0%) at day 180, there was no statistically significant difference in responder rate. For secondary outcomes, there was no significant difference between the two groups. Noninferiority of Botulax® was confirmed. There were no serious adverse effects with either toxin.
Conclusion: New botulinum toxin type A (Botulax®) is equally as effective as Onabotulinumtoxin A (Botox®) for treatment of moderate to severe Crow's feet. Both toxins were well tolerated.
Keywords: Botulinum toxin type A, Onabotulinumtoxin A (Botox®), Botulax®, Crow's feet

---

Introduction

Crow's feet (periorbital wrinkles) are wrinkles extending laterally from the periorbital area and are usually a result of aging. In most cases, the wrinkles are caused by contraction of the orbicularis oculi muscles. (Carruthers & Carruthers, 1997)

Many procedures are available to treat crow's feet, Surgical procedures such as temporal facelifts and lateral extension of blepharoplasty, can result in facial nerve injury and scars, whereas nonsurgical techniques such as medical treatment (e.g., retinoid), laser skin resurfacing and soft tissue augmentation, have only a cutaneous effect and do not target the underlying musculature. (Lowe et al., 2005)

Botulinum neurotoxin type A (BoNT-A) has been used extensively in clinical practice to treat hyperfunctional facial lines. Injection into the muscle causes a reversible reduction in muscle contractions by inhibition of acetylcholine release from the cholinergic nerve terminal innervating the muscle. It has been shown to be safe and efficacious in the treatment of crow's feet. (Lowe, et al., 2005)

Several licensed BoNT formulations are approved by the United States Food and Drug Administration (FDA) . The available BoNT formulations are unique and are not bioequivalent. Individual BoNT products differ in active ingredient composition, excipients, dosage labeling,and potency. (Chen & Dashtipour, 2013; Pickett & Perrow, 2010)

Botulax® is a new BoNT-A products manufactured by HUGAL Inc., South Korea. That is approved for cosmetic applications in Korean, Japan, Thailand and other Asian countries, but not marketed in the United States.

Studies comparing Botox® (Onabotulinumtoxin A) with Botulax® (New BoNT-A) for cosmetic use are not available in the medical literature**.**

Objective

To compare the efficacy and safety of new botulinum toxin type A (Botulax®) and OnabotulinumtoxinA (Botox®) in treatment of Crow's feet.

Materials and Methods

Spilt-fact, Randomized, Double-blind Clinical Trial was performed.

Twenty Thai participants with bilaterally symmetric moderate or severe crow's feet at maximum smile were randomly assigned to treatment with the Botox® 12 units and the Botulax® 12 units injected on each of periorbital areas (dose ratios of 1:1).

The primary efficacy outcome was the responder rate according to investigator assessment at days 7, 14, 21, 30, 60, 90, 120, 150, and 180 after treatment.

Mean of Facial Wrinkle Scale (FWS) change from baseline**,** duration of action**,** Subject satisfaction after injection were analyzed for secondary efficacy outcomes, and adverse effects were demonstrated for the safety evaluation.

Data analysis

Efficacy Analysis

- The Mcnemar test was used to compare the Responder rates (%) after the treatment with Botox® and Botulax®.
- The paired t-test (normal distribution) or The Wilcoxon match-pairs signed rank test (non-normal distribution) was used to compare the mean of FWS change from baseline.
- The estimated time to return to baseline severity was analyzed using the Kaplan-Meier survival method.
- The log rank test for the duration of action after treatment with Botox® and Botulax® comparisons.
- The paired t- test (normal distribution) or The Wilcoxon match-pairs signed rank test (non-normal distribution) was used to compare the mean of Subject satisfaction

Side effects Analysis

- The Mcnemar test was used to compare the side effect after the treatment with Botox® and Botulax®.

Significance levels for all analyses were set at p-value < .05.

Results

Twenty Thai participants, 3 men (15%) and 17 women (85%) were enrolled in the study. All of the subjects was completed this clinical study.

The Responder rates : The incidences of treatment responders (change of at least one grade from baseline), could be remarked as 100% since day 7, gradually decreased in day 60 for Botox® group and in day 90 for Botulax® group; however, there was no significant difference between two treatment groups. ($p = 0.375$) (Picture 1)

Mean of Facial Wrinkle Scale change from baseline : Difference of averaged FWS of both groups had no significant difference; however, maximum improvements of averaged FWS were seen at day 21 in both groups; Differences of averaged FWS scores were -2.22 ± 0.53 in Botox® group and -2.20 ± 0.56 in Botulax® group and then difference would gradually subside to the baseline FWS indicated the return of the crow's feet lines.(Picture 2)

Duration of action : The estimated average time to return to baseline was 165 days in Botox®-treated group and 171 days in Botulax®-treated group, whereas the estimated median time to return to baseline values were 180 days in both groups. Moreover, group comparison showed no significant difference between both groups. (Picture 3,4)

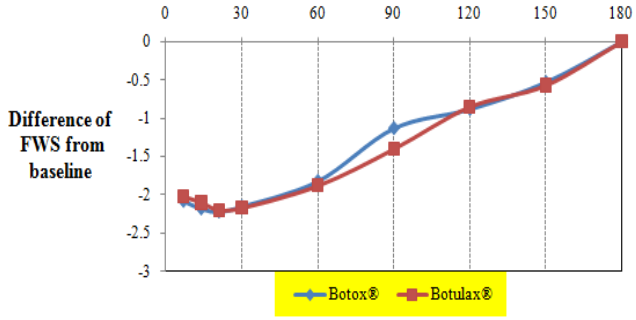
Subject satisfaction : Comparison between two groups demonstrated that Botulax®-treated group had significantly higher score at day 60, 90 and 150 ($p = 0.014$, 0.025 and 0.046 respectively). (Picture 5)

Side effects : Bruising were taken place in three cases (3/20 = 15%) and two cases (2/20 = 10%) in Botox®- and Botulax®-treated sides respectively that could remark at day 7 after treatment, there was no statistical significance for the incidences of side effects between two groups. ($p = 1.000$) (Picture 6)

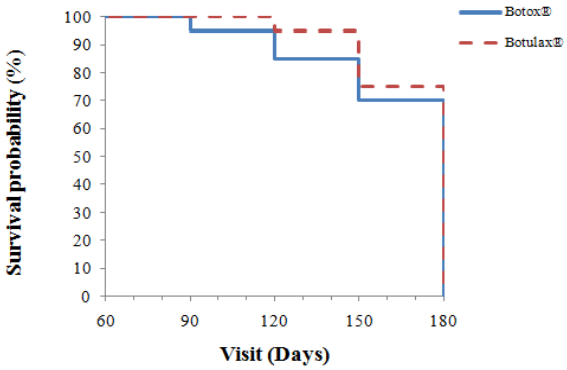
Visit	Responder Rates, %		P-value*
	Botox® (n=20)	Botulax® (n=20)	
Day7	100.0 (20/20)	100.0 (20/20)	-
Day14	100.0 (20/20)	100.0 (20/20)	-
Day21	100.0 (20/20)	100.0 (20/20)	-
Day30	100.0 (20/20)	100.0 (20/20)	-
Day60	95.0 (19/20)	100.0 (20/20)	1.000
Day90	70 (14/20)	85 (17/20)	0.375
Day120	60 (12/20)	55 (11/20)	1.000
Day150	30 (6/20)	30 (6/20)	1.000
Day180	0 (0/20)	0 (0/20)	-

* p-value compared between 2 groups with McNemar test

Picture 1 Responder rates for facial wrinkle scale in each visits between the side injected Botox® and Botulax®



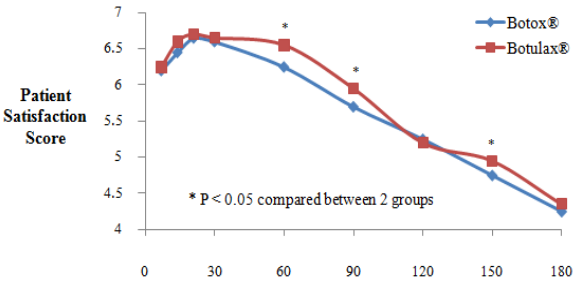
Picture 2 Linear graph shows comparison of mean FWS from baseline in each visit between the side injected Botox® and Botulax®



Picture 3Kaplan-Meier survival analysis of individual outcome of estimated time to return to baseline

Factor	Mean	S.E.	Median	p-value
Botox®	165.00	5.809	180.00	0.636
Botulax®	171.00	3.735	180.00	
Overall	**168.00**	**3.351**	**180.00**	

Picture 4 Mean and median survival of estimated time to return to baseline and comparison of survival curve (log-rank test)



Picture 5 Linear graph shows comparison of subject satisfaction scores in each period

Side Effects	Botox® (n=20)		Botulax® (n=20)		P-value
	Numbers (Percentage)	Time of Occurence	Numbers (Percentage)	Time of Occurence	
Bruising	3 (15%)	Day 7	2 (10%)	Day 7	1.000
Infection	-	-	-	-	
Headache	-	-	-	-	
Ectropion	-	-	-	-	
Diplopia	-	-	-	-	
Lip ptosis	-	-	-	-	
Others	-	-	-	-	

p-value compared between 2 groups with McNemar test, *Significant at p < 0.05

Picture 6 Side effects

Discussion

The peak of responder rates of both agents were seen in all subjects (100%) since day 7 after treatment, gradually decreased in day 60 for Botox® group and in day 90 for Botulax® group, there was no statistically significant difference in responder rate. According to the previous study, Lowe et al (2005) reported responder rates for investigator's assessment of crow's feet severity at maximum smile become the peak at day 30 (87.1%) and 24.4% at day 180 after 12 U of botulinum toxin A injection. For such difference, it might be caused by investigators' variation in the ratings of individuals. Furthermore, in 2013, Won *et al* had demonstrated the comparison of therapeutically equivalent efficacy between Meditoxin® (Neuronox®, Siax®), Korean tradenames, and Botox® for the treatment of moderate to severe

glabellar lines and the results showed no statistically significant difference in the responder rate between the groups at any time point for 16 weeks. According to the concomitant results to our present study, this may imply the therapeutic equivalence among Korean products (Neuronox®, Botulax®) and Botox®, including safety aspect.

This study showed the similarity in the tendency of averaged FWS changes of Botox® and Botulax® reached the maximum improvement at day 21 (-2.22 ± 0.53 for Botox® and -2.20 ± 0.56 for Botulax®), and gradually declined to the baseline at day 180 with not reaching the statistical significance at any post-treatment time point. In addition, the maximum improvement at day 30 of 12 U botulinum toxin type A for treatment of crow's feet was reported by Lowe and colleagues (2005), resembling to this study.

The estimated return to baseline severity analysis disclosed lack of differentiation between both groups, with showing equal median duration as 180 days. Comparing to the previous researches, Lowe et al (2005) documented the results of estimated median duration was 120 days for 12 U of botulinum toxin type A in subjects with crow's feet. It is possible that longer lasting duration of action was due to differences of severity of subjects at baseline and racial differences.

For the subject's assessment of satisfaction scores, Botulax® had gotten the significantly higher score than Botox® at day 60, 90 and 150.

In terms of safety, treatment-related adverse events that found in this study included only temporary bruising on the injection site in 5 participants at day 7 that caused from 3 in Botox®-treated side and 2 in another side of Botulax®. No statistically significant difference between their incidences of adverse events was shown.

Conclusion

The results from this study demonstrate that Botox® (Onabotulinumtoxin A) and Botulax® (New BoNT), which are both botulinum toxins type A, had the same therapeutic equivalent dose for treatment of moderate to severe periorbital wrinkles in the efficacy and duration of action over a period of 180 days. Besides they were safe and well tolerated, with no significant difference of subject satisfactions and safety profiles.

Suggestions

- The study may be tested to compare among various dosages of botulinum toxins type A**.**
- It should study the efficacy and safety for other cosmetic applications (e.g. glabellar lines, brow position, hyperhidrosis).
- It is possible to research about the efficacy and safety of Botulax® for clinical indications (e.g. hemifacial spasm, blepharospasm, spasticity, torticollis, cervical dystonia, etc.).

References

Carruthers, A., & Carruthers, J. (1997). Cosmetic uses of botulinum A exotoxin. *Adv Dermatol, 12*, 325-347; discussion 348.

Chen, J. J., & Dashtipour, K. (2013). Abo-, inco-, ona-, and rima-botulinum toxins in clinical therapy: a primer. *Pharmacotherapy, 33*(3), 304-318. doi: 10.1002/phar.1196

Lowe, N. J., Ascher, B., Heckmann, M., Kumar, C., Fraczek, S., & Eadie, N. (2005). Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. *Dermatol Surg, 31*(3), 257-262.

Pickett, A., & Perrow, K. (2010). Formulation composition of botulinum toxins in clinical use. *J Drugs Dermatol, 9*(9), 1085-1091.

Won, C. H., Lee, H. M., Lee, W. S., Kang, H., Kim, B. J., Kim, W. S., . . . Huh, C. H. (2013). Efficacy and safety of a novel botulinum toxin type A product for the treatment of moderate to severe glabellar lines: a randomized, double-blind, active-controlled multicenter study. *Dermatol Surg, 39*(1 Pt 2), 171-178. doi: 10.1111/dsu.12072