의학석사 학위논문

Botulinum Toxin-A Effects on the Muscle Architecture of Hemiplegic Upper Extremity in Stroke Patients:

An Ultrasonographic Study

뇌졸중 환자의 편측마비 상지의 근육 구조에 미치는 보툴리눔 톡신-A의 효과:

초음파 연구

2015년 2월

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초음파 연구

지도 교수 이 시 욱

이 논문을 의학석사 학위논문으로 제출함

2014년 10월

서울대학교 대학원

의학과 재활의학전공

임 채 영

임채영의 의학석사 학위논문을 인준함

2014년 12월

위 원 장 _____ (인)

부위원장 _____ (인)

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Abstract

Effects of Botulinum Toxin-A on the Muscle Architecture in Stroke Patients:

An Ultrasonographic Study

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Introduction:
Muscle architecture is main determinant of muscle function and there was no study about the change of muscle architecture in spastic upper extremity after botulinum toxin-A (BoNT-A) injection. The aim of this study was to evaluate the effects of BoNT-A injection on the hemiplegic upper extremity muscle architecture of stroke patients using ultrasonography.

Methods:
Fifteen consecutive hemiplegic patients (mean age: 60.3±8.8 years) who were injected with BoNT-A for the treatment of upper extremity spasticity in April to June 2014 were enrolled. Flexor carpi radialis muscle of hemiplegic side was evaluated using ultrasonography. Muscle length, anterior and posterior pennation angle, muscle thickness, cross-sectional area of muscle

and muscle volume were measured. Ultrasonographic evaluations were performed before BoNT-A injection and repeated 1 month and 3 months after injection.

Results:

Muscle thickness at a neutral position and posterior pennation angle at maximal extension significantly decreased 3 months after injection (p=0.001, p=0.023, respectively), fascicle length increased at neutral, maximal flexion and maximal extension positions after 1 month (p=0.001, p=0.004, p=0.002, respectively) and this increase was maintained at neutral and maximal extension after 3 months (p=0.041). Proximal muscle volume around the injection site significantly decreased after 3 months (p=0.036) and distal volume from injection site increased 1month and 3 months after injection (p=0.002, p=0.027).

Conclusions:

These results confirm the change in muscle architecture in spastic upper extremity hemiplegia after BoNT-A injection, elucidating the effects of BoNT-A injection on spastic muscle of stroke patients.

Keywords: Muscle Architecture, Pennation Angle, Muscle Volume, Hemiplegia, Stroke, Botulinum Toxin-A

Student Number: 2010-21822

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Introduction

Skeletal muscle architecture refers to the arrangement of muscle fibers within muscle relative to the force generation axis.(1) Muscle architecture is the main determinant of muscle function and comprises muscle fascicle or fiber length, pennation angle and cross-sectional area.(2-4) Muscle fascicle and fiber length is proportional to the velocity of muscle contraction, pennation angle relates with the muscle's capacity to produce force and cross sectional area is directly proportional to maximal force- generating capacity. (5-9)

In spasticity of post-stroke patients, a few studies have investigated the change of muscle architecture, reporting that the muscle fascicle length and pennation angle were decreased in the gastrocnemius muscle.(10, 11) The effects of botulinum toxin-A (BoNT-A) on muscle architecture of stroke patients was evaluated in only one study.(12) In this study, pennation angle and muscle thickness decreased and fascicle length increased. However, no study has examined changes in muscle architecture in spastic upper extremity after BoNT-A injection.

The objective of this study was to evaluate the effects of BoNT-A injection on the upper extremity muscle architecture of stroke patients using ultrasonography.

Materials and methods

Participants

The reports of 15 consecutive hemiplegic patients (12 male, 3 female) who were injected with BoNT-A for the treatment of upper extremity spasticity from April to June 2014 were collected. The mean age of the patients was 60.3±8.8 years. Inclusion criteria included age over 20 years, time from stroke onset of at least 1 year, wrist flexor spasticity graded at least 2 on the Modified Ashworth Scale (MAS), and absence of recent injection in the upper extremity (BoNT-A, alcohol or phenol). Exclusion criteria included presence of peripheral neuropathy, fixed contractures (MAS = 4), bony deformities of affected upper extremity, recent start or change of anti-spastic medication within 6 months and inclusion in other clinical trials. All participants were informed about the BoNT-A injection and study procedure and gave written informed consent. This study protocol was approved by the Institutional Review Board.

Protocols

Data regarding age, sex, height, body weight, etiology of stroke, date of stroke onset, dominant hemisphere, MAS scores of upper extremity, anti-spastic medication record, range of motion (ROM) and ultrasonographic measure record of muscle architecture of hemiplegic upper extremity were collected.

BoNT-A 50U was injected around the motor point, in the proximal one-third of the flexor carpi radialis (FCR) muscle on the hemiplegic upper extremity. When the patients had spasticity of the elbow, hand or finger,

the related muscles including biceps, flexor digitorum superficialis and profundus, flexor carpi ulnaris or intrinsic finger muscles were also injected according to spasticity severity. The total amount of BoNT-A did not exceed 360U.

FCR muscle of the hemiplegic side was evaluated ultrasonographically, using a General Electric LOGIQ 500 unit (General Electric Systems, Milwaukee, WI, USA) by means of a 7-13 MHz linear array transducer. FCR measurements were obtained in the anatomical supinated neutral position, full-wrist volar-flexion and full-wrist dorsi-flexion position of forearm, while the patients were supine on the examination table. Before the BoNT-A injection, maximal ROMs of wrist flexion and extension were checked using a goniometer. and FCR measurements were repeated at the same degrees with these initial ROMs 1 month and 3 months after injection.

Muscle length between the proximal and distal musculotendinous junctions (MTJs) of the FCR was evaluated by using ultrasonography (Fig.1). Anterior pennation angle between the fascicle path and the anterior muscle fascia, posterior pennation angles between the fascicle path and the posterior deep aponeurosis of the muscle, and fascicle length were scanned at the midpoint of the proximal and distal MTJs by using ImageJ software, a public image processing and analysis program from the National Institutes of Health (Fig. 2). Muscle length, fascicle length, anterior pennation angle and posterior pennation angle were measured using ultrasonography at neutral, maximal flexion,

initial flexion, maximal extension and initial extension positions.

Muscle thickness was measured by drawing a line perpendicular to the long axis of the muscle cross-section and cross-sectional area was also measured (Fig. 3).

Cross-sectional areas were measured at the midpoint between the proximal and distal MTJs, at 1 and 2 cm proximal to the midpoint, and at 1 and 2 cm distal the midpoint (Fig. 4). Since muscle fibers were gathering to a point on both ends of the tendon, volume can be determined by assuming the horn using the following formula:

$$\mathrm{V} = \frac{1}{3}h\left(S_1 + \sqrt{S_1 * S_2} + S_2\right)$$

Where V = volume of the muscle (cm^3); h = height between cross-sections; S_1 and S_2 = cross-sectional areas (cm^2). The proximal (between the midpoint and 2 cm proximal to the midpoint), distal (between the midpoint and 2 cm distal to the midpoint), and total (the sum of proximal and distal) volumes were calculated. The proximal volume was subdivided into upper proximal volume (between 1 cm and 2 cm proximal to the midpoint) and lower proximal volume (between the midpoint and 1 cm proximal to the midpoint). Distal volume was Distal volume was also divided into upper distal volume (between the midpoint and 1cm distal to the midpoint) and lower distal volume (between 1 and 2 cm distal to the midpoint).

Statistical analysis

Data were analyzed by using SPSS version 18.0 package (SPSS Inc., Chicago, IL, USA). The ultrasonographic parameters were analyzed using by Wilcoxon signed-rank test for comparison between baseline, 1 month and 3 months after BoNT-A injection and were checked for correlations with ROM and MAS. Descriptive statistics were reported as mean ± standard deviation (SD), and the significance level was set at $p<0.05$.

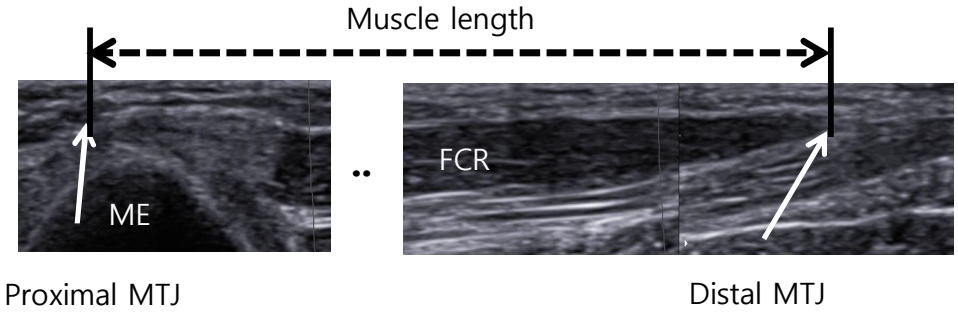

Figure 1. Muscle length between proximal and distal musculotendinous junction (MTJ; white arrows). ME: medial epicondyle of the humerus; FCR: flexor carpi radialis muscle

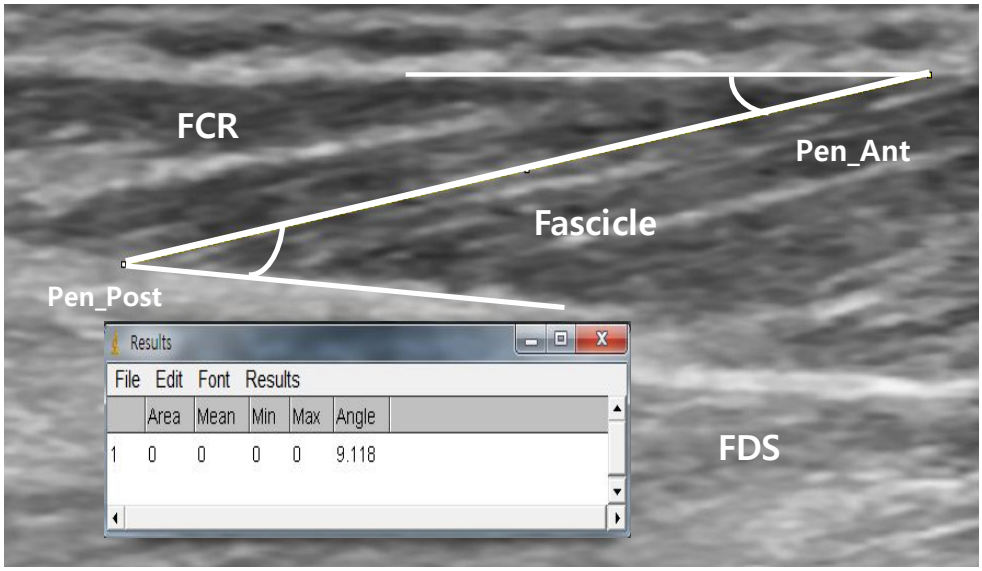

Figure 2. Pennation angle was measured by using ImageJ. 1) anterior pennation angle: angle between the muscle fascicle and the anterior fascia of FCR; 2) posterior pennation angle: angle between the muscle fascicle and the posterior aponeurosis dividing the FCR and FDS. Pen_Ant, anterior pennation angle; FCR, flexor carpi radialis; Pen_Post, posterior pennation angle; FDS, flexor digitorum superficialis

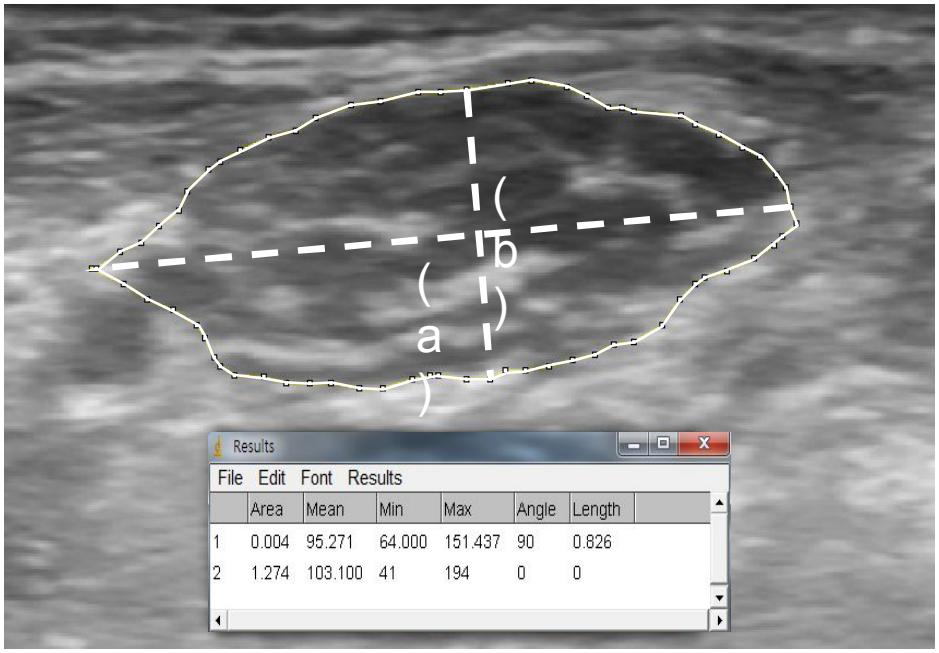

Figure 3. Muscle thickness was measured by drawing a perpendicular line (b) to the long axis (a) of flexor carpi radialis muscle. Cross-sectional area was also measured by drawing a polygon around the muscle.

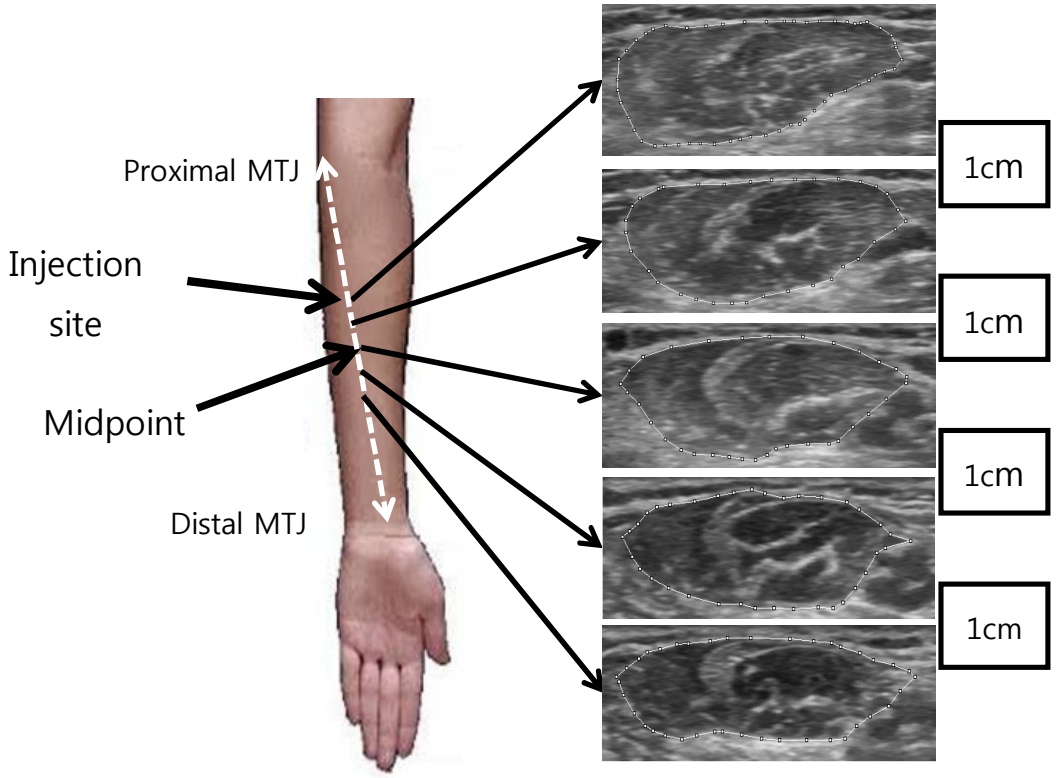

Figure 4. Volume was evaluated based on serial cross-sectional areas measured at the midpoint of proximal and distal musculotendinous junctions, at 1cm and 2cm proximal to the midpoint, and at 1 cm and 2 cm distal to the midpoint.

Results

Mean duration between stroke onset and BoNT-A injection was 9.9±5.1 years. Mean height and weight of the patients were 167.1±6.3 cm and 68.1±6.3 kg, respectively. Upper extremity hemiplegia was caused by cerebral infarction in 10 patients and by cerebral hemorrhage in 5 patients. Fourteen patients had left hemisphere dominance and only 1 patient had right hemisphere dominance. Only 2 patients had previously received anti-spastic medications, but they did not change the doses until 2 months after BoNT-A injection. The mean injection amount of BoNT-A was 329.3±50.3 U.

ROMs increased after BoNT-A injection; wrist flexion increased from 73.7±12.8 to 77.3±11.8° after 3 months (p=0.041) and wrist extension increased from 36.0±25.5 to 43.3±21.9° after 1 month (p=0.011). Mean wrist MAS scores decreased from 3.4±0.5 to 0.6±1.1 1 month after injection (p=0.001), and remained lower 3 months after injection, 0.5±0.8 (p<0.001). Mean elbow (3.1±1.1, 1.3±1.2 and 1.1±0.8) and finger (2.7±1.3, 0.8±1.1 and 0.7±0.9) MAS scores also decreased from before the injection, to 1 month and 3 months post-injection, respectively (Table 1).

Muscle thickness significantly decreased from 0.85±0.16 to 0.74±0.14 cm (p=0.011) after 3 months. Cross-sectional area also tended to decrease after 3 months (1.55±0.35 to 1.48±0.30 cm^2, p=0.112). Total volume calculated using serial cross-sectional areas at 1-cm intervals did not change after injection. However, the volume proximal to the

midpoint decreased from 3.40±0.84 to 3.20±0.80 cm^3 after 3 months (p=0.036) while distal volume increased from 2.68±0.73 to 3.29±0.86 cm^3 after 1 month (p=0.002) and remained elevated after 3 months (3.20±0.80 cm^3; p=0.027) (Table 2). In particular, the upper proximal volume, which was close to the BoNT-A injection site, decreased after 1 month (p=0.027) and 3 months (p=0.027). The upper and lower distal volumes increased after 1 month (p=0.002; p=0.002).

Muscle length between the proximal and distal MTJs and anterior pennation angle did not change after BoNT-A injection. Fascicle length increased at neutral, maximal flexion, and maximal extension positions after 1 month (neutral: from 4.21±0.58 to 4.56±0.64 cm, p=0.001; maximal flexion: 3.85±0.66 cm, 4.21±0.91 cm, p=0.004; maximal extension: 4.57±0.69 cm, 5.05±0.83 cm, p=0.002) and neutral and maximal extension remained elevated after 3 months (neutral: 4.55±0.75 cm, p=0.002; maximal extension: 4.93±0.91 cm, p=0.041). Posterior pennation angle tended to decrease at all positions after BoNT-A injection. At maximal extension, posterior pennation angle decreased from 9.31±2.34 to 8.19±2.45° after 1 month (p=0.005) and remained lower after 3 months (8.01±2.74°; p=0.023). At initial flexion, the posterior angle also decreased from 11.28±3.04 to 9.40±3.61° 3 months after injection (p=0.041).

All the muscle parameters were analyzed for possible correlations with the clinical parameters ROM and MAS scores. Posterior pennation angle, cross-sectional area, total volume, and distal volume at neutral

position negatively correlated with ROM upon extension (r^2=0.158, p=0.007; r^2=0.121, p=0.019; r^2=0.160, p=0.007; r^2=0.191, p=0.003, respectively). Proximal volume tended to correlate negatively with ROM upon extension (r^2=0.086, p=0.051), but the other parameters did not correlate with flexion or extension ROM. MAS scores, representing the muscle spasticity, were not correlated with any of the muscle parameters.

Table 1. Range of motion and modified Ashworth Scales scores

	Before	1 Mo	*p*	3 Mo	*p*
ROM (°)					
Flexion	73.7±12.8	77.7±14.0	0.084	77.3±11.8	0.041†
Extension	36.0±25.5	43.3±21.9	0.011*	39.3±24.0	0.172
MAS					
Wrist	3.4±0.5	0.6±1.1	0.001*	0.5±0.8	<0.001†
Elbow	3.1±1.1	1.3±1.2	0.001*	1.1±0.8	0.001†
Finger	2.7±1.3	0.8±1.1	0.002*	0.7±0.9	0.001†

*Before injection vs. 1 month after injection (1 Mo); †Before injection vs. 3 months after injection (3 Mo).

Table 2. Muscle thickness, cross-sectional area and volume at neutral position

	Before	1 Mo	*p*	3 Mo	*p*
Muscle thickness (cm)	0.85±0.16	0.84±0.15	0.773	0.74±0.14	0.011†
CSA (cm^2)	1.55±0.35	1.56±0.35	0.650	1.48±0.30	0.112
Volume (cm^3)					
Proximal	3.40±0.84	3.30±0.79	0.532	3.20±0.80	0.036†
Upper	1.80±0.46	1.62±0.46	0.027*	1.62±0.46	0.027†
Lower	1.60±0.40	1.68±0.35	0.427	1.57±0.38	0.460
Distal	2.68±0.73	3.29±0.86	0.002*	2.83±0.67	0.027†
Upper	1.43±0.36	1.68±0.38	0.002*	1.50±0.35	0.211
Lower	1.25±0.38	1.61±0.50	0.002*	1.33±0.34	0.061
Total	6.08±0.15	6.58±1.47	0.078	6.03±1.42	0.820

CSA: cross-sectional area; *Before injection vs. 1 month after injection (1 Mo); †Before injection vs. 3 months after injection (3 Mo).

Table 3. Ultrasonographic measurements at neutral, maximal flexion, initial flexion, maximal extension and initial extension.

	Before	1 Mo	*p*	3 Mo	*p*
Muscle length (cm)					
Neutral	19.0±2.3	19.1±2.2	0.646	18.4±2.0	0.396
Max. FL	18.1±2.5	18.1±2.3	0.801	17.3±2.0	0.222
Max. EX	19.6±2.5	19.8±2.3	0.495	19.6±2.5	0.683
Initial FL	18.1±2.5	17.9±2.9	1.000	17.4±2.0	0.363
Initial EX	19.6±2.5	19.6±2.2	0.875	19.0±1.9	0.362
Fascicle length (cm)					
Neutral	4.21±0.58	4.56±0.64	0.001*	4.55±0.75	0.002†
Max. FL	3.85±0.66	4.21±0.91	0.004*	3.91±0.96	0.955
Max. EX	4.57±0.69	5.05±0.83	0.002*	4.93±0.91	0.041†
Initial FL	3.85±0.66	4.13±0.80	0.088	4.02±1.03	0.609
Initial EX	4.91±0.89	4.89±0.79	0.733	4.83±0.89	0.281
Ant. PA (°)					
Neutral	8.87±2.49	9.33±2.62	0.570	8.79±2.94	0.865
Max. FL	11.05±3.04	10.92±2.51	0.865	10.53±3.16	0.691
Max. EX	7.48±2.27	8.32±2.38	0.307	7.65±2.23	0.955
Initial FL	11.05±3.04	10.44±2.41	0.609	9.78±2.60	0.069
Initial EX	7.48±2.27	8.30±2.35	0.570	8.13±2.11	0.334

Post. PA (°)					
Neutral	10.16±2.13	9.26±2.21	0.112	9.06±2.82	0.112
Max. FL	11.28±3.04	10.8±3.55	0.691	9.95±3.30	0.191
Max. EX	9.31±2.34	8.19±2.45	0.005*	8.01±2.74	0.023†
Initial FL	11.28±3.04	10.93±3.22	0.532	9.40±3.61	0.041†
Initial EX	9.31±2.34	8.44±2.29	0.088	8.56±2.58	0.211

Max.: maximal; FL: flexion; EX: extension; Ant.: anterior; Post.: posterior; PA: pennation angle;

*Before injection vs. 1 month after injection (1 Mo); †Before injection vs. 3 months after injection (3 Mo).

Discussion

This study evaluated the effects of BoNT-A injection on muscle architecture of the hemiplegic upper extremity in stroke patients. Some studies have reported muscle atrophy of the lower extremity after BoNT-A injection, using MRI to demonstrate reductions in cross-sectional area or volume. (13-16) However, none of these studies have evaluated the changes in muscle architecture after BoNT-A injection by using ultrasonography. Muscle architecture in stroke patients can be evaluated and quantified using ultrasonography (17-19), and although one study has evaluated the gastrocnemius muscle architecture of stroke patients using ultrasonography, it did not evaluate cross-sectional area or volume changes in the muscle after BoNT-A injection.(12)

To the best of our knowledge, this study is the first to measure the muscle architecture of the upper extremity after BoNT-A injection in stroke patients using ultrasonography. The muscle thickness decreased 3 months after BoNT-A injection and the cross-sectional area of the muscle also tended to decrease 3 months after injection. The muscle fascicle length at neutral, maximal flexion, and maximal extension positions increased 1 month after injection and remained elevated at neutral and maximal extensions 3 months after BoNT-A injection. These results were similar to a previous study that evaluated the lower extremity muscle architecture after BoNT-A injection using ultrasonography (12); however, this study only measured the muscle

architecture in resting posture. We confirmed that the fascicle length increased and pennation angle decreased at maximal wrist extension 3 months after injection, which could indicate that the muscle architecture became more suitable for stretching and thus could contribute to increased joint ROM and reduced spasticity. These advantageous changes in muscle architecture may prevent spasticity after stroke, as one study has demonstrated that early BoNT-A injection can reduce the development of spasticity.(20)

Our study evaluated not only the pennation angle, muscle length, and fascicle length, but also the serial cross-sectional areas and used these to calculate muscle volume. The ROM upon extension was negatively correlated with posterior pennation angle, cross-sectional area, and the volume of muscle after BoNT-A injection. As some of the muscle architecture parameters decreased, the ROM upon extension increased after BoNT-A injection. Total volume did not change after injection, however, the proximal volume significantly decreased 3 months after injection and the distal volume significantly increased 1 month and 3 months after injection. These findings may be the result of injecting BoNT-A only proximal to the midpoint between proximal and distal MTJs. As the proximal volume decreased, tension may have been reduced due to the muscle atrophy caused by BoNT-A injection; this may have caused the muscle to be pulled distally, causing an increase in distal muscle volume. Despite these local changes, total muscle volume was unaffected by BoNT-A injection. This means that

the BoNT-A injection may only have a focal effect on muscle architecture near the injection site. Supporting this idea, the BoNT-A injection site was near the upper proximal volume, and the upper proximal volume decreased more than the lower proximal volume (Table 2). Therefore, multiple injections of BoNT-A over a broader area may enhance the effect of the treatment effects on spasticity in stroke patients.

Limitations of this study include the lack of control group, limited duration of follow-up after BoNT-A injection, and focus on the FCR muscle. We evaluated the effects of BoNT-A on muscle architecture 1 and 3 months after injection because most studies have reported that the effects of BoNT-A last up to 3 months for spasticity management (21, 22); however, some studies have reported that the effects remained through 6 months of follow-up (23-25), so future studies are needed to determine the duration of the effects of BoNT-A. In this study, only the FCR muscle was evaluated, but it is also necessary to determine if BoNT-A changes the muscle architecture in other upper extremity muscles as well.

Conclusion

Muscle thickness and posterior pennation angle decreased and fascicle length increased in the upper extremity after BoNT-A injection in stroke patients. The muscle volume was not changed, but the volume around the injection site decreased while the volume distal to the injection site increased after BoNT-A injection. This study is the first to evaluate the change in muscle architecture of the upper extremity after BoNT-A injection in stroke patients. Understanding the changes in muscle architecture in response to BoNT-A injection may have clinical utility to improve the treatment of spastic muscles of stroke patients.

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초 록

뇌졸중 환자의 편측마비 상지의 근육 구조에 미치는 보툴리눔 톡신 A의 효과:

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서론:

근육 구조(muscle architecture)는 근육 기능의 주된 결정인자로 지금까지 보툴리눔 톡신-A 주사 후 상지 경직에서 근육 구조의 변화를 본 연구는 없었다. 이에 이 연구에서는 초음파를 이용하여 뇌졸중 환자의 편마비 상지 근육의 근육 구조에 대한 보툴리눔 톡신-A 주사의 효과를 보고자 하였다.

방법:

2014년 4월부터 6월까지 상지 경직 치료를 위해 보툴리눔 톡신-A를 주사 받은 평균 나이 60.3±8.8세의 15명의 편마비 환자가 조사되었다. 편마비측 요측수근굴근(flexor carpi radialis muscle)을 초음파를 이용하여 확인하였다. 근육의 길이, 전방과 후방의 근섬유각도(pennation angle), 근육 두께, 근육의 단면적과 부피를 확인하였다. 초음파 측정은 보툴리눔 톡신-A 전과 주사 후 한 달, 석 달

후에 시행하여 전후 비교하였다.

결과:

중립위에서 근육의 두께와 최대 신전시 후방 근섬유 각도가 주사 후 3개월 후에 의미있게 감소하는 것을 확인하였고 (각각 p=0.001, p=0.023), 근섬유 길이가 중립위, 최대굴곡과 최대신전 모두에서 주사 후 1개월 후에 의미 있게 증가하였고(각각 p=0.001, p=0.004, p=0.002), 이러한 증가는 중립위와 최대신전에서 주사 후 3개월까지 지속되었다(p=0.041). 주사 부위 주변이었던 근위부 근육 부피는 주사 3개월 후 의미 있게 감소하였고(p=0.036), 반대로 주사 부위에서 원위부 근육의 부피는 주사 1개월과 3개월 후에 유의하게 증가하였다(각각 p=0.002, p=0.027).

결론:

이러한 결과는 보툴리눔 톡신-A 주사 후 경직이 있는 상지 편마비에서 근육 구조의 변화를 확인시켜 주었다. 이러한 근육 구조의 변화는 임상적으로 뇌졸중 환자의 경직 근육에 미치는 보툴리눔 톡신-A의 효과를 이해하는데 도움을 줄 수 있다.

주요어: 근육 구조, 근섬유 각도, 근육 부피, 편마비, 뇌졸중, 보툴리눔 톡신-A

학 번: 2010-21822