의학석사 학위논문

Efficacy and Safety of Clostridium botulinum toxin type A (NABOTA®) in treatment of post-stroke upper extremity spasticity : multi-center, phase IV clinical trial

뇌졸중 후 상지 경직 치료로 Clostridium botulinum toxin type A (NABOTA®)의 투여에 대한 안전성 및 유효성 연구 : 다기관, 제4상 임상시험

2021년 2월

서울대학교 대학원

임상의과학과

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이 논문을 의학석사 학위논문으로 제출함

2020년 10월

서울대학교 대학원

임상의과학과

강 성 민

강성민의 의학석사 학위논문을 인준함

2021년 1월

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Abstract

Efficacy and Safety of Clostridium botulinum toxin type A (NABOTA®) in treatment of post-stroke upper extremity spasticity : multi-center, phase IV clinical trial

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Introduction: Clostridium botulinum toxin type A injection has been widely used in managing post-stroke upper limb spasticity. Through the phase III trial, a new botulinum toxin type A, NABOTA® showed non-inferior efficacy and safety, and was introduced in the market.

Objective: This study was to evaluate efficacy and safety of NABOTA® after its launch on the market.

Methods: This prospective, multi-centered, and open-label phase IV clinical study was performed with 222 patients. Up to 360 international unit (IU) of NABOTA® was injected at wrist flexor, elbow flexor, and finer flexor depending on the degree of spasticity. The change of wrist flexor Modified Ashworth Scale (MAS) grade between baseline and 4 weeks was evaluated as primary outcome. The changes of MAS grade of injected muscles, Disability Assessment Scale (DAS), and Caregiver Burden Scale at baseline, 4-, 8-, and 12-weeks post-injection were also confirmed. Global Assessment Scale (GAS) was assessed at 12 weeks after injection.

Results: There was statistically significant change in MAS grade of wrist flexor from baseline to 4 weeks after the injection (-1.53±0.95, *p*-value < .0001). There were also significant improvements in MAS of all injected muscles, DAS, and Caregiver Burden scale at every follow-up period. The incidence of adverse outcome was 14.41% (32 of 222), smaller than that of pervious trial.

Conclusions: NABOTA® showed considerable efficacy and safety in managing upper limb spasticity in stroke patients.

Keywords: Botulinum toxin A, Stroke, Upper extremity, Spasticity, Efficacy, Safety, Phase IV

Student Number **: 2019-23204**

목 차

표 목차

그림 목차

Introduction

A large portion of stroke survivors are having decreased quality of life due to variety of functional impairments after stroke. 50 to 70% of post-stroke patients experience functional limitation in upper limb, including weakness, diminished sensation, dysmetria, and spasticity.[1,2] As post-stroke survival rate is continuously increasing with the help of newer interventions, medications and rehabilitation protocols, improving the function of upper limb is crucial for the quality of life after stroke.

Clostridium botulinum toxin type A injection has been widely performed to manage upper limb spasticity after stroke. One of the novel botulinum toxin type A products, NABOTA® (Daewoong botulinum toxin type A, Daewoong Pharmaceutical, Seoul, Korea), originated from wild-type *Clostridium botulinum* Hall A, was introduced recently. NABOTA® was produced by High-Pure Technology®, a patented high-efficiency purification technology including delicate anaerobic fermentation process and anion exchange chromatography analysis to sort out single 900 kDa peak (>98%).[3] We already demonstrated its effect and safety in in vivo studies, and non-inferior efficacy and safety in double-blinded randomized controlled trial for post-stroke patients.[4,5] After these studies, NABOTA® obtained permission from the Ministry of Food and Drug Safety in South Korea on December 7, 2015, for its indication of upper extremity spasticity after stroke in adults aged 18 or older.

As newer botulinum toxin type A products are being introduced in general population, evaluating safety and efficacy of the products post-marketing is mandatory to further develop standardized injection protocols and to find out potent side effects.

In this study, we tried to investigate the efficacy of NABOTA® injection in relieving the upper extremity spasticity and disability in stroke patients, and any potent adverse effect after the injection.

Materials and Methods

This study was a prospective, multi-center, and open-label phase IV clinical study of NABOTA®. The study was performed between June 2019 and December 2019 in 7 university hospitals (Seoul National University Boramae Medical Center, Seoul National University Hospital, Severance Hospital, Gangnam Severance Hospital, Dongguk University Ilsan Hospital, National Health Insurance Service Ilsan Hospital, and Presbyterian (Jesus) Medical Center) in South Korea. Patients with the age of 18 or older, diagnosed with stroke at least 6 weeks ago were recruited. Among the patients, those who were evaluated to need NABOTA® injection in order to relieve symptoms associated with upper extremity spasticity were included in the study. Modified Ashworth Scale (MAS) and Disability Assessment Scale (DAS) were not considered for the inclusion criteria to confirm efficacy and safety of NABOTA® in generalized actual clinical environment. All the subjects were thoroughly informed about the contents of the study, and were given informed consent before the study.

Patients were assessed as ineligible if they (1) had hypersensitivity to the ingredients of NABOTA®, (2) were diagnosed with generalized neuromuscular diseases including myasthenia gravis and Lambert-Eaton syndrome, and (3) were pregnant, had possibility of pregnancy, or were breastfeeding at the time of recruitment.

A group of medications which were considered to have possibility to affect the efficacy of botulinum toxin was listed and defined as concomitant drug. The concomitant drug included muscle relaxants (affecting central, peripheral nervous system, or skeletal muscles), benzodiazepines, antibiotics (especially including aminoglycosides), and anticholinergics. Medication history of each patient was checked during the screening process. For those eligible, muscle relaxants and benzodiazepines were prohibited from being taken at the time of screening unless it was taken stably before 4 weeks. If a stable dose was taken at least four weeks before screening, changing in dose was not allowed during the clinical trial period. In addition, the patients were made not to take any antibiotics (especially including aminoglycosides) and

anticholinergics during the study period.

For the clinical trial, 100 IU of NABOTA® was dissolved with 2 mL of 0.9% sodium chloride solution. Injection was performed at 5 muscles: Biceps brachii, Flexor digitorum profundus, Flexor digitorum sublimis, Flexor carpi ulnaris, and Flexor carpi radialis. 100 to 200 international unit (IU) was injected at biceps brachii up to 4 sites, 15 to 60 IU was at 1 to 2 site of flexor carpi radialis, and 15 to 50 IU was at 1 to 2 sites of the other muscles, respectively (Table 1). Up to total of 360 IU injection in each patient were allowed.

The subjects were guided to visit the clinic 4, 8, and 12 weeks after the injection. MAS grade of injected muscles were evaluated every visit including pre-injection.[6] The grading was performed in a comfortable environment with the subjects in a supine position. MAS grade 1+ was regarded as 1.5.[5] DAS was scored in a 4-point scale with functional disability in 4 domains; hygiene, dressing, limb position, and pain (0; no disability, 1; mild disability, 2; moderate disability, 3; severe disability).[7] It was reported that DAS had shown significant interrater reliability and good or excellent intrarater reliability.[7] Before the injection, one functional domain that most needs improvement was selected by physician and the subject (or the caregiver). If the subject was unable to make his or her decision, caregiver replaced the decision. Evaluation of each subject's domain was done at every visit including pre-injection by the identical physician. Caregiver Burden Scale was performed at every visit from pre-injection to 12-weeks post-injection. The Caregiver Burden Scale was assessed with 4 domains (cleaning the palm, cutting the fingernails, dressing, and cleaning under the armpit), and scored into 5-point Likert scale from 0 (no difficulty) to 4 (impossible).[8] Global Assessment Scale (GAS) was rated at 12 weeks after the injection in a 4-point scale to evaluate overall functional benefit from the treatment (1; very good, 2; good, 3; regular, 4; poor). Assessment of GAS was performed respectively by both physician and the subject (or the caregiver).

Table 1. The number of injection sites and total doses for each targeted muscle.

Muscles	Total injection dose	Number of sites
Biceps brachii	100-200U	Up to 4 sites
Flexor digitorium profundus	15-50U	1-2 sites
Flexor digitorium sublimis	15-50U	1-2 sites
Flexor carpi ulnaris	15-50U	1-2 sites
Flexor carpi radialis	15-60U	1-2 sites

Primary outcome was changes in MAS grade of wrist flexor muscles between two distinct time points: prior to injection and 4 weeks after injection. Secondary outcome were set up as (1) changes in MAS grade of wrist flexor at 8 and 12 weeks after injection from pre-injection, (2) changes in MAS grade of elbow flexor and finger flexor at 4, 8, and 12 weeks after injection from pre-injection, (3) therapeutic response rate in wrist flexor, elbow flexor, and finger flexor muscles at 4, 8, and 12 weeks after the injection, (4) change in DAS at 4, 8, and 12 weeks after injection in comparison with the baseline, (5) physician rated GAS at 12 weeks, and subject or caregiver rated GAS at 12 weeks, and (6) degree of caregiver burden at 4-, 8-, and 12-weeks post-injection evaluated by the caregiver with Caregiver Burden Scale. Therapeutic response was defined as decrement of MAS grade at least 1 point in the muscle assessed.[7]

Safety evaluation was also performed during the study period. All subjects were asked if they had any suspected symptoms or unexpected events when they visited each follow-up clinic. Every adverse event was collected and monitored during the study period. Any abnormality in laboratory examination, vital sign, and physical examination were also checked, according to the study protocol, during the follow-up period. Physicians analyzed each event including the severity or seriousness of the event, and whether the event was associated with the drug. Adverse events were sorted into general events and adverse drug reactions. Among the adverse events, those evaluated as fatal, life-threatening, causing permanent disability, or requiring long term hospital care were classified as serious adverse events.[9]

Full analysis set (FAS) and per-protocol set (PPS) were utilized for analysing the data regarding the efficacy. FAS encompassed every subject who met inclusion and exclusion criteria except the ones who failed to visit for assessing primary outcome measurements. PPS was defined as analyzing the subjects who were thoroughly assessed for primary and secondary outcome measurements without any missing data. The safety population, those who had study drug injection since registration in this clinical trial, was included in the safety analysis.

To evaluate changes in MAS grade for upper limb muscles, DAS, GAS, and Caregiver

Burden Scale between the baseline and each follow-up visit, the mean and standard deviation were presented for each measurement, and paired t-test and Wilcoxon Signed rank test were used. A 2-sided confidential interval (CI) were considered statistically significant ($P < .05$). Statistical analysis was performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

Total of 233 patients were screened in the study. Among them, 10 patients were evaluated as ineligible for the study and excluded, and 223 patients were enrolled. 222 patients were included in Safety Analysis Set and Full Analysis Set, because 1 patient was failed to have drug administration (Figure 1). 175 patients were included in Per Protocol analysis, because 47 patients were excluded for taking prohibited medication during the follow-up (30 patients), and drop out (17 patients) (Figure 1). Among the 222 subjects who had injection, 75.68 % were male, and mean age was 59.53 ± 11.99 (Table 2). More than half of the patients had previous medical history of hypertension, and about 41% of the patients were having concomitant medications at the time of the study participation (Table 2). Most of the patients (99.10%) had no history of previous botulinum toxin injection (Table 2).

Figure 1. Study flowchart is shown.

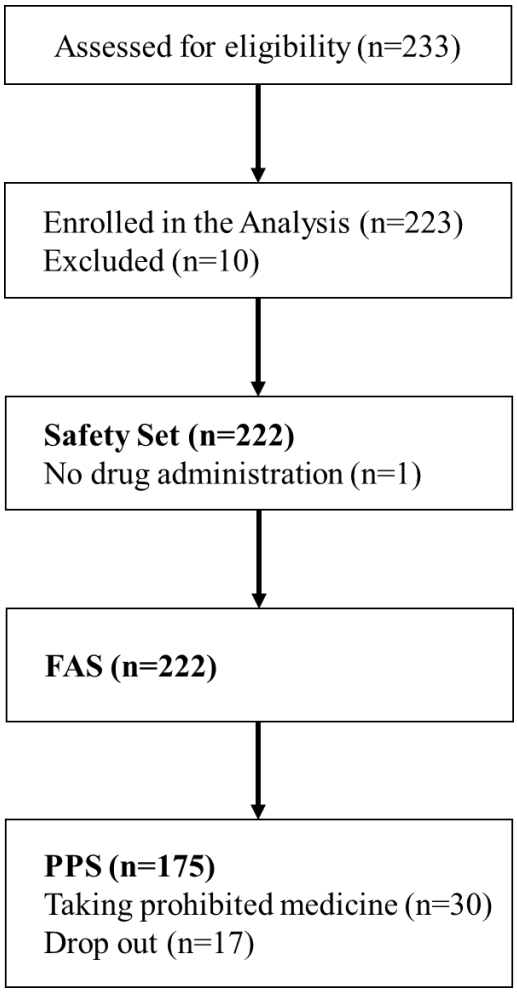


Table 2. Demographic data.

		FAS (n=222)	
		n	**(%)**
Sex			
	Men	168	(75.68)
	Women	54	(24.32)
Age			
	Mean ± SD	59.53 ± 11.99	
Previous medical history or Surgery history			
	Hypertension	155	(69.82)
	Diabetes mellitus	58	(26.13)
	Dyslipidemia	20	(9.01)
	Atrial fibrillation	14	(6.31)
	Myocardial infarction	2	(0.90)
	Malignancy	11	(4.95)
	Seizure	22	(9.91)
	Alzhemier's dementia	17	(7.66)
	Parkinson's disease	7	(3.15)
	History of surgery	3	(1.35)
Previous history of Allergy			
	Yes	12	(5.41)
	No	210	(94.59)
Previous botulinum toxin injection			
	Yes	2	(0.90)
	No	220	(99.10)
Concomitant drugs			
	Yes	91	(40.99)
	No	131	(59.01)

Primary outcome

Average MAS grade of wrist flexor muscle was 2.66±1.06 before the injection, and 1.15±0.88 after 4 weeks after the injection in FAS analysis, which showed statistically significant change (-1.53±0.95, *p*-value < .0001) (Table 3, Figure 2). PPS analysis also revealed statistically significant change in average MAS grade.

Table 3. Change of modified Ashworth Scale measurements in wrist flexor muscle at 4 weeks after injection by FAS and PPS analysis.

	FAS			PPS		
	N	Mean ± SD	*p*-value	N	Mean ± SD	*p*-value
Baseline	222	2.66 ± 1.06		175	2.74 ± 1.08	
4 Weeks after injection	216	1.15 ± 0.88		175	1.18 ±0.90	
Change from baseline	216	-1.53 ± 0.95	<.0001	175	-1.56 ± 0.99	<.0001

p-value : Paired t-test

Secondary outcome

There were statistically significant changes in MAS grade of wrist flexor muscle 8 and 12 weeks after the injection in comparison with pre-injection in FAS analysis (-1.42 ± 0.98; *p*-value < .0001 and -1.24 ± 1.00; *p*-value < .0001, respectively) (Table 4, Figure 2). MAS grade of elbow flexor muscles at 4-, 8-, and 12-weeks post-injection also showed statistically significant changes when compared with pre-injection (-1.20 ± 0.96; *p*-value < .0001, -1.10 ± 1.02; *p*-value < .0001, and -0.87 ± 0.96; *p*-value < .0001, respectively). In addition, there were statistically significant changes in MAS grade of finger flexor muscles at 4-, 8-, and 12-weeks post-injection in comparison with pre-injection (-1.61 ± 0.99; *p*-value < .0001, -1.43 ± 0.43; *p*-value < .0001, -1.17 ± 1.02; *p*-value < .0001, respectively) (Table 5, Figure 3). Similar significant changes were observed regarding changes in MAS grade of wrist flexor, elbow flexor, and finger flexor muscles in PPS analysis.

Table 4. Change of modified Ashworth Scale measurements in wrist flexor muscle at 8 and 12 weeks after injection by FAS and PPS analysis.

	FAS			PPS		
	N	Mean ± SD	*p*-value	N	Mean ± SD	*p*-value
Baseline	222	2.66 ± 1.06		175	2.74 ± 1.08	
8 Weeks	213	1.26 ± 0.96		175	1.31 ± 0.99	
Change from baseline	213	-1.42 ± 0.98	<.0001	175	-1.43 ± 1.02	<.0001
12 Weeks	205	1.44 ± 1.06		175	1.50 ± 1.09	
Change from baseline	205	-1.24 ± 1.00	<.0001	175	-1.25 ± 1.03	<.0001

p-value : Paired t-test

Figure 2. Change of modified Ashworth Scale measurements in wrist flexor muscle at 4, 8 and 12 weeks after injection by FAS and PPS analysis. Changes are reported as mean ± SE (standard error).

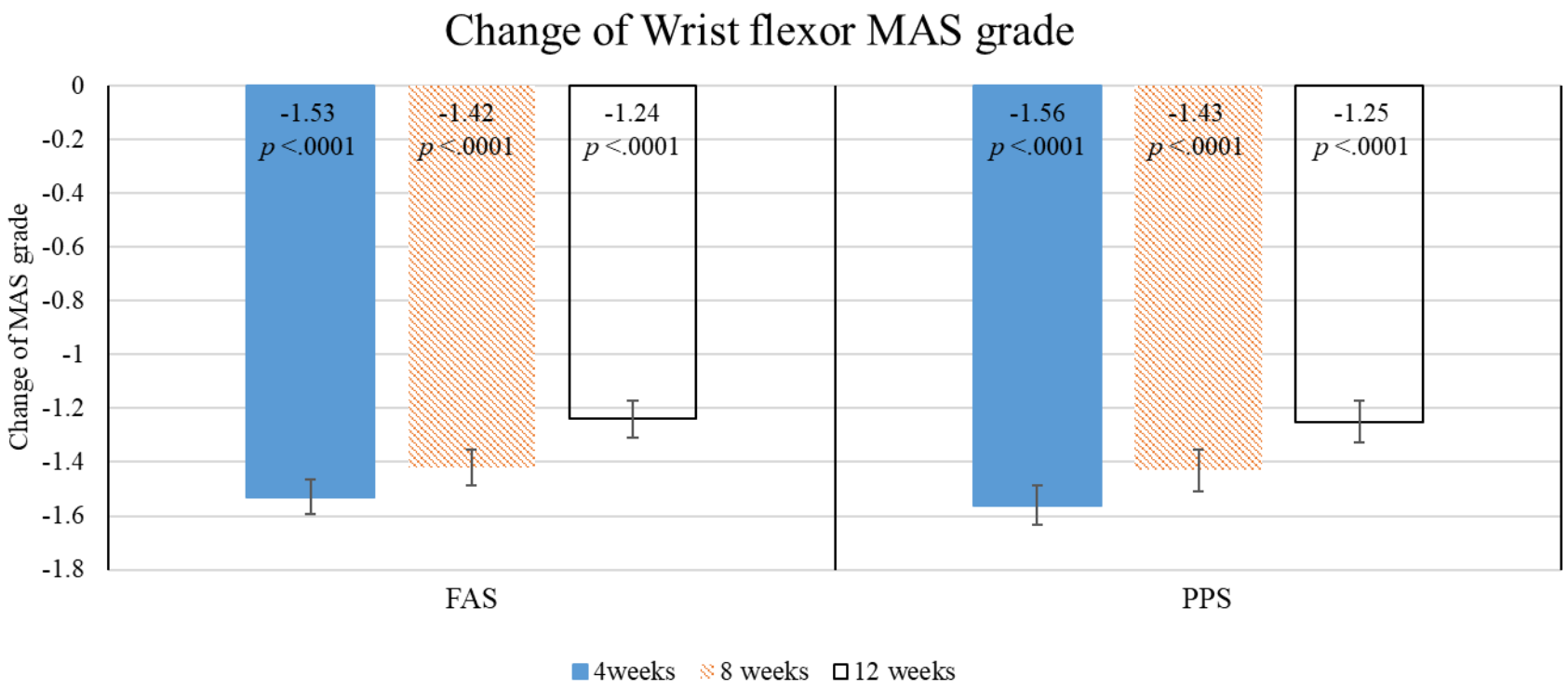
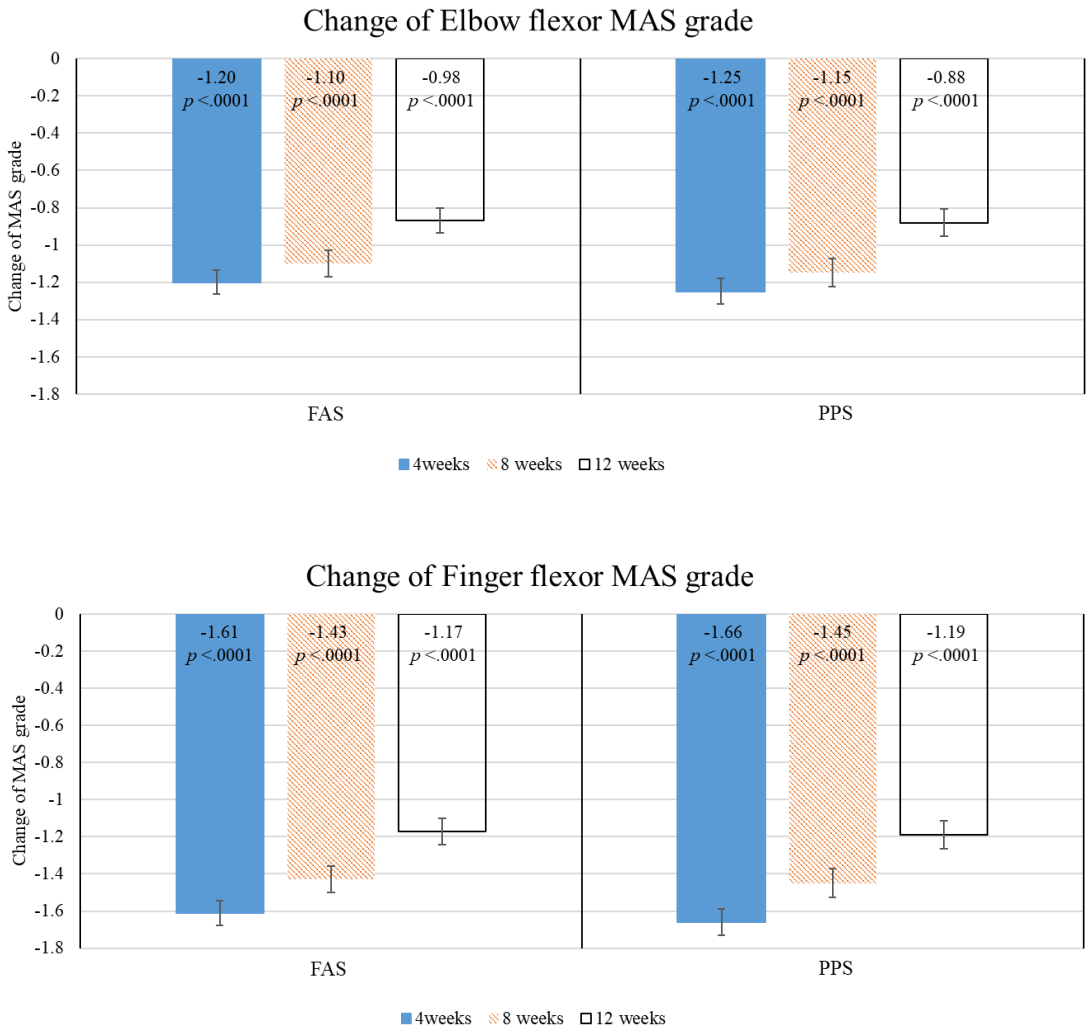


Table 5. Change of modified Ashworth Scale measurements in elbow flexor and finger flexor muscles at 4, 8 and 12 weeks after injection by FAS and PPS analysis.

		Elbow flexor			Finger flexor		
		N	Mean ± SD	*p*-value	N	Mean ± SD	*p*-value
FAS							
	Baseline	221	2.45 ± 1.27		222	2.97 ± 1.13	
	4 Weeks	216	1.26 ± 1.00		216	1.40 ± 0.99	
	Change from baseline	215	-1.20 ± 0.96	<.0001	216	-1.61 ± 0.99	<.0001
	8 Weeks	213	1.34 ± 0.98		213	1.58 ± 1.12	
	Change from baseline	212	-1.1 ± 1.02	<.0001	213	-1.43 ± 1.03	<.0001
	12 Weeks	205	1.58 ± 1.08		205	1.85 ± 1.17	
	Change from baseline	204	-0.87 ± 0.96	<.0001	205	-1.17 ± 1.02	<.0001
PPS							
	Baseline	175	2.48 ± 1.26		175	3.06 ± 1.09	
	4 Weeks	175	1.23 ± 1.00		175	1.40 ± 0.98	
	Change from baseline	175	-1.25 ± 0.91	<.0001	175	-1.66 ± 0.96	<.0001
	8 Weeks	175	1.33 ± 0.99		175	1.62 ± 1.12	
	Change from baseline	175	-1.15 ± 1.00	<.0001	175	-1.45 ± 1.03	<.0001
	12 Weeks	175	1.60 ± 1.10		175	1.87 ± 1.19	
	Change from baseline	175	-0.88 ± 0.97	<.0001	175	-1.19 ± 1.01	<.0001

p-value : Paired t-test

Figure 3. Change of modified Ashworth Scale measurements in elbow flexor and finger flexor muscles at 4, 8 and 12 weeks after injection by FAS and PPS analysis. Changes are reported as mean ± SE (standard error).



Therapeutic response rate in wrist flexor were 85.65% (185 of 222), 84.04% (179 of 222) and 78.54% (161 of 222) in FAS analysis at 4, 8, and 12 weeks after injection, respectively (Table 6). The response rate in elbow flexor were 77.21% (166 of 222), 72.17% (153 of 222), and 67.16% (137 of 222) in FAS analysis at 4, 8, and 12 weeks after injection, respectively. The response rate in finger flexor were 88.43% (191 of 222), 83.10% (177 of 222), and 75.61% (155 of 222) in FAS analysis at 4, 8, and 12 weeks after injection, respectively. The highest response rate was shown at 4 weeks after the injection, and then gradual decline was observed over time. Similar to FAS analysis, PPS analysis also showed the highest therapeutic response rate in all examined muscles at 4-weeks post-injection in comparison with baseline, and then revealed decreased response rate.

Table 6. Therapeutic response rate in wrist flexor, elbow flexor, and finger flexor muscles at 4, 8 and 12 weeks after injection by FAS and PPS analysis.

		Wrist flexor	Elbow flexor	Finger flexor
FAS				
4 Weeks	N (%)	185 (85.65)	166 (77.21)	191 (88.43)
	95% C.I.	[80.97, 90.32]	[71.60, 82.82]	[84.16, 92.69]
8 Weeks	N (%)	179 (84.04)	153 (72.17)	177 (83.10)
	95% C.I.	[79.12, 88.96]	[66.14, 78.20]	[78.07, 88.13]
12 Weeks	N (%)	161 (78.54)	137 (67.16)	155 (75.61)
	95% C.I.	[72.92, 84.16]	[60.71, 73.60]	[69.73, 81.49]
PPS				
4 Weeks	N (%)	148 (84.57)	137 (78.29)	158 (90.29)
	95% C.I.	[79.22, 89.92]	[72.18, 84.39]	[85.90, 94.67]
8 Weeks	N (%)	145 (82.86)	131 (74.86)	147 (84.00)
	95% C.I.	[77.27, 88.44]	[68.43, 81.28]	[78.57, 89.43]
12 Weeks	N (%)	138 (78.86)	118 (67.43)	135 (77.14)
	95% C.I.	[72.81, 84.91]	[60.49, 74.37]	[70.92, 83.36]

DAS scores related with principal therapeutic targets decreased after the injection regardless of time, and statistically significant changes from the baseline were observed in every domain in FAS analysis (Table 7, Figure 4). However, the score failed to show functional improvement over time. Similar to the FAS analysis, the PPS analysis revealed significant improvement at 4 weeks after injection in comparison with the baseline. The physician rated GAS at 12 weeks revealed that the physicians evaluated the functional outcomes of 86.8% of subjects as ‘very good’ or ‘good’. In the subject or caregiver rated GAS at 12 weeks, 60.0% of the subjects or caregivers rated their outcomes as ‘very good’ or ‘good’ (Table 8).

Table 7. Comparison of DAS score between baseline and 4, 8 and 12 weeks after injection by FAS and PPS analysis.

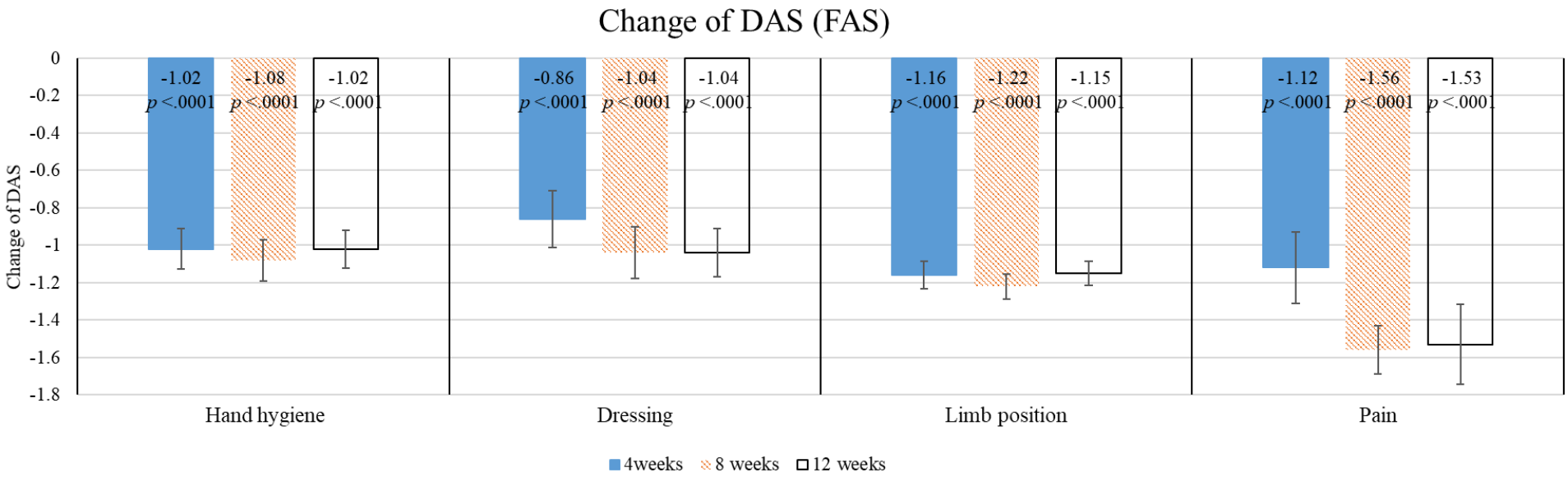
	Hand hygiene		Dressing		Limb position		Pain	
	N	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**
FAS								
Baseline	60	2.42 ± 0.70	32	2.34 ± 0.70	113	2.50 ± 0.67	17	2.41 ± 0.62
4 Weeks	60	1.40 ± 0.85	28	1.54 ± 0.79	111	1.34 ± 0.72	17	1.29 ± 1.05
Change from baseline	60	-1.02 ± 0.83	28	-0.86 ± 0.80	111	-1.16 ± 0.79	17	-1.12 ± 0.78
p-value		<.0001		<.0001		<.0001		<.0001
8 Weeks	59	1.32 ± 0.75	27	1.33 ± 0.68	111	1.29 ± 0.69	16	0.88 ± 0.81
Change from baseline	59	-1.08 ± 0.84	27	-1.04 ± 0.71	111	-1.22 ± 0.71	16	-1.56 ± 0.51
p-value		<.0001		<.0001		<.0001		<.0001
12 Weeks	56	1.38 ± 0.73	26	1.31 ± 0.74	108	1.35 ± 0.67	15	0.87 ± 0.92
Change from baseline	56	-1.02 ± 0.75	26	-1.04 ± 0.66	108	-1.15 ± 0.69	15	-1.53 ± 0.83
p-value		<.0001		<.0001		<.0001		<.0001

p-value : Paired t-test

	Hand hygiene		Dressing		Limb position		Pain	
	N	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**
PPS								
Baseline	50	2.38 ± 0.73	20	2.35 ± 0.67	93	2.55 ± 0.62	12	2.33 ± 0.65
4 Weeks	50	1.32 ± 0.82	20	1.40 ± 0.82	93	1.35 ± 0.69	12	1.33 ± 1.15
Change from baseline	50	-1.06 ± 0.84	20	-0.95 ± 0.76	93	-1.19 ± 0.78	12	-1.00 ± 0.74
p-value		<.0001		<.0001		<.0001		0.0007
8 Weeks	50	1.28 ± 0.76	20	1.25 ± 0.64	93	1.30 ± 0.67	12	0.83 ± 0.83
Change from baseline	50	-1.10 ± 0.84	20	-1.10 ± 0.72	93	-1.25 ± 0.69	12	-1.50 ± 0.52
p-value		<.0001		<.0001		<.0001		<.0001
12 Weeks	50	1.30 ± 0.71	20	1.25 ± 0.79	93	1.37 ± 0.66	12	0.92 ± 1.00
Change from baseline	50	-1.08 ± 0.75	20	-1.10 ± 0.64	93	-1.18 ± 0.67	12	-1.42 ± 0.90
p-value		<.0001		<.0001		<.0001		0.0002

p-value : Paired t-test

Figure 4. Change of Disability Assessment Scale (DAS) in each domain at 4, 8 and 12 weeks after injection by FAS and PPS analysis. Changes are reported as mean ± SE (standard error).



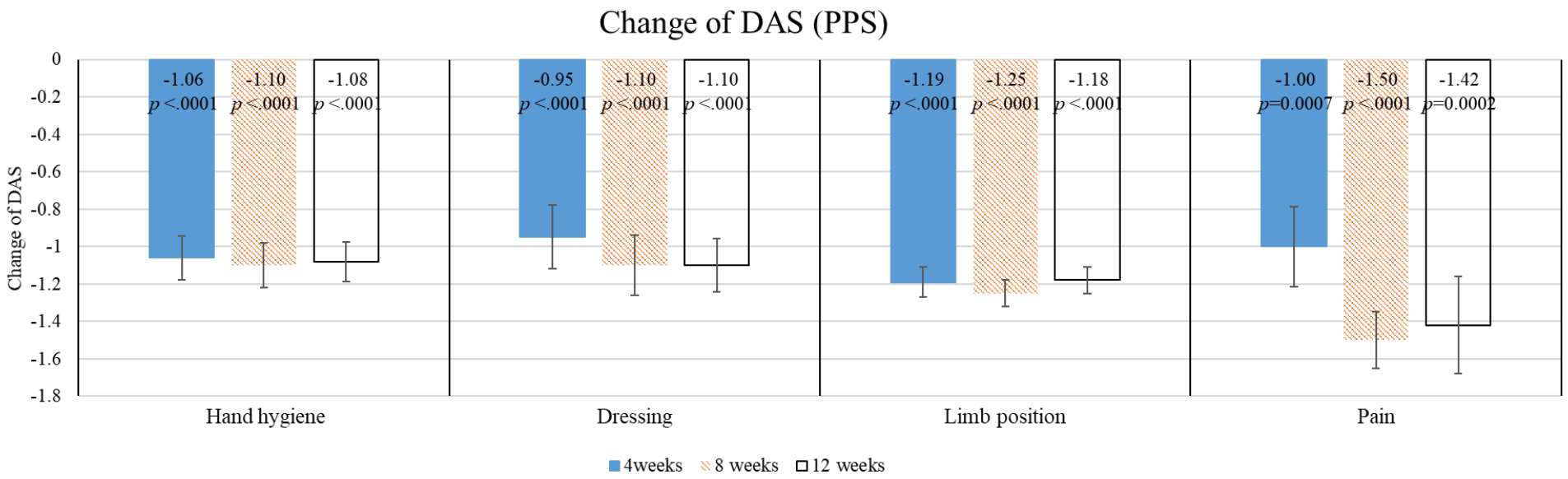

Change of DAS (PPS)
Change of DAS
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
-1.06
p <.0001
-1.10
p <.0001
-1.08
p <.0001
-0.95
p <.0001
-1.10
p <.0001
-1.10
p <.0001
-1.19
p <.0001
-1.25
p <.0001
-1.18
p <.0001
-1.00
p=0.0007
-1.50
p <.0001
-1.42
p=0.0002
Hand hygiene
Dressing
Limb position
Pain
4weeks
8 weeks
12 weeks

Table 8. The physician and the subject or caregiver rated Global Assessment Scale.

	FAS	PPS
	N (%)	N (%)
Physician		
Very good	40 (19.5)	34 (19.4)
Good	138 (67.3)	118 (67.4)
Moderate	26 (12.7)	22 (12.6)
Poor	1 (0.5)	1 (0.6)
Subject/caregiver		
Very good	17 (8.3)	13 (7.4)
Good	106 (51.7)	91 (52.0)
Moderate	65 (31.7)	56 (32.0)
Poor	17 (8.3)	15 (8.6)

The changes in Caregiver Burden Scale (4 domains) at 4-, 8-, and 12-weeks post-injection in comparison with pre-injection evaluated by the care givers showed statistically significant decrease, regardless of the time after the injection, compared to pre-injection in every domain in FAS analysis (Table 9, Figure 5). For the 'cleansing palm' domain, scores for pre-injection, 4 weeks, 8 weeks, and 12 weeks after injection were 2.91±1.25, 2.51±1.17, 2.55±1.17, and 2.42±1.14. For the 'cutting the fingernails' domain, scores for pre-injection, 4 weeks, 8 weeks, and 12 weeks after injection were 3.31±1.33, 3.03±1.40, 3.14±1.44, and 3.10±1.40. For the 'dressing' domain, scores for pre-injection, 4 weeks, 8 weeks, and 12 weeks after injection were 2.93±1.17, 2.60±1.16, 2.57±1.17, and 2.54±1.12. For the 'cleaning under the armpit' domain, scores for pre-injection, 4 weeks, 8 weeks, and 12 weeks after injection were 3.04±1.31, 2.79±1.30, 2.76±1.26, 2.77±1.28. Similar results were observed in PPS analysis.

Table 9. Changes in Caregiver Burden Scale between baseline and 4, 8 and 12 weeks after injection by FAS and PPS analysis.

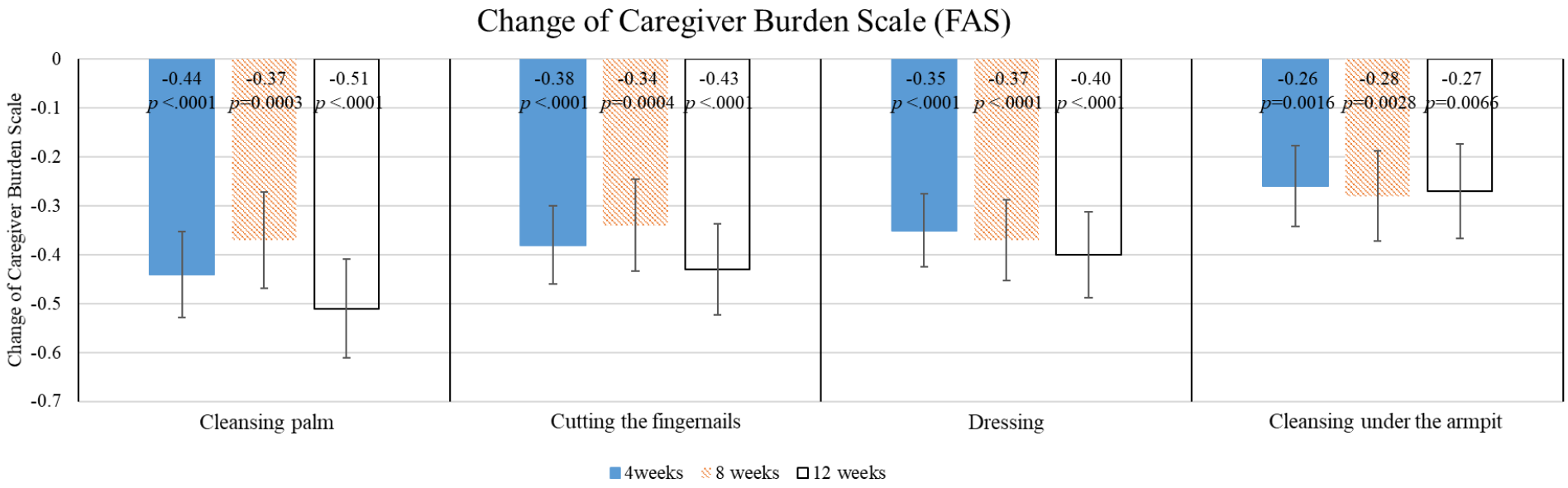
		Cleansing palm		Cutting the fingernails		Dressing		Cleansing under the armpit	
		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
FAS									
	Baseline	199	2.91 ± 1.25	199	3.31 ± 1.33	199	2.93 ± 1.17	199	3.04 ± 1.31
	4 Weeks	198	2.51 ± 1.17	198	3.03 ± 1.40	198	2.60 ± 1.16	198	2.79 ± 1.30
	Change from baseline	193	-0.44 ± 1.22	193	-0.38 ± 1.12	193	-0.35 ± 1.03	193	-0.26 ± 1.15
	p-value		<.0001		<.0001		<.0001		0.0016
	8 Weeks	199	2.55 ± 1.17	199	3.14 ± 1.44	199	2.57 ± 1.17	199	2.76 ± 1.26
	Change from baseline	189	-0.37 ± 1.36	189	-0.34 ± 1.29	189	-0.37 ± 1.14	189	-0.28 ± 1.27
	p-value		0.0003		0.0004		<.0001		0.0028
	12 Weeks	195	2.42 ± 1.14	195	3.10 ± 1.40	195	2.54 ± 1.12	195	2.77 ± 1.28
	Change from baseline	181	-0.51 ± 1.36	181	-0.43 ± 1.25	181	-0.40 ± 1.18	181	-0.27 ± 1.30
	p-value		<.0001		<.0001		<.0001		0.0066

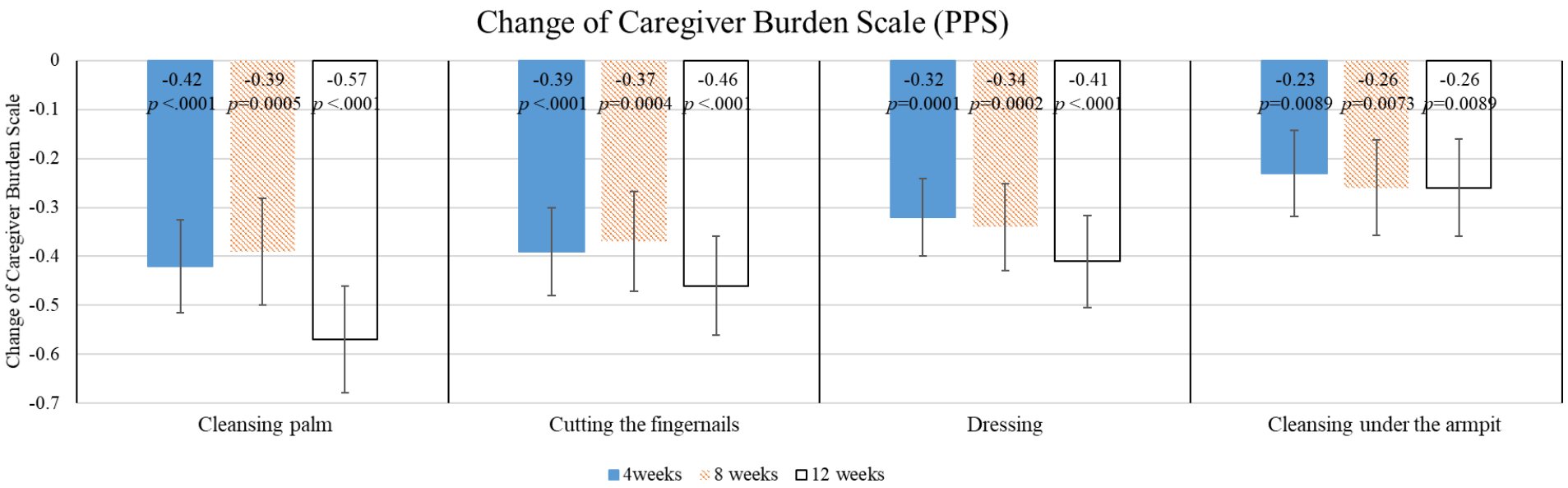
p-value : Paired t-test

	Cleansing palm		Cutting the fingernails		Dressing		Cleansing under the armpit	
	N	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**
PPS								
Baseline	155	2.95 ± 1.27	155	3.40 ± 1.30	155	2.94 ± 1.17	155	3.05 ± 1.30
4 Weeks	159	2.55 ± 1.16	159	3.06 ± 1.39	159	2.62 ± 1.17	159	2.82 ± 1.34
Change from baseline	155	-0.42 ± 1.18	155	-0.39 ± 1.12	155	-0.32 ± 0.99	155	-0.23 ± 1.09
p-value		<.0001		<.0001		0.0001		0.0089
8 Weeks	164	2.54 ± 1.18	164	3.14 ± 1.45	164	2.57 ± 1.17	164	2.76 ± 1.26
Change from baseline	155	-0.39 ± 1.36	155	-0.37 ± 1.27	155	-0.34 ± 1.10	155	-0.26 ± 1.21
p-value		0.0005		0.0004		0.0002		0.0073
12 Weeks	167	2.38 ± 1.17	167	3.09 ± 1.43	167	2.51 ± 1.15	167	2.77 ± 1.30
Change from baseline	155	-0.57 ± 1.36	155	-0.46 ± 1.25	155	-0.41 ± 1.17	155	-0.26 ± 1.24
p-value		<.0001		<.0001		<.0001		0.0089

p-value : Paired t-test

Figure 5. Change of Caregiver Burden Scale in each domain at 4, 8 and 12 weeks after injection by FAS and PPS analysis. Changes are reported as mean ± SE (standard error).




Change of Caregiver Burden Scale (PPS)
Change of Caregiver Burden Scale
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.42
p <.0001
-0.39
p=0.0005
-0.57
p <.0001
-0.39
p <.0001
-0.37
p=0.0004
-0.46
p <.0001
-0.32
p=0.0001
-0.34
p=0.0002
-0.41
p <.0001
-0.23
p=0.0089
-0.26
p=0.0073
-0.26
p=0.0089
Cleansing palm
Cutting the fingernails
Dressing
Cleansing under the armpit
4weeks
8 weeks
12 weeks

Safety assessment

The incidence of adverse event was 14.41% (32 of 222), with 43 cases occurred (Table 10). The most frequently reported cases were seizure (3 cases from 3 people) and abnormal perception (3 cases from 2 people). Headache, nasopharyngitis, urinary tract infection, fever, and cough were reported in 2 cases from 2 people, respectively. There was no adverse drug reaction event reported. 5 cases of major adverse event were reported from 5 people. Among the subjects with major adverse event, one subject was dropped out from the clinical trial due to pneumonia. Other major adverse events included seizure (2 patients), subdural hemorrhage (1 patient), and fever (1 patient) (Table 11). There were no clinically significant changes in vital signs and physical examination results during the clinical trials.

Table 10. Summary of total adverse events (Safety Set Analysis).

	Number of patients (N)	Incidence per 222 patients (%)	Number of cases (N)	95% C.I. of the Incidence
Adverse event	32	14.41	43	9.79 , 19.03
Adverse drug reaction event	0	0.00	0	0.00 , 0.00
Major adverse event	5	2.25	5	0.30 , 4.20
Adverse event which led to drop out	1	0.45	4	0.00 , 1.33

Table 11. Summary of major adverse events (Safety Set Analysis).

System organ class/preferred term	**Number of patients (N)**	**Incidence per 222 patients (%)**	**Number of cases (N)**
Neurological impairment			
Seizure	2	0.90	2
Infection			
Pneumonia	1	0.45	1
Trauma, Intoxication, Procedural complication			
Subdural hemorrhage	1	0.45	1
General disorders and administration site conditions			
Fever	1	0.45	1
Total	**5**	**2.25**	**5**

Discussion

This is the first multi-centered phase IV study evaluating the efficacy and safety of NABOTA® injection for managing upper limb spasticity after stroke. The result of this study showed significant improvement spasticity of upper extremity muscles after NABOTA® injection up to 12 weeks after the administration. The injection also revealed considerable effect on easing the burden of the caregivers up to 12 weeks after injection. Although we have shown the efficacy of NABOTA® with previous study,[5] it was performed with relatively small number of patients (99). Through this study, it was also confirmed that the efficacy was valid even for larger population.

The MAS grade of wrist flexor was reduced from 2.66 to 1.15 (-1.51) 4 weeks after injection, the degree of which was greater than that of phase III trial,[5] and within the range suggested by previous studies; from -1.10 to -1.66.[9-12] This result could be derived from the fact that the spasticity at the baseline was more severe than that of phase III trial (2.30).[5] Changes in MAS grade of wrist flexor muscle got smaller as time goes by; -1.42 at 8 weeks and -1.24 at 12 weeks after injection, which showed similar tendency when compared with the results of the phase III trial.[5]

Elbow flexor and finger flexor muscles showed greater changes 4 weeks after injection, compared with that of phase III trial; -1.20 and -1.61, respectively.[5] Those muscles also demonstrated similar trends, decrement in degree of changes in MAS grade over time, but all the changes compared with pre-injection, regardless of time, were greater than that of phase III trial.[5] Previous studies with Neuronox and Meditoxin® also demonstrated similar tendency with this study.[13,14] The subjects showed prominent reduction in MAS at injected muscles (wrist flexor, elbow extensor, and finger flexor) 4 weeks after the injection, and the effect sustained until 12-weeks post-injection, though the degree of change decreased.[13,14]

The changes in upper limb function were also prominent, and the majority of the patients

were satisfied with efficacy of the injection. The result was consistent with previous studies, including phase III trial.[5,7,8,12] Among the 4 domains evaluated by DAS, upper limb position domain, which the largest number of patients and caregivers wanted improvement, showed better changes (-1.16, -1.22, and -1.15 at 4, 8, and 12 weeks, respectively), than those of hand hygiene (-1.02, -1.08, and -1.02) or dressing (-0.86, -1.04, and -1.04) regardless of time, and this was consistent with previous trial.[5] The result of this study, showing greater change in most wanted domain, would have given the patients and caregivers positive effect on satisfaction with NABOTA®. Previous study with Neuronox also showed greater change in upper limb position than hygiene and dressing domain, and largest number of subjects wanted to improve upper limb position function,[13] which was similar to our study.

There was significant decrement in every domain of Caregiver Burden Scale at all-time points evaluated, but the amount of changes was not considerable, only approximately ranging from 0.2 to 0.3, which was similar to phase III study.[5] There was still discrepancy regarding GAS between the physicians and the subjects or caregivers when compared with phase III trial; about 87% of physicians assessed the treatment effective, however only 60% of subjects or caregivers admitted efficacy of the injection.[5] This result supports the fact that botulinum toxin injection may relieve upper limb spasticity significantly, but the improvement of upper limb function in activities of daily life is still limited, according to the subjects or the caregivers,[5] even after performing analysis with larger population. There is a study reporting that the botulinum toxin injection was more related with improving basic functions or pain than improving active functions.[15] The expectations of the subjects or the caregivers would have been much greater for the active functions. There might be several specific conditions for the benefit after the injection as another study suggesting that the stroke patients with relatively better distal upper limb function would show greater functional outcome after the botulinum toxin injection,[16] but further studies are needed to find out such conditions and confirm the effect on functional improvement after the injection. Previous trial interpreted the discrepancy of GAS that the physicians would mainly focus on the change of spasticity whereas the subjects or the caregivers would put more weight

on functional impairments.[5] We have also confirmed that there remains a difference in perspective between physician and patients or caregivers even after the drug has hit the market.

This study showed lower rate of adverse event (14.41%), compared with that of previous phase III trial (19.59%).[5] Moreover, there was no adverse drug reaction events reported in this trial while there were 3 cases of adverse drug reaction in previous trial.[5] Throughout these results, it suggests that frequency of adverse event did not deviate from the expected range of previous study, even after being used by greater population. Previous study with Neuronox reported larger number of adverse events (93 events in 39 patients) including nasopharyngitis and cough.[13] Another study with Meditoxin® reported 35 cases of adverse events, mostly with diarrhea, vomiting, peripheral edema, nasopharyngitis, and pain.[14] Throughout those results, we may assume that NABOTA® is showing similar to better safety compared to other medications, but further studies are needed.

This study had several limitations. First, we did not check the long-term efficacy and safety after the 12-week follow-up period. Previous phase III trial also had follow-up period of 12 weeks,[5] and we could have demonstrated more concrete evidence if the study were performed with longer follow-up period. There was a study with other Clostridium botulinum toxin type A injection showing that the effect was reduced to baseline at 10 to 16 weeks after the injection.[17] Further studies with longer follow-up period could give us exact effect period of NABOTA® and we may compare the period with those of other drugs. Second, there may be intra- or inter-rater variability, as the spasticity was evaluated from physical examination by the physician. To minimize these variabilities, identical measurement guideline was thoroughly shared among the examiners, and the identical physician checked the spasticity by the MAS grade through entire follow-up period. Third, we did not perform comparing process with the placebo group. It would be helpful to present more robust evidence in efficacy of the drug if the placebo group were added into the analysis. Moreover, although cerebral hemorrhage or seizure might be complication of the stroke itself, association between NABOTA® and the complications cannot be thoroughly

ruled out. Setting placebo group would be helpful in confirming the adverse effects of the drug more clearly. However, there may be ethical issue about the placebo drug injection because it requires invasive procedure.

Conclusion

This study showed that NABOTA®, a new botulinum toxin A, had considerable efficacy and effect duration in managing upper limb spasticity after stroke, after hitting the market. The study also revealed that it shows considerable safety after the market. NABOTA® may be effectively and safely used as one of the treatments using botulinum toxin A in managing post-stroke upper limb spasticity.

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요약 (국문 초록)

뇌졸중 후 상지 경직 치료로 Clostridium botulinum toxin type A (NABOTA®)의 투여에 대한 안전성 및 유효성 연구 : 다기관, 제4상 임상시험

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서론: 클로스트리디움 보툴리눔 독소 A 형 (Clostridium botulinum toxin type A) 주사는 뇌졸중 후 상지 경직을 관리하는데 널리 사용된다. 3 상 임상시험을 통해 새로운 보툴리눔 독소 A 형 (NABOTA®)이 열등하지 않은 효능과 안전성을 보여 시장에 출시된 바 있다. 본 연구를 통해 NABOTA®가 시장에 출시된 후 효능과 안전성을 평가하고자 하였다.

방법: 222 명의 환자를 대상으로 전향적, 다기관, 공개 4 상 임상 연구를 수행했다. 손목 굴곡근, 팔꿈치 굴곡근 및 손가락 굴곡근에 경직 정도에 따라 최대 360 IU (International Unit)의 NABOTA®를 주사하였다. NABOTA® 주사 전, 그리고 주사 4 주 뒤 사이의 손목 굴곡근 Modified Ashworth Scale (MAS) 등급의 변화를 일차 유효성 평가변수로 설정하였다. 아울러, 주사한 근육에 대한 MAS 등급, 장애 평가 척도 (Disability Assessment Scale, DAS) 및 간병인 부담 척도 (Caregiver Burden Scale)의 변화를 각각 주사 전, 그리고 주사 후 4, 8, 12 주에 평가하였다. 전반적 평가 척도 (Global Assessment Scale, GAS)는 주사 후 12 주에 확인하였다.

결과: 주사 전과 비교했을 때, 주사 후 4 주 때 손목 굴곡근의 MAS 등급에서 통계적으로 유의한 변화가 있었다 (−1.53±0.95, *p*-value < .0001). 또한 주사 된 모든 근육에서 MAS 등급, 장애 평가 척도 및 간병인 부담 척도에서 모든 추적관찰 기간에 걸쳐 상당한 개선을 확인할 수 있었다. 부작용 발생률은 14.41 % (222 명 중 32 명)로 기존 임상 시험보다 적었다.

결론: NABOTA®는 뇌졸중 환자의 상지 경직을 관리하는 데 있어 상당한 수준의 효과와 안전성을 보여주었다.

주요어: 뇌졸중, 경직, 상지, 보툴리눔 독소 A 형, 효과, 안전성, 4 상

학 번: 2019−23204