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Efficacy and safety of NABOTA in post-stroke upper limb spasticity: A phase 3 multicenter, double-blinded, randomized controlled trial☆

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ABSTRACT

Botulinum toxin A is widely used in the clinics to reduce spasticity and improve upper limb function for post-stroke patients. Efficacy and safety of a new botulinum toxin type A, NABOTA (DWP450) in post-stroke upper limb spasticity was evaluated in comparison with Botox (onabotulinum toxin A). A total of 197 patients with post-stroke upper limb spasticity were included in this study and randomly assigned to NABOTA group (n = 99) or Botox group (n = 98). Wrist flexors with modified Ashworth Scale (MAS) grade 2 or greater, and elbow flexors, thumb flexors and finger flexors with MAS 1 or greater were injected with either drug. The primary outcome was the change of wrist flexor MAS between baseline and 4 weeks post-injection. MAS of each injected muscle, Disability Assessment Scale (DAS), and Caregiver Burden Scale were also assessed at baseline and 4, 8, and 12 weeks after the injection. Global Assessment Scale (GAS) was evaluated on the last visit at 12 weeks. The change of MAS for wrist flexor between baseline and 4 weeks post-injection was −1.44 ± 0.72 in the NABOTA group and −1.46 ± 0.77 in the Botox group. The difference of change between both groups was 0.0129 (95% confidence interval −0.2062–0.2319), within the non-inferiority margin of 0.45. Both groups showed significant improvements regarding MAS of all injected muscles, DAS, and Caregiver Burden Scale at all follow-up periods. There were no significant differences in all secondary outcome measures between the two groups. NABOTA demonstrated non-inferior efficacy and safety for improving upper limb spasticity in stroke patients compared to Botox.

1. Introduction

Stroke is one of the leading single disease entities for morbidity in Korea, and 73 out of 100,000 people die due to stroke [1,2]. Many stroke survivors suffer from impaired quality of life owing to functional limitations. Over 50–70% of stroke patients present functional limitation of the upper limb such as weakness, spasticity, sensory loss and decreased coordination [1,3]. Especially, spasticity in upper extremities affects quality of life more than in lower extremities [1,3]. Incidence of upper limb spasticity in stroke patients is reported at 30–60% in various studies [3].

Considering a relatively high survival rate of stroke, managing functional impairments of the upper extremity, especially spasticity, is important because spasticity results in decreased range of motion, contracture, pain, and eventually decreased quality of life [1]. Treatment of upper limb spasticity involves physical therapy, medication, electrical stimulation, local nerve block, or surgery. Generalized spasticity requires antispasmodic agents such as baclofen, diazepam, gabapentin, and dantrolene. But these agents induce sedation, sleepiness, and dizziness which may lead to cessation of the drugs [4]. In focal spasticity, botulinum toxin injection is widely used in clinics. Botulinum toxin A is

Abbreviations: MAS, modified Ashworth Scale; DAS, Disability Assessment Scale; GAS, Global Assessment Scale; FAS, full analysis set; PPS, per protocol set.

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known to reduce spasticity and improve upper limb function in stroke patients. One botulinum toxin A product, onabotulinum toxin A (Botox; Allergan Inc., Irvine, CA), has been approved by the U.S. Food and Drug Administration for treatment of upper limb spasticity in stroke patients. Numerous studies have revealed efficacy and safety for spasticity in stroke [5–7].

NABOTA (Daewoong botulinum toxin type A, Daewoong Pharmaceutical, Seoul, Korea), a new botulinum toxin type A originating from wild-type *Clostridium botulinum* Hall A, was recently introduced. NABOTA was manufactured by High-Pure Technology®, a patented technology of strictly controlled anaerobic fermentation and highly efficient purification, confirmed by size exclusion high-performance liquid chromatography analysis with single 900 kDa peak (>98%) [8]. NABOTA has shown similar pharmacological characteristics and electrophysiological effects compared to Botox in in vivo studies using a rat model [9]. NABOTA also showed higher safety compared to Botox in animal toxicology study and non-inferior safety in the clinical study for glabellar lines [10]. But clinical efficacy and safety of NABOTA for treatment of spasticity in stroke patients have not been established yet. In this study, we aimed to evaluate the efficacy and safety of NABOTA in post-stroke spasticity of the upper limb. The hypothesis of this study was that NABOTA has acceptable efficacy and safety in treating post-stroke spasticity, and that the efficacy is non-inferior to that of Botox.

2. Material and methods

2.1. Study design

This study was designed as a prospective, double-blinded, randomized, active-controlled multicenter phase III clinical trial, conducted in 5 university hospitals (Seoul National University Boramae Medical Center, Seoul National University Hospital, Seoul National University Bundang Hospital, Gangnam Severance Hospital, Asan Medical Center) in Seoul, Korea between September 2013 and July 2014. This study was approved by Ministry of Food and Drug Safety and Institutional Review Boards of each institution under principles of Good Clinical Practice and Declaration of Helsinki. Written informed consent from all participants was obtained before enrollment.

2.2. Participants and randomization

Post-stroke patients with age ≥18, more than 6 weeks since stroke onset, spasticity of wrist flexor with score of 2 or greater by modified Ashworth Scale (MAS) [11], spasticity of elbow flexor or finger flexor with score of MAS 1 or greater, and rating of 2 or greater by Disability Assessment Scale (DAS) on 1 principal therapeutic target for functional disability among hygiene, dressing, limb position or pain were recruited for this study [12]. Exclusion criteria were neuromuscular junction disease or motor neuron disease, phenol or alcohol block for the target limbs within 6 months before screening, botulinum toxin injection within 3 months before screening, history or plan for tendon lengthening surgery, significant contracture or muscle atrophy at the target joint or muscle, concurrent treatment with intrathecal baclofen, hypersensitivity or allergy to study drug or its components, pregnancy or planned pregnancy, breastfeeding, and abnormal lab findings for alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, and serum creatinine. Physical therapy, occupational therapy, splinting, benzodiazepine, and muscle relaxants had to be stable from 4 weeks preceding the study until the end of the study.

At each institute, eligible patients were randomly assigned to either NABOTA or Botox treatment group in a 1:1 ratio using a computer-generated randomization schedule. An independent pharmacist diluted the medication with normal saline according to the randomization code. Investigators and patients were blinded to the drug throughout the study. In each institute, one physician performed all the MAS grading throughout the study period.

2.3. Treatment

One vial of botulinum toxin (100 units) was diluted with 2 mL 0.9% NaCl. Target muscles and dose for injection were selected by the physician according to the degree of spasticity and study guidelines. Injection was performed by either ultrasonography or electromyography/stimulator guidance. Wrist flexors (flexor carpi radialis, flexor carpi ulnaris) were mandatory for the injection. Injection sites and dose for each upper limb muscles are shown in Table 1. Up to 360 units in each patient were allowed.

2.4. Spasticity measurement method

All measurements for spasticity were performed by the modified Ashworth Scale [11]. The subjects were in a supine position in a comfortable environment. For the wrist flexors, MAS was measured by the examiner from wrist volarflexed position. Elbow flexors and finger flexors were also examined from full flexed position within a tolerable range. All investigators received an education regarding the measurement protocols before the study and shared the same guidelines.

2.5. Clinical outcome measures

As the primary outcome we used the change of MAS for wrist flexor between baseline and 4 weeks post-injection. Secondary outcomes included MAS change for wrist flexor at 8 and 12 weeks post-injection compared to the baseline, MAS change for elbow flexor, finger flexor and thumb flexor at 4, 8, and 12 weeks post-injection compared to the baseline, effective ratio for each muscle at 4, 8, and 12 weeks, change of DAS at 4, 8, and 12 weeks compared to the baseline, Global Assessment Scale (GAS) at 12 weeks rated by both physician and caregiver, and Caregiver Burden Scale at 4, 8, and 12 weeks compared to the baseline. Response rate was defined as the proportion of subjects whose MAS score was decreased by at least 1 point at the target muscle. DAS is a 4-point scale (0: no disability, 1: mild disability, 2: moderate disability, 3: severe disability) to assess functional disability for hygiene, dressing, limb position or pain [12]. GAS is a 4-point scale (1: very good, 2:

Table 1
Injection sites and doses for each target muscles.

Function	Target muscle	Recommended injection dose (U: units)	Number of injection sites	Mean injection dose	
				NABOTA group	Botox group
Wrist flexors	Flexor carpi radialis	15–60	1–2	53.51 ± 9.13	54.80 ± 5.78
	Flexor carpi ulnaris	15–50	1–2	47.84 ± 6.80	49.39 ± 3.46
Elbow flexor	Biceps brachii	100–200	Maximum 4	134.57 ± 33.57	134.48 ± 25.98
Finger flexors	Flexor digitorum profundus	15–50	1–2	45.17 ± 10.54	47.04 ± 8.17
	Flexor digitorum sublimis	15–50	1–2	47.50 ± 7.50	48.86 ± 4.59
Thumb flexors	Flexor pollicis longus	0–20	1–2	17.09 ± 4.54	17.50 ± 5.50
	Flexor pollicis brevis	0–10	1–2	10.24 ± 1.56	10.00 ± 0.00
	Adductor pollicis	0–10	1–2	10.00 ± 0.00	10.00 ± 0.00