ANESTHESIOLOGY

Botulinum Toxin Type A for Lumbar Sympathetic Ganglion Block in Complex Regional Pain Syndrome: A Randomized Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Complex regional pain syndrome is a poorly understood condition sometimes responsive to sympathetic blockade
- Botulinum toxin blocks cholinergic transmission and sympathetic outflow if administered near sympathetic ganglia

What This Article Tells Us That Is New

- Lumbar sympathetic ganglion block with botulinum toxin type A caused a greater increase in temperature in the blocked limb at 1 month than did levobupivacaine
- Botulinum toxin administration also provided better analgesia at 1 and 3 months after injection than did levobupivacaine, while no adverse events were observed

ABSTRACT

Background: The present study was designed to test the hypothesis that botulinum toxin would prolong the duration of a lumbar sympathetic block measured through a sustained increase in skin temperature. The authors performed a randomized, double-blind, controlled trial to investigate the clinical outcome of botulinum toxin type A for lumbar sympathetic ganglion block in patients with complex regional pain syndrome.

Methods: Lumbar sympathetic ganglion block was conducted in patients with lower-extremity complex regional pain syndrome using 75 IU of botulinum toxin type A (botulinum toxin group) and local anesthetic (control group). The primary outcome was the change in the relative temperature difference on the blocked sole compared with the contralateral sole at 1 postoperative month. The secondary outcomes were the 3-month changes in relative temperature differences, as well as the pain intensity changes.

Results: A total of 48 participants (N = 24/group) were randomly assigned. The change in relative temperature increase was higher in the botulinum toxin group than in the control group (1.0°C ± 1.3 *vs.* 0.1°C ± 0.8, respectively; difference: 0.9°C [95% CI, 0.3 to 1.5]; $P = 0.006$), which was maintained at 3 months (1.1°C ± 0.8 *vs.* –0.2°C ± 1.2, respectively; $P = 0.009$). Moreover, pain intensity was greatly reduced in the botulinum toxin group compared with the control group at 1 month (–2.2 ± 1.0 *vs.* –1.0 ± 1.6, respectively; $P = 0.003$) and 3 months (–2.0 ± 1.0 *vs.* –0.6 ± 1.6, respectively; $P = 0.003$). There were no severe adverse events pertinent to botulinum toxin injection.

Conclusions: In patients with complex regional pain syndrome, lumbar sympathetic ganglion block using botulinum toxin type A increased the temperature of the affected foot for 3 months and also reduced the pain.

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Complex regional pain syndrome is a chronic pain disorder characterized by sensory, vasomotor, sudomotor/edema, and/or motor/trophic symptoms.[1] Although the pathophysiology of this unique pain syndrome remains unclear, it could involve an erroneous coupling between peripheral efferent sympathetic and afferent sensory neurons, which causes sympathetic overflow.[1,2] Sympathetic blocks are effective in the management of complex regional pain syndrome[3,4]; however, pivotal studies have hardly reported its effect in clinical practice.

Lumbar sympathetic ganglion block is a widely used treatment for patients with complex regional pain syndrome in their lower extremities.[3,5] It uses a local anesthetic exerting a temporary blocking effect in patients with chronic refractory complex regional pain syndrome. To achieve prolonged pain relief, neurodestructive procedures, including radiofrequency thermocoagulation or chemical neurolysis, can be subsequently considered.[3,6] However, the technical uncertainty while stimulating the lumbar sympathetic ganglion during radiofrequency thermocoagulation could be confusing for physicians.[6] Furthermore, neurodestructive procedures result in potential morbidities, such as genitofemoral neuralgia[7–9] and postsympathectomy neuralgia.[10]

In addition to its cosmetic uses, botulinum toxin is an emerging treatment option for numerous pain conditions.[11] It results in muscle tone relaxation and pain reduction

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in certain headache types[11–13] by inhibiting exocytosis of acetylcholine and other mediators within the neuromuscular synapse.[11] It also improved certain neuropathic pain attributed to protecting the peripheral and central sensitization.[14,15] Further, small pilot and retrospective studies have reported prolonged pain relief without severe adverse events in patients with complex regional pain syndrome[16–18] after botulinum toxin injection onto the lumbar sympathetic ganglia. Because presynaptic fibers of the sympathetic ganglia are cholinergic, these positive outcomes of the botulinum toxin could be attributed to its prolonged blocking effect on the lumbar sympathetic ganglia.[16] In a rabbit study, botulinum toxin blocked the superior cervical sympathetic ganglion for 1 month or longer without pathologic cellular changes.[19] However, clinical reports have described prolonged botulinum toxin effects based on self-reported pain intensity rather than its sympathetic blocking effects.[14,16–18] It remains unclear whether the sympathetic blocking effect, including increased temperature or blood flow, is prolonged after botulinum toxin injection accompanying pain relief in clinical practice.

Further, there is low-level evidence regarding the use of botulinum toxin for sympathetic block in the management of complex regional pain syndrome. In this study, we hypothesized that the injection of botulinum toxin type A would prolong the sympathetic blocking effect when compared to local anesthetic for lumbar sympathetic ganglion block. Therefore, we aimed to assess the clinical effect of botulinum toxin type A on the lumbar sympathetic ganglia for maintaining temperature increase and pain reduction in patients with complex regional pain syndrome in their lower extremity.

Methods and Methods

Study Design and Participants

This investigator-initiated, randomized, double-blind, controlled, parallel-group clinical trial was approved by the institutional review board of the Seoul National University Hospital (Seoul, Republic of Korea) and registered in the Clinical Research Information Service (https://cris.nih.go.kr/cris/index.jsp; Identifier: KCT0003569; principal investigator: J.Y. Moon; released on February 28, 2019). All the methods and results have been reported based on the Consolidated Standards of Reporting Trials guidelines.[20] We included patients diagnosed with complex regional pain syndrome at a single pain management center between April 2019 and November 2020. Written informed consent was obtained from each participant before enrollment. The study complied with the Declaration of Helsinki.

The inclusion criteria were as follows: (1) patients aged 18 to 85 yr who were diagnosed with unilateral lower-extremity complex regional pain syndrome based on the Budapest clinical criteria,[1] a revised version initially proposed by the International Association for the Study of Pain (Washington, D.C.); (2) an average 11-pointed numerical rating scale pain score of 4 or higher within the previous week from the screening day; (3) complex regional pain syndrome-attributable pain duration of at least 6 months despite conventional pain management; (4) confirmed temperature increase (greater than 1.5°C in 20 min) in the ipsilateral foot during the screening lumbar sympathetic ganglion block, which was conducted on the same day of the randomization; and (5) ability to comprehend the questionnaires. The exclusion criteria were as follows: (1) history of peripheral vascular diseases (*e.g.*, Burger's disease or thromboangitis obliterans) or neuromuscular junction disorders (*e.g.*, myasthenia); (2) having undergone neurodestructive procedures using radiofrequency thermocoagulation, chemicals, or botulinum toxin injection onto the lumbar sympathetic ganglia; (3) having received botulinum toxin injections for cosmetic or other medical purposes within 6 months; (4) ongoing treatment with aminoglycosides, curare, or topical therapy (cream or patch) on their foot; (5) having significant anatomic variations on their lumbar spines; (6) allergic to local anesthetics or botulinum toxin; (7) females who were pregnant, breastfeeding, or not using a reliable contraception method; (8) having coagulation disorders or any infectious condition; and (9) participating in another clinical trial within 30 days of registration.

Concomitant analgesic medications were maintained if they had been used at stable doses for at least 4 weeks before enrollment. However, new analgesics, vasoactive drugs, or interventions, including intravenous prostaglandin or lidocaine infusion, were not permitted throughout the study period. Acetaminophen was provided as a rescue medication, as appropriate. The initial analgesic dosage could be altered after obtaining the primary outcome at the 1-month follow-up visit. The corresponding author (J.Y. Moon) evaluated eligibility, obtained informed consent, and enrolled the participants before the screening lumbar sympathetic ganglion block.

Randomization and Masking

Randomization was conducted in an operating room after the screening lumbar sympathetic ganglion block on the same day. After obtaining consent in a preoperative holding room, the patient was transferred to the operating room. Initially, screening lumbar sympathetic ganglion blocks were performed at the L2 and L3 vertebral levels using 1.5 ml of 0.5% levobupivacaine. The patient was considered eligible if there was a temperature increase (greater than 1.5°C in 20 min) in the ipsilateral foot and randomly assigned (1:1) into the control group or the botulinum toxin group. A pharmacist who was not involved in the study or data analysis prepared a concealed allocation schedule for random treatment assignments based on computer-generated random numbers. According to the group allocation code, the pharmacist aseptically formulated the syringe with active treatment and control solutions, which were

transparent and indistinguishable. All the patients and investigators were blinded to treatment assignment.

Procedures

To minimize procedural variations, a pain physician (Y.Yoo) with more than 5 years of experience in lumbar sympathetic ganglion block performed all the procedures. Before randomization, screening lumbar sympathetic ganglion blocks were performed in the operating room with fluoroscopic guidance. Here, the patients were prone positioned on a table with a pillow underneath the abdomen to alleviate lumbar lordosis; further, temperature probes were tightly attached to both soles using transparent patches. The patient subsequently received an intravenous infusion of lactated Ringer's solution and was monitored through pulse oximetry, electrocardiogram, and blood pressure measurements. After sterilizing the skin around the puncture sites, the body was covered using a sterile surgical drape for temperature stabilization. Subsequently, a 21-gauge 15-cm Chiba needle (Cook Inc., USA) was advanced at the L2 vertebral level after skin infiltration with 1% lidocaine under fluoroscopy-guided oblique projection. When the needle reached the target site (anterolateral border of the L2 vertebral body), 1 to 2 ml of the contrast agent was injected to confirm adequate spread around the target. A similar process was conducted at the L3 vertebral level; subsequently, 1.5 ml of 0.5% levobupivacaine was injected into both needles. After identifying a temperature increase in the ipsilateral sole within 20 min, treatment or control solution was injected into the Chiba needles, as appropriate. Specifically, 8 ml of 0.25% levobupivacaine and botulinum toxin type A 75 IU (Nabota, Daewoong, South Korea) mixed with 8 ml of nonpreserved saline solution (both 4 ml into each Chiba needle) were injected in the patients in the control and botulinum toxin groups, respectively.

Outcomes

The primary outcome was the change in the relative temperature difference on the affected sole compared with the unaffected sole at 1 postprocedure month (Δt at 1 month, °C), as follows: Δt (°C) = (between-sole temperature difference at baseline) − (between-sole temperature difference at 1 month).[3] Temperatures were measured using digital infrared thermography (IRIS 9000, MEDICORE Inc., South Korea) by a research nurse blinded to the group allocation. We measured the temperature at five or more sites in each foot as the region of interest and calculated the average temperature difference (Supplemental Digital Content 1, http://links.lww.com/ALN/C756). Using the same digital infrared thermography, the temperature was measured before the procedure, immediately after the procedure, after 1 month, and after 3 months. All the measurements were conducted in the same room with a temperature and humidity of approximately 23°C and 50%, respectively, without direct sunlight or radiant heat sources. During the measurements, the patients' feet were clean, dry, and not blocked. Before all the measurements, the patient stayed in the testing room for 30 min, except the postprocedure temperature, which was measured immediately after the procedure.

The secondary outcomes included changes in the between-sole temperature asymmetries from the baseline to the 3-month follow-up visits, using the aforementioned formula. Mean pain intensity attributable to complex regional pain syndrome over the previous 24 h was assessed using an 11-point numerical rating scale pain score (0 = no pain, 10 = maximum pain imaginable)[21] at baseline, 1 month, and 3 months by asking "what was your average pain score over the past 24 h?" The peak systolic velocity (cm/s) of the ipsilateral popliteal artery was measured in the central portion of the popliteal fossa before the procedure, as well as immediately, 1 month, and 3 months after the procedure. One medical doctor (J. Kim) performed the measurements of peak systolic velocities using the pulsed-wave spectral Doppler ultrasound mode of an ultrasound device (Philips Ultrasound, USA) with a 5- to 12-MHz linear transducer. The patients were assessed using the 6-item modified cold intolerance symptom severity questionnaire at baseline, 1 month, and 3 months.[22] We excluded the first item, which assesses the symptom type (pain, numbness, stiffness, aching, swelling, and skin color change), from the scoring, and multiple symptoms could be answered concurrently. The remaining items measured the symptom frequency, occurrence time, behavior change for symptom relief, symptom aggravation degree when performing certain activities, and the effect of symptoms on their daily lives. Their scores were classified as mild (4 to 25), moderate (26 to 50), severe (51 to 75), and very severe (76 to 100).[22] The patient's global impression of change after the procedure was obtained using a 5-point Likert scale at 1 month and 3 months; moreover, we calculated the proportion of "very much improved" (score 5) and "much improved" (score 4). We collected changes in analgesic dosages after the 1-month visit.

Demographic characteristics, comorbidity (hypertension, diabetes mellitus, hyperlipidemia, and neuropsychiatric disorders, including depression and anxiety), smoking status, previous surgical history on the affected foot, and pain characteristics attributable to complex regional pain syndrome (types, onset, etiology, side, relevant litigation status, and current medications) were collected at baseline. Considering the safety, possible procedure-related complications (*e.g.*, lower-leg motor weakness assessed by the manual muscle testing scored from 0 for normal to 3 for complete loss of strength, sensory change, and genitofemoral neuralgia) were recorded throughout the study period.

Statistical Analysis

The sample size was calculated based on pilot data obtained from 10 patients with a 1.5°C (SD 1.2) temperature increase

in the ipsilateral foot at 1 month after lumbar sympathetic ganglion block with botulinum toxin type A 100 IU. We hypothesized an average temperature increase of 1.3°C (SD 1.2) and 0°C (SD 1.2) at 1 month in the botulinum toxin and control groups, respectively. We calculated that 19 patients/group were required to yield a 90% statistical power for detecting differences in a two-sample two-tailed *t* test with a type I error of 0.05. Considering a 20% dropout rate, we included 48 participants (24 in each group).

The clinical effect and safety outcomes were analyzed for all the participants. Demographic and baseline clinical characteristics were analyzed based on the intent-to-treat population, which comprised all patients who received any study treatment. Fisher's exact test or *t* test was used, as appropriate. Analyses for effectiveness were performed on both the intent-to-treat and per-protocol population for the primary endpoint. Only the intent-to-treat population was analyzed for secondary endpoints.

For the primary outcome, an independent *t* test with a last-observation-carried-forward imputation was employed (Δt at 1 month, °C). For the secondary outcomes, we investigate the changes in the relative between-sole temperature differences, changes in the numerical rating scale pain scores from the baseline, and cold intolerance symptom severity scores, and the peak systolic velocity (cm/s) using the linear mixed model analyses with the group, time, and interaction between group and time as fixed effects and subject as a random effect to account for multiple measurements per subject. They are presented as the means and standard error. The Bonferroni adjustment procedure was employed for follow-up analysis to control for type I errors for multiple measurements in terms of temperatures, pain scores, and cold intolerance questionnaire with an adjusted *P* value of less than 0.025 as significant. The frequencies (%) of symptoms in the cold intolerance symptom severity questionnaire and the patient's global impression of change scores were assessed using a generalized linear mixed model with the group, time, and interaction between group and time as fixed effects and subject as a random effect. In the *post hoc* subanalysis, we used Spearman's Rho to explore correlations among clinical variables and measurements, including temperature asymmetries, numerical rating scale pain scores, cold intolerance symptom severity scores, and blood flow velocity.

Categorical, normally distributed, nonnormally distributed variables were presented as proportions (%), means ± SD (95% CI for the primary endpoint), and medians with interquartile ranges, respectively. Data normality was assessed using the Shapiro–Wilk test. Categorical and continuous variables were analyzed using the chi-square/Fisher's exact test and independent *t* test, respectively. Statistical significance was set a two-sided *P* value of <0.05. Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Austria) and SPSS version 22.0 (IBM Corp., USA).

Role of the Funding Source

The study funders provided botulinum toxin and study-related costs; however, they had no role in study design, data collection, data analysis, data interpretation, or report writing. All the authors had full access to the study data and agreed to the submission for publication.

Results

Between April 2019 and November 2020, we screened 64 participants with lower-extremity complex regional pain syndrome (fig. 1); among them, we excluded 16 participants owing to declining (N = 2), undergoing botulinum toxin injection for cosmetic purposes within 6 months (N = 2), previous lumbar sympathetic ganglia neurodestructive procedures (N = 3), and failure to obtain a temperature increase from the screening lumbar sympathetic ganglion block (N = 9). Consequently, we randomly assigned 48 participants (N = 24/group). Enrollment ceased when the target sample size was obtained. After randomization, 1 patient in the botulinum toxin group withdrew consent before solution administration in the operating room; therefore, 24 in the control group and 23 patients in the botulinum toxin group were included in the analyses. All the participants visited at 1 month; however, at 3 months, 2 patients in the control group and 1 patient in the botulinum toxin group dropped out; therefore, 22 patients in each group finally remained, and 3 individuals had incomplete data at the 3-month follow-up visit.

There was no between-group difference in the demographics and pain characteristics (table 1). Both groups reported mean baseline pain scores higher than 7 of 10, which indicated severe pain intensity. Both groups showed a higher frequency of complex regional pain syndrome type I than type II. More than half (N = 27, 57%) of the patients had comorbid neuropsychiatric disorders, including depression and anxiety. There was no between-group difference in the temperature asymmetries in both soles, which was relatively lower in the affected sole than in the nonaffected sole (–0.6°C ± 1.1 and –0.9°C ± 0.9 in the control and botulinum toxin groups, respectively; *P* = 0.273). Although there were no significant between-group differences in the baseline cold intolerance symptom severity scores (*P* = 0.091), they reached "very severe" (77.6 ± 9.9) in the botulinum toxin group but "severe" (70.3 ± 17.7) in the control group. Overall, pain was the most frequent symptom in the cold intolerance symptom severity questionnaire (N = 46 of 47, 98%), followed by aching (N = 32 of 47, 68.1%), stiffness (N = 28 of 47, 60%), color change (N = 22 of 47, 47%), numbness (N = 20 of 47, 43%), and swelling (N = 16 of 47, 34%), without between-group differences at baseline. There was no between-group difference in the initial peak systolic velocity at the popliteal artery of the affected leg (*P* = 0.783). Both groups showed increased postprocedural temperatures and peak systolic velocity

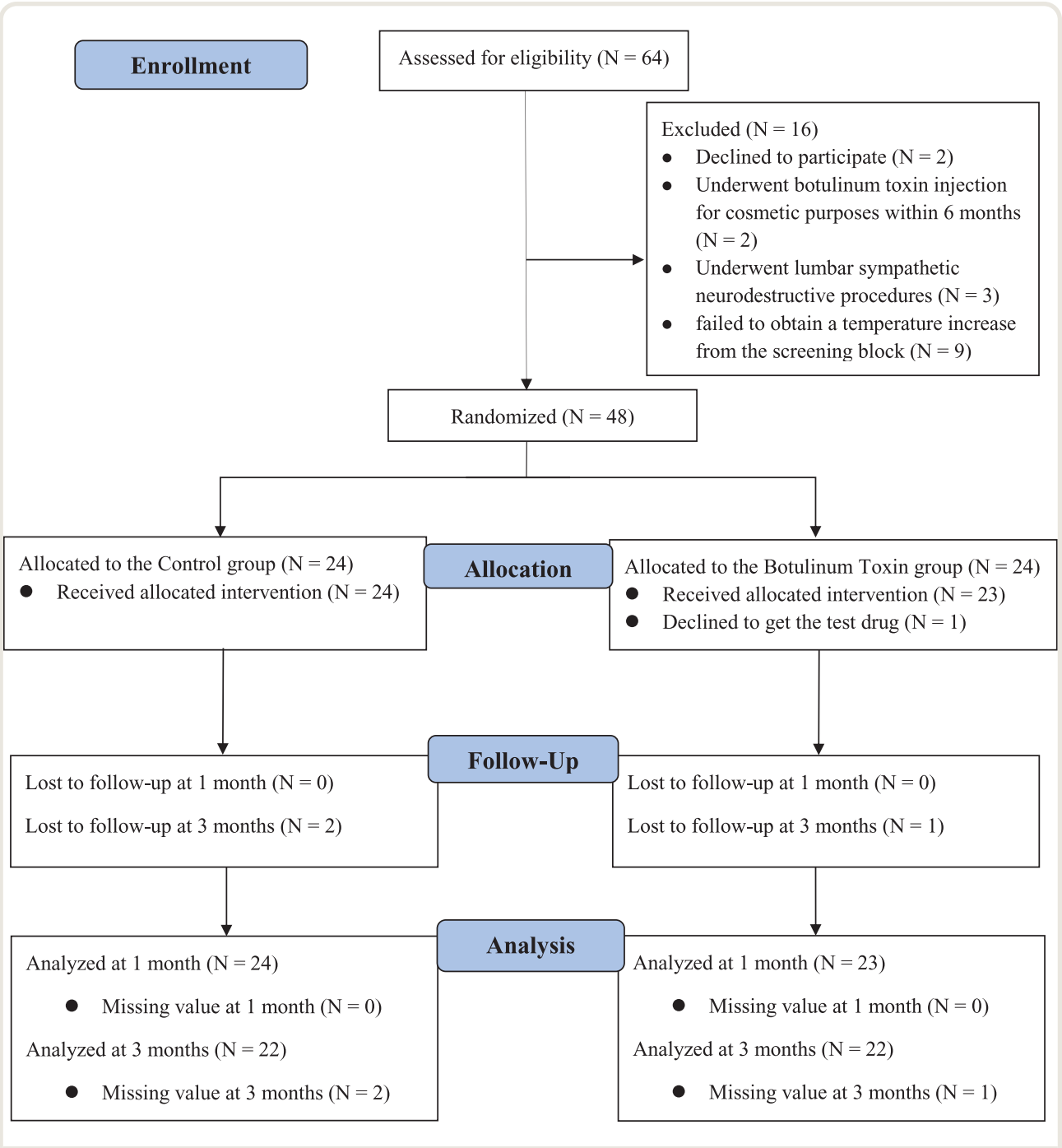

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

on the affected foot without significant between-group differences in the temperature increase from the baseline (P = 0.272); however, the control group showed a more increased peak systolic velocity (P = 0.049) immediately.

Considering the primary outcome, both groups showed a temperature increase in the blocked foot compared with the contralateral foot at the 1-month follow-up visit (fig. 2). However, the botulinum toxin group showed a greater increase (1.0°C ± 1.3; 95% CI, 0.4 to 1.5) from the baseline temperature asymmetry than the control group (0.1°C ± 0.8; 95% CI, –0.3 to 0.4), with a significant between-group difference (0.9°C; 95% CI, 0.3 to 1.5; P = 0.006). There was no missing data for the 1-month time point. The increased temperature in the affected sole remained in the botulinum toxin group at 3 months, with a relative change of 1.1°C ± 0.8 from the baseline asymmetry. Contrastingly, the control

Table 1. Demographics and Baseline Clinical Characteristics

	Control Group (N = 24)	Botulinum Toxin Group (N = 23)
Age, yr	43.7 ± 12.3	44.8 ± 12.2
Male/female	12 (50)/12 (50)	12 (52)/11 (48)
Body mass index, kg/cm^2	25.7 ± 4.6	24.6 ± 3.7
Hypertension	2 (8)	4 (17)
Diabetes mellitus	1 (4)	2 (9)
Dyslipidemia	4 (17)	5 (22)
Smoking	7 (29)	5 (22)
Previous surgical history on the affected foot	5 (21)	5 (22)
Neuropsychiatric disease*	12 (50)	15 (65)
Litigation	11 (46)	8 (35)
Diagnosis		
Complex regional pain syndrome type I	22 (92)	20 (87)
Complex regional pain syndrome type II	2 (8)	3 (13)
Pain duration, months	25.2 ± 10.7	26.7 ± 10.3
Laterality, left/right	13 (54)/11 (46)	10 (44)/13 (56)
Temperature on the affected sole, °C	31.0 ± 2.7	31.0 ± 2.7
Temperature asymmetry on the blocked sole compared to the contralateral sole, °C	–0.6 ± 1.1	–0.9 ± 0.9
Eleven-point numerical rating scale pain score (0 to 10)	7.2 ± 1.5	7.6 ± 1.4
Concomitant medications		
Opioids	14 (58)	16 (70)
Calcium channel blocker	16 (67)	12 (52)
Serotonin–norepinephrine reuptake inhibitors	5 (21)	6 (26)
Tricyclic antidepressants	5 (21)	4 (17)
Nonsteroidal anti-inflammatory drugs	5 (21)	4 (17)
Others†	5 (21)	5 (22)
Cold Intolerance Symptom Severity score (0 to 100)	70.3 ± 17.7	77.6 ± 9.9
Cold Intolerance Symptom Severity symptoms		
Pain	23 (96)	23 (100)
Numbness	7 (29)	13 (57)
Stiffness	15 (63)	13 (57)
Aching	14 (58)	18 (78)
Swelling	7 (29)	9 (39)
Color change	8 (33)	14 (61)
Peak systolic velocity on the popliteal artery, cm/s	26.6 ± 6.8	27.1 ± 4.4
Postprocedure measurement		
Numerical rating scale pain score (0 – 10)	4.0 ± 2.8	3.9 ± 2.0
Temperature increase from baseline, °C	7.5 ± 2.3	6.9 ± 3.2
Peak systolic velocity increase from baseline, cm/s‡	14.4 ± 7.1	8.7 ± 7.6

The data are presented as proportions (%) for categorical variables or means ± SD for normally distributed variables.

*Neuropsychiatric disorder includes depression and anxiety. †Others include oral aspirin, limaprost, beraprost, clopidogrel, cilostazol, and sarpogrelate. ‡$P < 0.05$.

group showed no temperature increase (–0.2°C ± 1.2) at 3 months. The group × time interaction showed statistical significance ($P < 0.001$; table 2). There were significant between-group differences in the changes in the relative temperature asymmetries at each visit ($P = 0.020$ and $P = 0.009$ at 1 and 3 months, respectively).

Both groups showed a decrease in the 3-month 11-pointed numerical rating scale pain scores (table 2; fig. 3). However, the botulinum toxin group showed significantly larger changes in the pain score than the control group ($P = 0.002$ for group × time) at 1 month (–2.1 ± 1.0 *vs.* –1.0 ± 1.6, respectively; $P = 0.004$) and 3 months (–2.0 ± 1.0 *vs.* –0.6 ± 1.6, respectively; $P = 0.003$). At 1 month, the cold intolerance symptom severity scores decreased in both groups without a between-group difference ($P = 0.038$; table 2; fig. 4); however, at 3 months, it increased and continued decreasing in the control and botulinum toxin groups, respectively, with a significant between-group difference ($P < 0.001$). Considering the peak systolic velocity at the affected popliteal artery, there was a post-procedural increase; however, it returned to baseline levels at 1 and 3 months without between-group differences ($P = 0.795$ and $P = 0.919$, respectively; table 2).

Considering symptoms in the cold intolerance symptom severity questionnaire, unlike the control group, the botulinum toxin group showed reduced frequency in all symptoms except for "pain" within 3 months (fig. 5). There were significant between-group differences of "aching" and "numbness" in group × time ($P = 0.002$ and $P = 0.041$, respectively). In *post hoc* analyses, those changes were statistically significant at the 3-month follow-up visit ($P = 0.014$ for "aching" and $P = 0.015$ for "numbness"). In the patient's

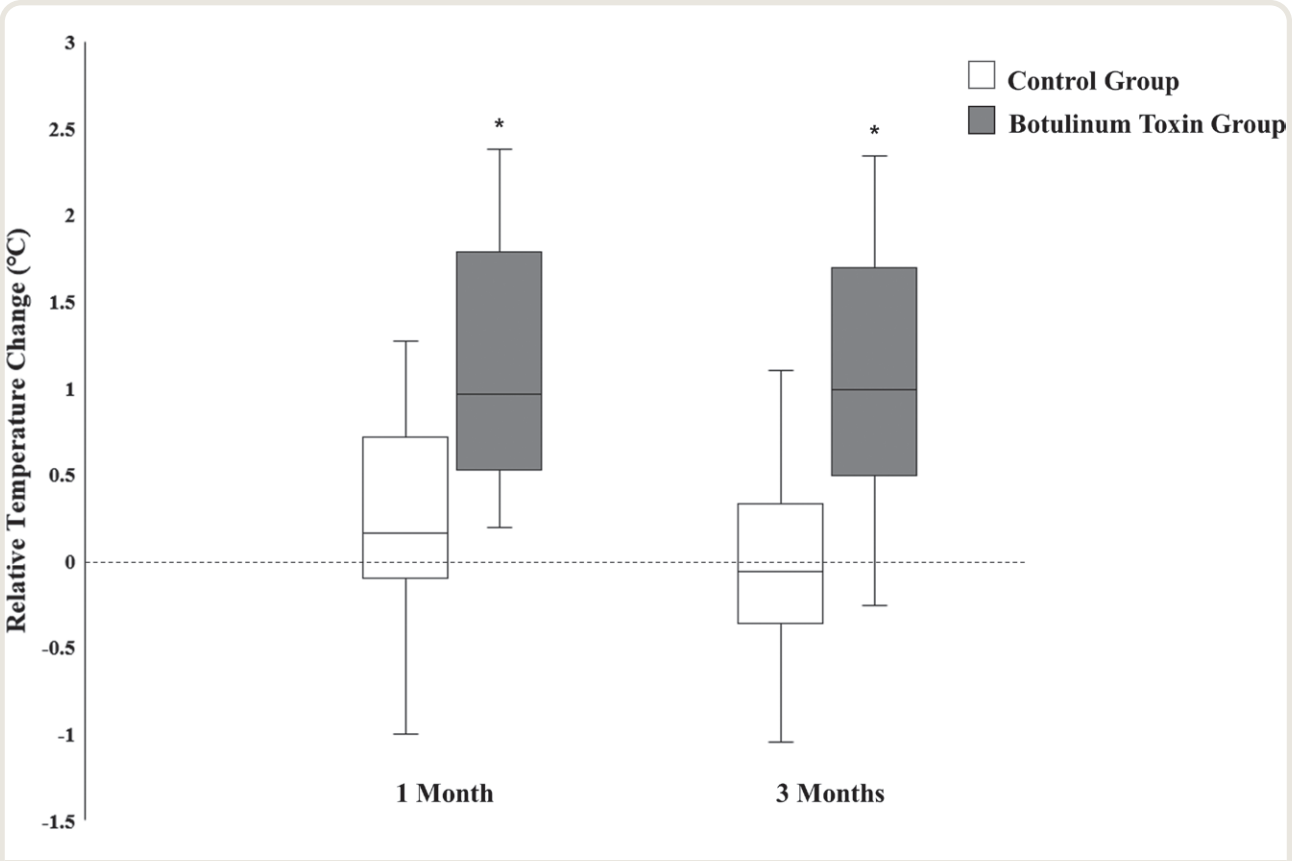

Fig. 2. Changes of relative temperature asymmetries from baseline on the affected foot. Δt (°C) = [between-sole temperature difference at baseline] – [between-sole temperature difference at 1 month]. The *asterisks* indicate significant between-group differences in the changes of the relative temperature asymmetries at 1 month ($P = 0.020$) and 3 months ($P = 0.009$).

global impression change, there were more frequent "very much improved" or "much improved" responses in the botulinum toxin group than in the control group (78% *vs.* 54% at 1 month and 70% *vs.* 46% at 3 months, respectively). However, there were no significant between-group differences at any time points ($P = 0.081$ at 1 month and $P = 0.100$ at 3 months).

Considering correlations among clinical measurements (Supplemental Digital Content 2, http://links.lww.com/ALN/C757), there were no correlations between the temperature increase and a reduction of the numerical rating scale pain score at any time points ($r = –0.16$, $P = 0.302$ at 1 month; $r = –0.21$, $P = 0.194$ at 3 months). However, there were positive correlations between the initial and postprocedural immediate peak systolic velocities ($r = 0.64$, $P < 0.001$), as well as between the initial peak systolic velocity and decrease in the 1-month cold intolerance symptom severity score ($r = 0.56$, $P < 0.001$), which suggested that a patient with a higher baseline peak systolic velocity presented a greater improvement in cold tolerance after the lumbar sympathetic ganglia procedure.

Considering the safety, nine patients reported mild postprocedure dizziness (six patients in the control and three patients in the botulinum toxin group; $P = 0.461$); however, it was transient and disappeared before discharge. No patient presented genitofemoral neuralgia, new postprocedural neuralgia, or muscle weakness. Three patients complained of back pain around the injection site at 1 month; however, it was tolerable without additive analgesics and improved within 3 months, with two patients requiring acetaminophen. Considering the changes in oral medications, four patients (three in the botulinum toxin group and one in the control group) and three patients (one in the botulinum toxin group and two in the control group) increased and decreased their analgesic dosages after 1 month, respectively.

Discussion

We found that botulinum toxin type A injection onto the lumbar sympathetic ganglia increased the affected foot temperature, which remained for 3 months. Contrastingly, local anesthetic alone did not cause prolonged temperature increases with significant between-group differences at 1 and 3 months. The pain intensity and cold intolerance, as well as "aching" and "numbness" symptoms, were more improved in the botulinum toxin group than in the control

Table 2. Follow-up Data of Clinical Variables

	Control Group (N = 24)			Botulinum Toxin Group (N = 23)			*P* Value between the Groups*		*P* Value (Group × Time)
	Baseline	1 Month	3 Months	Baseline	1 Month	3 Months	1 Month	3 Months	
Temperature asymmetry on the blocked sole, °C†	–0.6 ± 1.1	–0.4 ± 0.9	–0.9 ± 1.4	–0.9 ± 0.9	0.2 ± 0.9	0.1 ± 0.9	0.020‡	0.009‡	< 0.001
Eleven-pointed numerical rating scale pain score, 0 to 10	7.2 ± 1.5	6.3 ± 2.1	6.6 ± 2.0	7.6 ± 1.4	5.4 ± 1.8	5.6 ± 2.1	0.004‡	0.003‡	0.002
Cold Intolerance Symptom Severity score, 0 to 100	70.3 ± 17.7	68.9 ± 19.0	71.7 ± 19.6	77.6 ± 9.9	71.0 ± 11.9	67.3 ± 13.7	0.038	< 0.001‡	< 0.001
Peak systolic velocity, cm/s§	26.6 ± 6.8	28.5 ± 7.4	26.0 ± 7.1	27.1 ± 4.4	28.9 ± 4.4	27.1 ± 4.9	0.795	0.919	0.972

The data are presented as means ± SD or a proportion (%).

*The comparison of the changes from baseline between the control and botulinum toxin groups. †Relative temperature difference on the affected sole compared to the contralateral sole, by using the following formula: Δt (°C) = [difference of temperatures between both soles] – [difference of temperatures between both soles]. ‡Adjusted $P < 0.025$ was considered to be statistically significant to minimize the chance of a type I error. §Peak systolic velocity was measured at the popliteal artery in the affected leg.

group during the 3-month follow-up period. Popliteal arterial velocity increased postprocedurally in both groups; however, it returned to the initial level at 1 month. Although the botulinum toxin group showed numerous "much" or "very much improved" responses, there was no significant between-group difference in the patient's global impression change at any time point. There were no severe adverse events regarding the botulinum toxin injection or procedures.

Botulinum toxin is preferred for its analgesic properties in various pain conditions. Previous studies on botulinum toxin for blocking sympathetic ganglia have reported a

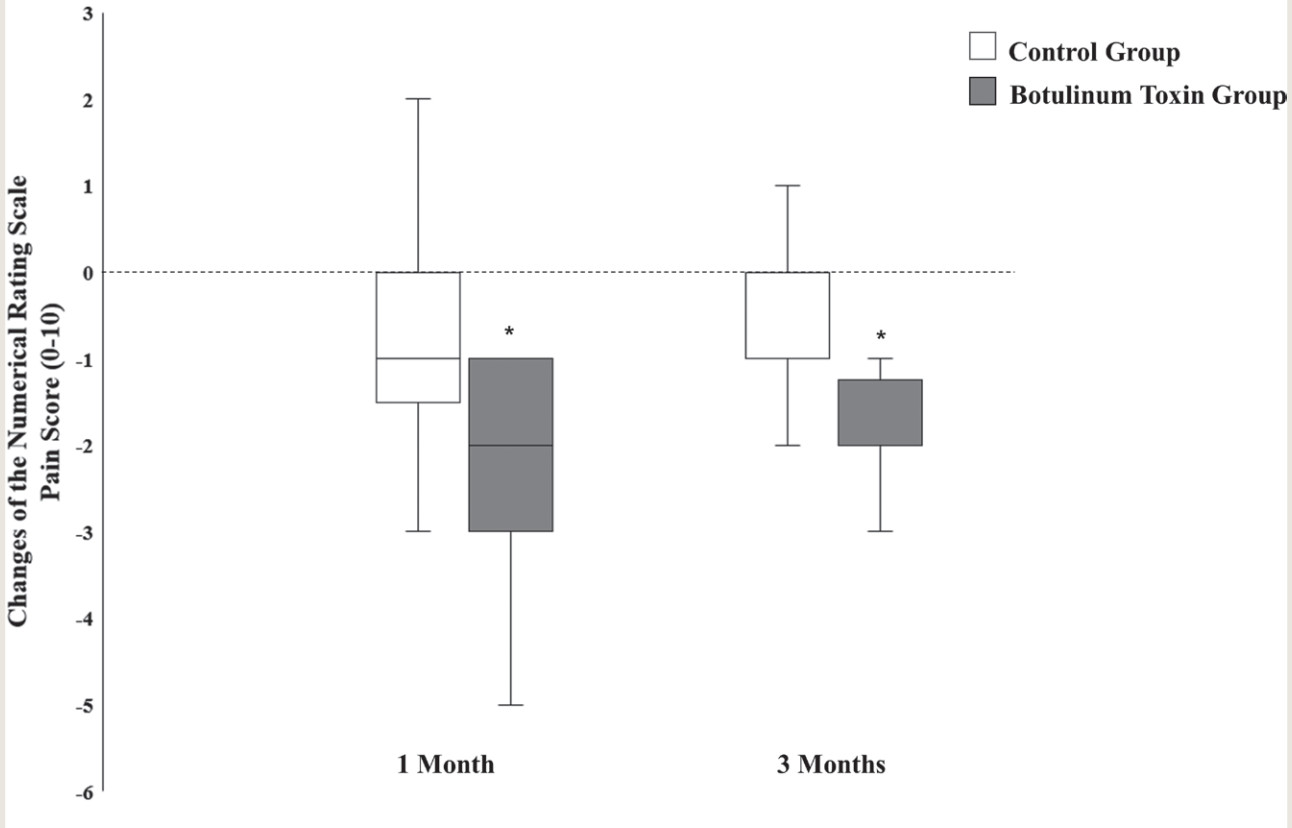

Fig. 3. Changes of the 11-pointed numerical rating scale pain score from baseline. The *asterisks* indicate significant between-group differences in the changes of the 11-pointed numerical rating scale pain score at 1 month ($P = 0.003$) and 3 months ($P = 0.003$).

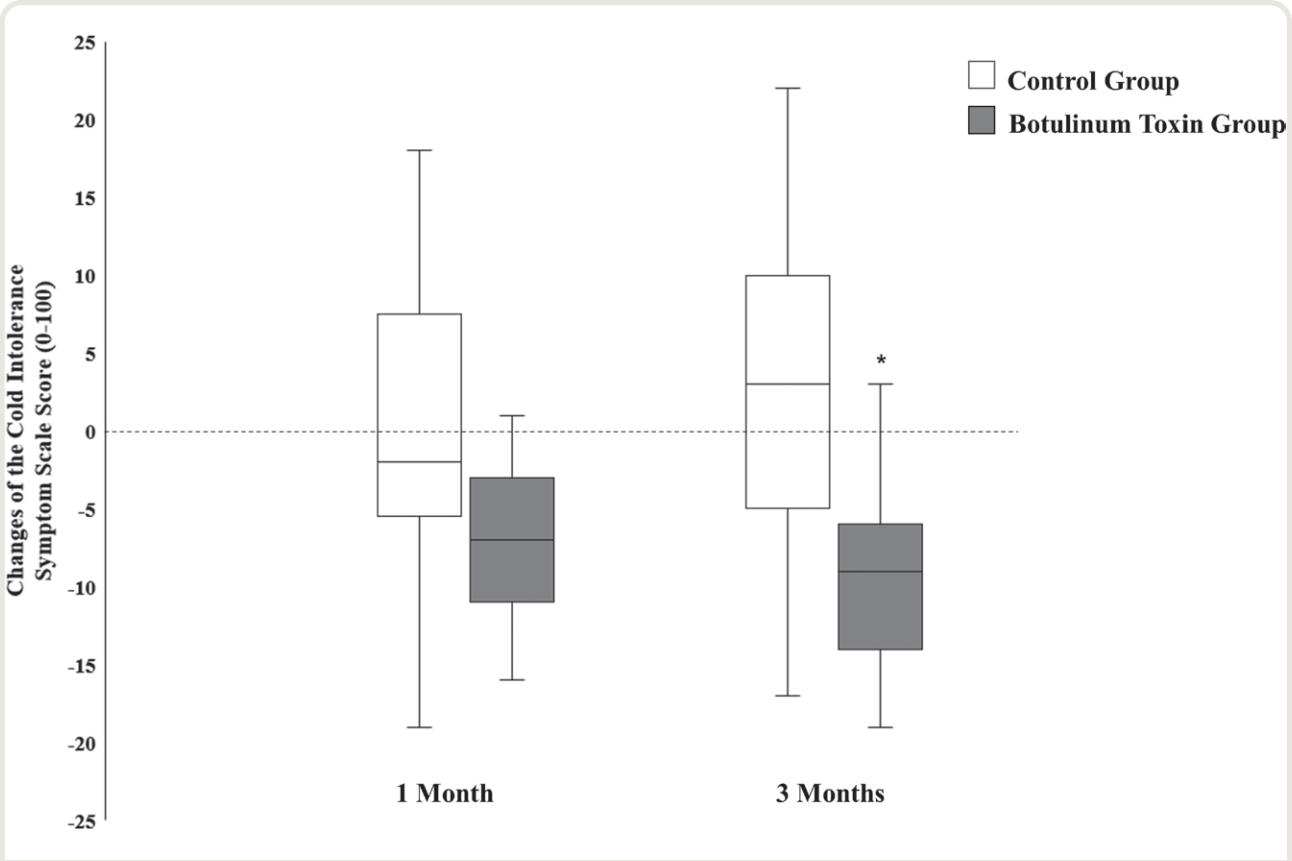

Fig. 4. Changes of the cold intolerance symptom severity score from baseline. The *asterisk* indicates a significant between-group difference in the change of the cold intolerance symptom severity score at 3 months ($P < 0.001$).

prolonged effect on self-reported pain reduction,[16–18] which indirectly presents the botulinum toxin effect on sympathetic ganglia. A rabbit study showed an extended blocking effect of botulinum toxin, including miosis, on the superior cervical sympathetic ganglia without histological changes.[19] Botulinum toxin type A dissolves the synaptosomal-associated protein 25, which is essential for membrane fusion with the synaptic vesicle.[10] Subsequently, it suppresses the exocytosis of acetylcholine and other neurotransmitters in the autonomic cholinergic synapse, neuromuscular junction, and sensory neurons.[11,12] Sympathetic overflow is a possible complex regional pain syndrome pathophysiology that exaggerates peripheral blood circulation through cholinergic, adrenergic, and substance P–related pathways.[1,2,23] This may be ameliorated by botulinum toxin type A injection onto the lumbar sympathetic ganglia, which might enhance peripheral microcirculation with a subsequent temperature increase in the ipsilateral foot.

Although botulinum toxin type A can attenuate various pain types, including headaches, postherpetic neuralgia, trigeminal neuralgia, and complex regional pain syndrome,[11,13–18,24,25] it is only approved for treating chronic migraines.[11] Moreover, scarce randomized, double-blind trials on botulinum toxin exist in pain medicine. This is the first randomized, double-blind study on the clinical effect of botulinum toxin type A to confirm prolonged temperature increase and pain reduction in complex regional pain syndrome, a rare but intractable pain syndrome. Unlike previous studies on botulinum toxin,[16–18] our primary outcome was the temperature increase rather than pain reduction. This is because patients with complex regional pain syndrome do not always respond to lumbar sympathetic ganglia procedures[3,26,27]; rather, most patients present temperature increase after lumbar sympathetic ganglion block.[3] Moreover, to avoid cases of incorrectly performed procedures, we excluded patients without an initial temperature increase during the screening block. Consequently, our results have the reliability to determine the effect of botulinum toxin type A on lumbar sympathetic ganglia in human beings.

Along with the continuous temperature increase, the botulinum toxin injection had a nonnegligible prolonged pain reduction in our study. Because this was a double-blinded study on patients with chronic and highly refractory complex regional pain syndrome, we suggest that small differences in pain reduction between the groups could have clinical value. Although botulinum toxin injection onto the lumbar sympathetic ganglia exerted pain reduction

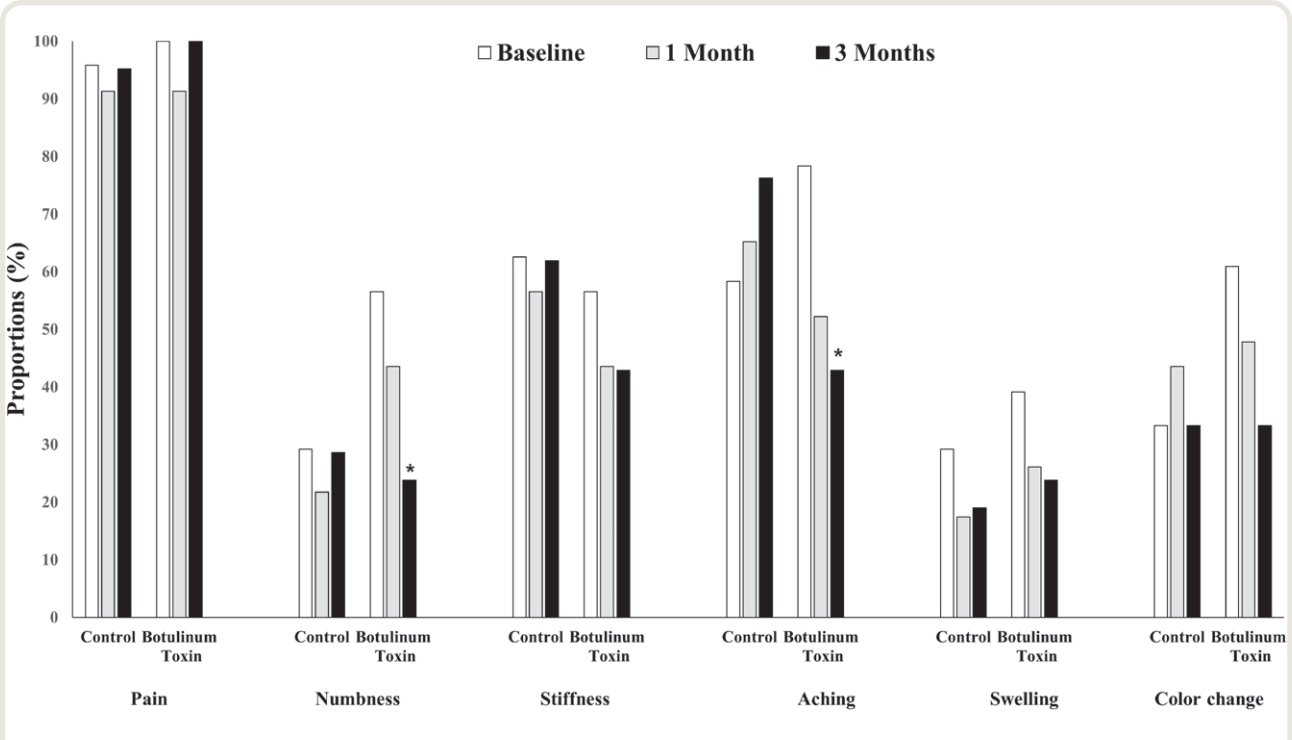

Fig. 5. Frequencies of symptoms in the cold intolerance symptom severity questionnaire. The *asterisks* indicate significant between-group differences in "aching" and "numbness" at the 3-month follow-up visit ($P = 0.014$ for "aching" and $P = 0.015$ for "numbness").

and temperature increase, they were weakly correlated in our results, as shown in the previous studies.[3,25] Further, it improved cold intolerance, according to the cold intolerance symptom severity questionnaire. Therefore, there are multiple domains for assessing responses to botulinum toxin injection onto the lumbar sympathetic ganglia, including pain reduction and cold intolerance, in patients with complex regional pain syndrome. Notably, the initial peak systolic velocity and its postprocedural change, which are indicative of vascular integrity,[28] were strongly correlated with reduced cold intolerance symptom severity scores after botulinum toxin injection; therefore, they could be alternative factors for anticipating the blocking effect.

Contrastingly, the postprocedural increase in popliteal arterial velocity was not maintained after botulinum toxin injection. Sun *et al.*[29] reported that chemical neurolysis, as well as continuous lumbar sympathetic ganglion block with local anesthetic and dexamethasone, enhanced peripheral microcirculation by improving skin temperature, capillary filling time, and blood oxygen saturation. Most likely, measurement of the peak systolic velocity in the popliteal artery could not reflect the capillary microcirculation changes. In addition, Sun *et al.*[29] reported that chemical lumbar sympathetic ganglion neurolysis decreased plasma norepinephrine, serotonin, and substance P levels in patients with diabetes. Further studies are warranted to determine whether botulinum toxin injection onto the lumbar sympathetic ganglia can reduce these vasoactive and pain-modulating mediators.

Attal et al. reported that subcutaneous injection of botulinum toxin type A reduced the peripheral neuropathic pain intensity.[14] Considering the pain characteristics, allodynia and hyperalgesia were improved in their study.[14] Since botulinum toxin injection did not significantly alter substance P and calcitonin gene-related peptide levels in skin punch biopsies, its clinical effect could involve a central mechanism.[14] Further, a small-scale study reported that subcutaneous or intramuscular botulinum toxin injections improved pain intensity in patients with complex regional pain syndrome.[25,26] Our results have added that botulinum toxin type A injection onto the lumbar sympathetic ganglia improved sensory symptoms, including "aching" and "numbness." Future studies should investigate whether simultaneous botulinum toxin injections (subcutaneous + blocking sympathetic ganglia) improve multiple symptom domains in patients with complex regional pain syndrome. Currently, there are various botulinum toxin injection techniques, including transdermal, subcutaneous, perineural, and sympathetic ganglion injections.[11] Therefore, more studies are required to investigate the most effective route and site of its injection for pain reduction.

This study has several limitations. First, this was a single-center small-scale trial. Our patients had highly intractable complex regional pain syndrome, which required visits to a tertiary university-based hospital. This limits the generalizability of our results in widespread pain practice. Second, this was a randomized, double-blinded, comparative study

that did not include a placebo group. Instead, we included patients in the control group, which underwent additive local anesthetic injection after the screening block. This could have resulted in the postprocedural between-group differences of peak systolic velocity in the popliteal artery (more increased in the control group) or frequent dizziness associated with a larger local anesthetic dosage in the control group. Normal saline injection instead of additive local anesthetic might have been a more appropriate placebo. Third, although we reported a prolonged effect of botulinum toxin type A for lumbar sympathetic ganglion block, our follow-up duration was only 3 months. There is a need for studies with a longer follow-up to investigate the more prolonged effect of botulinum toxin type A. Moreover, further studies are warranted to evaluate whether repeated botulinum toxin injections would exert better therapeutic effects for lumbar sympathetic ganglion block, similar to the study by Attal et al..[14] Fourth, we did not examine inflammatory cytokines or pain-related mediators, nor electrophysiologic tests for verifying changes in sensory symptoms. As aforementioned, the patients' self-reported pain score and symptoms allowed subjective assessment of the clinical effect of botulinum toxin type A for lumbar sympathetic ganglion block. Finally, 75 IU botulinum toxin type A may not be sufficient for exerting its full effectiveness for lumbar sympathetic ganglia block. As shown in the animal study, botulinum toxin might have a dose-dependent blocking effect.[18] Compared to previous clinical studies on botulinum toxin,[14,16] 75 IU is a relatively small amount. Considering the lack of clear guidelines on the dose and route, as well as the number of injections, further well-designed randomized double-blinded studies are warranted.

In conclusion, compared with local anesthetic, injections of botulinum toxin type A onto the lumbar sympathetic ganglia increased temperature on the affected foot for 3 months, which was accompanied by pain reduction and cold tolerance improvement. Moreover, we found that it improved "aching" and "numbness." There were no severe adverse events pertinent to botulinum toxin injection. Lumbar sympathetic ganglion block using botulinum toxin type A could be considered a therapeutic alternative for patients with complex regional pain syndrome with prolonged effects.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: jymoon0901@gmail.com. Raw data available at: jymoon0901@gmail.com.

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