ANESTHESIOLOGY

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

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Criteria for CRPS

Table 1. Budapest Criteria for CRPS

All of the following statements must be met:
- The patient has continuing pain that is disproportionate to any inciting event
- The patient has ≥1 sign in ≥2 of the categories below
- The patient reports ≥1 symptom in ≥3 of the symptoms listed below and ≥1 sign in ≥2 signs listed below
- No other diagnosis can better explain the signs and symptoms

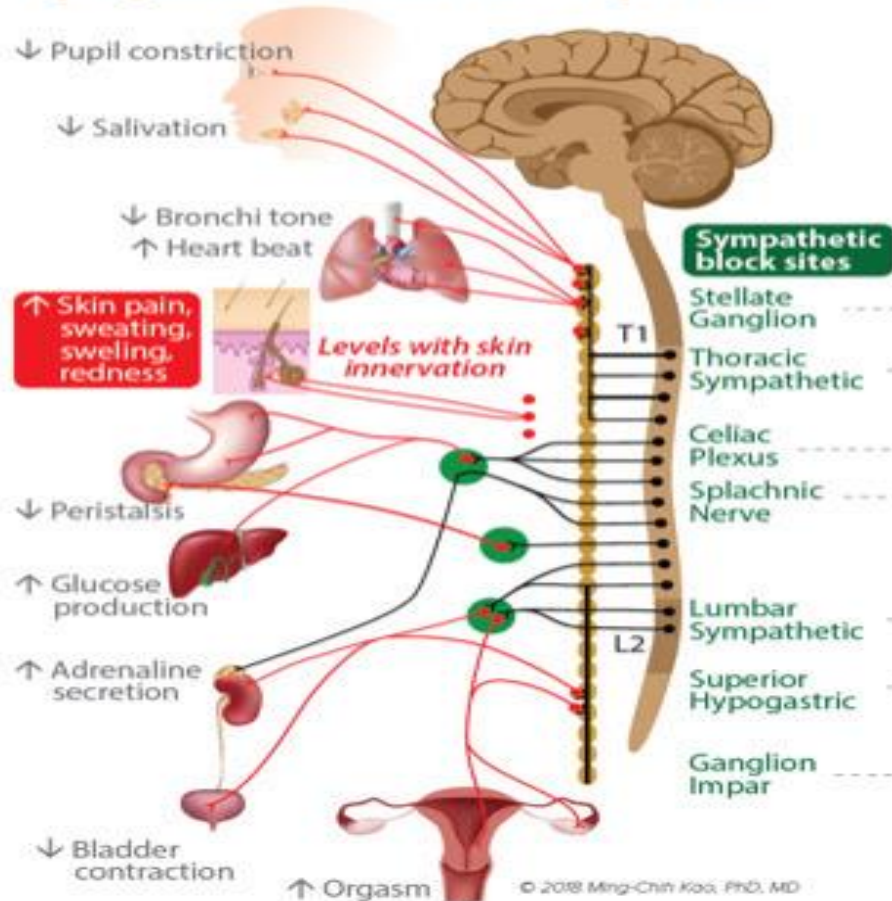| No.	Category	Signs/Symptoms
1	Sensory	**Symptoms** Reported hyperesthesias and/or allodynia **Signs** Evidence of allodynia (to light touch and/or deep somatic pressure and/or joint movement) and/or Hyperalgesia (to pinprick)
2	Vasomotor	**Symptoms** Reported temperature asymmetry and/or skin color changes and/or skin color asymmetry **Signs** Evidence of the above symptoms
3	Sudomotor/edema	**Symptoms** Reports of edema and/or sweating changes and/or sweating asymmetry **Signs** Evidence of the above symptoms
4	Motor/trophic	**Symptoms** Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin) **Signs** Evidence of the above symptoms

Adapted from Harden et al.[3]

Background

- Sympathetic blocks are effective in the management of CRPS

- Lumbar sympathetic ganglion block is widely used treatment for CRPS in their lower extremities

- It uses a LA exerting a temporary blocking effect in chronic refractory CRPS

- Neurodestructive procedure ; radiofrequency, thermocoagulation, chemical neurolysis can be considered

- Potential morbidity : genitofemoral neuralgia, postsympathectomy neuralgia

Sympathetic blocks for pain

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The sympathetic nervous system lets the brain control the organs to maintain body system balance. In many chronic pain conditions, it worsens inflammation & pain; in some, it can even become a source of pain. Sympathetic blocks can help reduce these effects.
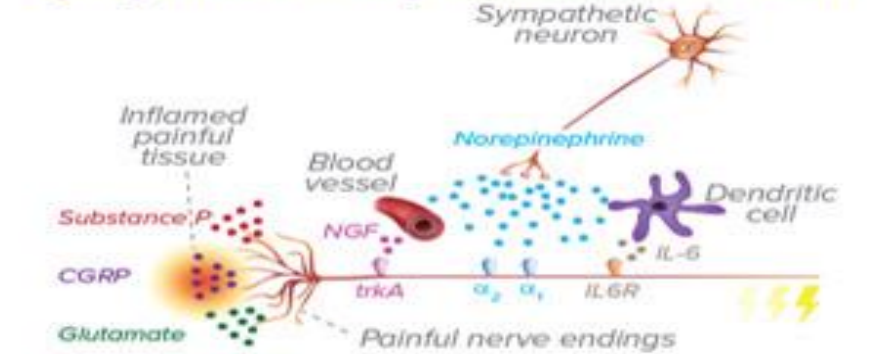
Sympathetic Nervous System

↓ Pupil constriction

↓ Salivation

↓ Bronchi tone
↑ Heart beat

↑ Skin pain, sweating, sweling, redness

Levels with skin innervation

↓ Peristalsis

↑ Glucose production

↑ Adrenaline secretion

↓ Bladder contraction

↑ Orgasm

T1

L2

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Sympathetic block sites

Stellate Ganglion

Thoracic Sympathetic

Celiac Plexus

Splachnic Nerve

Lumbar Sympathetic

Superior Hypogastric

Ganglion Impar

Pain that may respond to sympathetic blocks

Facial, oral, chest, abdominal, pelvic, arm, & leg pain. Most importantly complex regional pain syndrome (CRPS).

Sympathetically Maintained Pain

Sympathetic neuron

Norepinephrine

Inflamed painful tissue

Blood vessel

Dendritic cell

Substance P

NGF

IL-6

CGRP

trkA

α_2 α_1

IL6R

Glutamate

Painful nerve endings

Sympathetic nerves release norepinephrine and:

❶ Sensitize **painful nerve endings**
❷ Widen arteries causing **redness & swelling**
❸ Activate dendritic cells causing **inflammation**

Benefits of sympathetic blocks

❶ Reduction of **pain, redness & swelling**
❷ Temporarily break sympathetic nerve contribution to the **chronic pain cycle** to promote participation in **complete pain care**
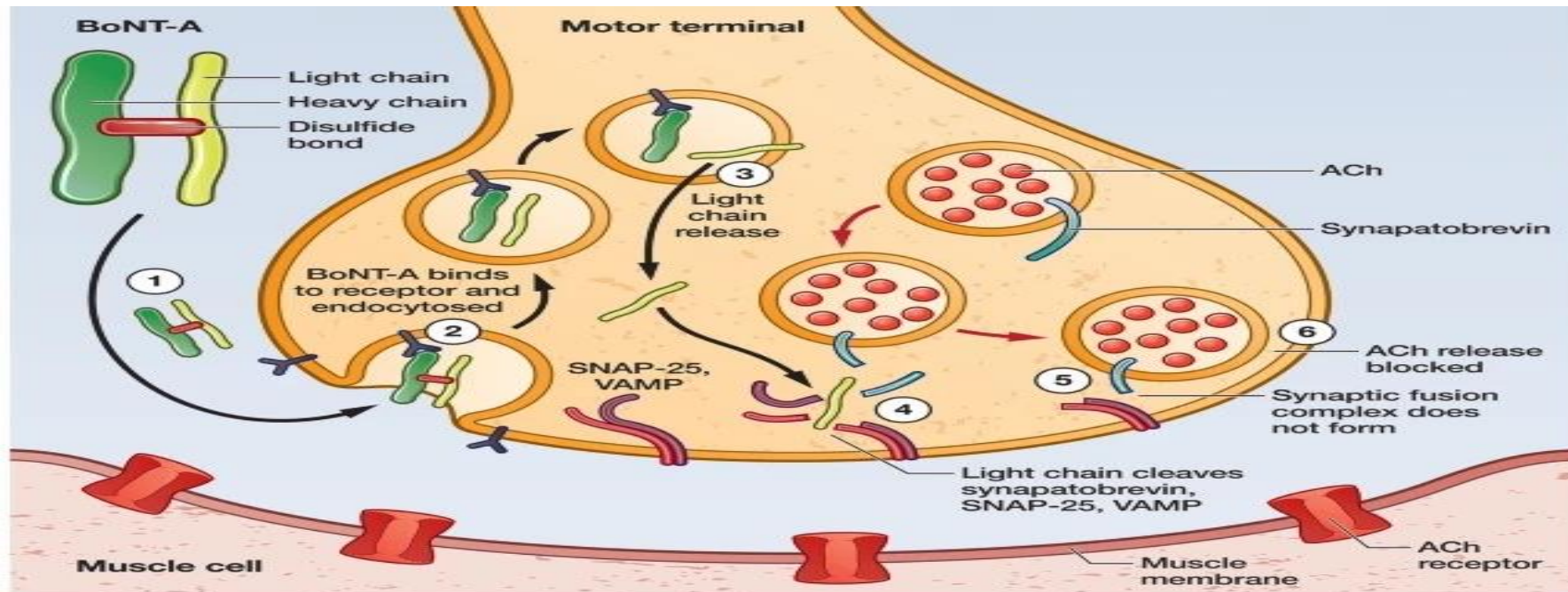
Risks of sympathetic blocks

❶ Possible non-response or **pain exacerbation**
❷ Other risks depend on the location. **Image guidance** for procedure is necessary.
❸ Be aware of **exclusive focus on procedures** without physical therapy & psychology.

Background

- Prolonged pain relief without severe adverse events in CRPS after BoNT-A via LSB

- Superior cervical sympathetic ganglion blocked for 1 month or longer

- Unclear sympathetic blocking effect ; increased temp or blood flow after BoNT-A accompanying pain relief in clinical practice

Botulinum toxin mechanism of action

Hypothesis

Injection of botulinum toxin A would prolong the sympathetic

blocking effect when compared to local anesthetic for lumbar

sympathetic ganglion block

Method

- Investigator-initiated, randomized , double blind , controlled trial

- Approved by institutional review board of the Seoul national university hospital

- Registered in the clinical research formation service ; Feb 28,2019

- All methods and results have been reported based on the consolidated standards of reporting trial guidelines

Randomization and masking

- After obtaining consent , randomization was conducted in OR after screening LSB on same day

- LSB were perform at L2 & L3 using 1.5 ml of 0.5%levobupivacaine

- $\Delta T > 1.5\ ^oC$ in 20 min in the ipsilateral foot

- Randomly assigned (1:1) into control group or botulinum toxin group

- Pharmacist prepared concealed allocation for random treatment assignments base on computer-generated random number

- Group allocation code, pharmacist aseptically formulated the syringe with active treatment or control solution ; transparent & indistinguishable

- Patients and investigators were blinded to treatment assignment

Procedure

Before randomization, screening LSB were perform in OR with fluoroscopic guidance

↓

NIBP,EKG, O saturation monitoring & prone position
RLS intravenous infusion + temperature probes were attached to both sole

↓

After sterilizing skin puncture size => surgical drape was covered

↓

21G 15 cm. Chiba needle was advanced at L2 after 1% lidocaine infiltration under fluoroscopy guided oblique projection

↓

Target site ; 1-2 ml of contrast agent was injected to confirm adequate spread around target

Similar process was conducted at L3

Procedure

0.5% levobupivacaine 1.5 ml injected into both needle

↓

After identifying a temperature increase in ipsilateral sole within 20 min

↓

0.25% levobupivacaine 8 ml (control) **VS** botulinum toxin A 75 IU+ NSS up to 8 ml
(both 4 ml into each Chiba needle)

Primary outcome	Secondary outcome
ΔT on affected sole compared with unaffected sole at 1 postprocedural month **measurement:** infrared thermography 　　　　　　　by blinded nurse Temperature sampling ≥ 5 site in each foot And calculated the average ΔT *(at 23 C & 50% without direct sunlight or radiant heat)*	• ΔT Of Sole asymmetries from baseline to 3 month • Mean pain intensity was assessed using NRS at baseline, 1 month, 3 month • peak systolic velocity of ipsilateral popliteal artery (before,immediately,1 month,3 month) • Modified intolerance symptom severity • Patient's global impression at 1 & 3 month

Statistical analysis

- Sample size was calculated base on pilot data

- Hypothesizes average ΔT 1.3 ^oC (SD1.2); botulinum toxin & 0 ^oC (SD1.2);control group at 1 month

- Calculated 19 patients/group (power 90%) ± 20% ; 48 participants (24 patients/group)

- Statical analyses : R version 3.6.1
- Categorical , normally distributed , nonnormally distributed were presented as proportion (%), mean ± SD, median with interquartile ranges
- Data normality : Shapiro-Wilk test
- Categorical & continuous : chi-square/Fisher's exact test, independent t test

- Statistical significant : $P < 0.05$

Enrollment

Assessed for eligibility (N = 64)

Excluded (N = 16)
- Declined to participate (N = 2)
- Underwent botulinum toxin injection for cosmetic purposes within 6 months (N = 2)
- Underwent lumbar sympathetic neurodestructive procedures (N = 3)
- failed to obtain a temperature increase from the screening block (N = 9)

Randomized (N = 48)

Allocation

Allocated to the Control group (N = 24)
- Received allocated intervention (N = 24)

Allocated to the Botulinum Toxin group (N = 24)
- Received allocated intervention (N = 23)
- Declined to get the test drug (N = 1)

Follow-Up

Lost to follow-up at 1 month (N = 0)

Lost to follow-up at 3 months (N = 2)

Lost to follow-up at 1 month (N = 0)

Lost to follow-up at 3 months (N = 1)

Analysis

Analyzed at 1 month (N = 24)
- Missing value at 1 month (N = 0)

Analyzed at 3 months (N = 22)
- Missing value at 3 months (N = 2)

Analyzed at 1 month (N = 23)
- Missing value at 1 month (N = 0)

Analyzed at 3 months (N = 22)
- Missing value at 3 months (N = 1)

Result

Table 1. Demographics and Baseline Clinical Characteristics

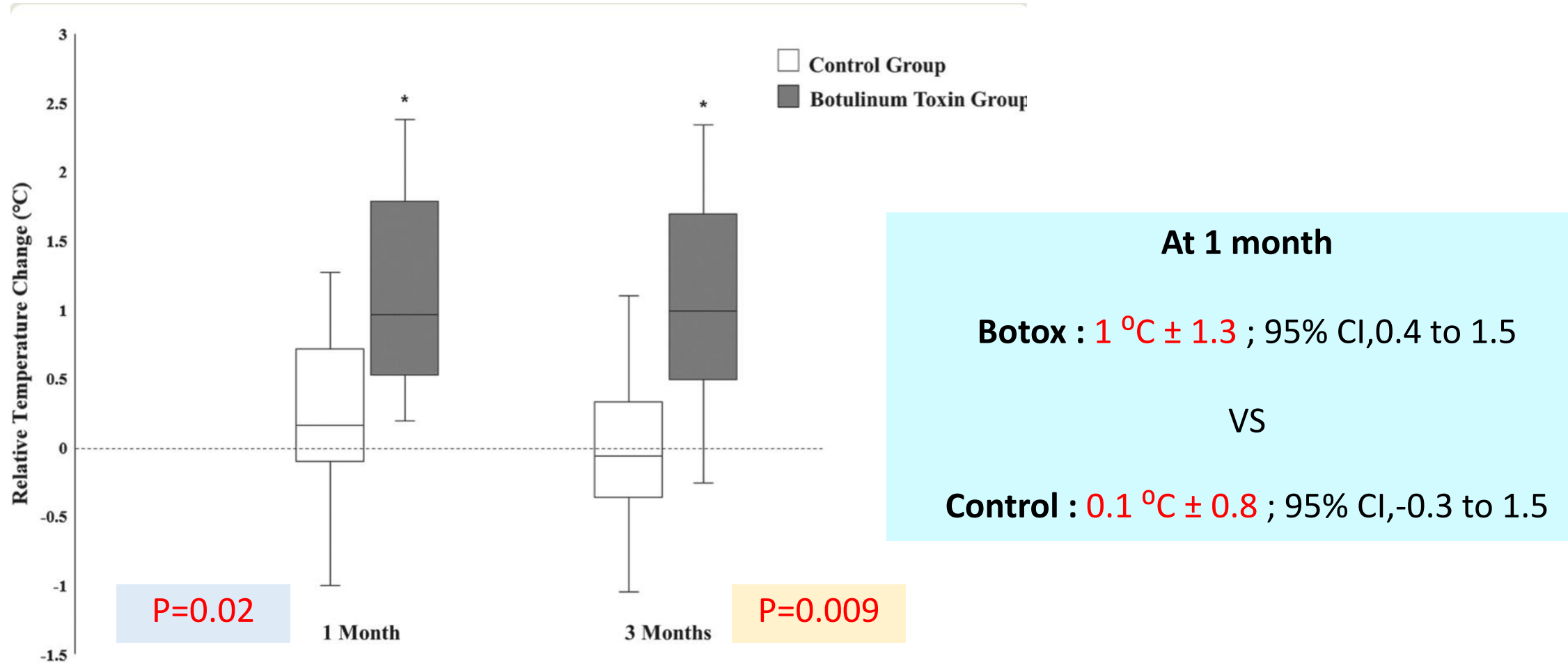|	Control Group (N = 24)	Botulinum Toxin Group (N = 23)
Age, yr	43.7 ± 12.3	44.8 ± 12.2
Male/female	12 (50)/12 (50)	12 (52)/11 (48)
Body mass index, kg/cm²	25.7 ± 4.6	24.6 ± 3.7
Hypertension	2 (8)	4 (17)
Diabetes mellitus	1 (4)	2 (9)
Dyslipidemia	4 (17)	5 (22)
Smoking	7 (29)	5 (22)
Previous surgical 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

No difference

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. ‡$P < 0.05$.

Change of relative temperature asymmetries from baseline

At 1 month

Botox : 1 °C ± 1.3 ; 95% CI,0.4 to 1.5

VS

Control : 0.1 °C ± 0.8 ; 95% CI,-0.3 to 1.5

P=0.02

P=0.009

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 ($P = 0.009$).

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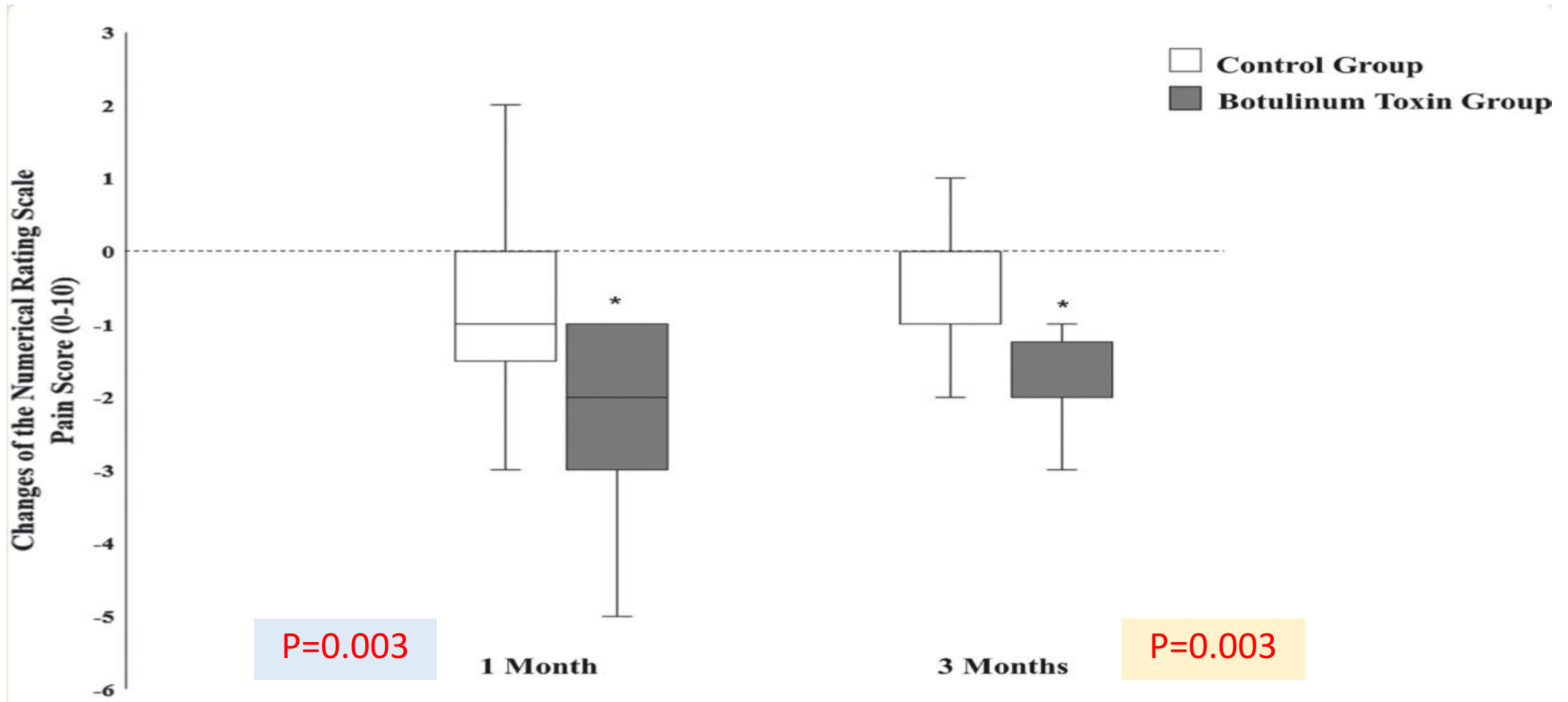
Fig. 3. Changes of the 11-pointed numerical rating scale pain score from baseline. The *asterisks* indicate significant between-group differences in the changes of the 11-pointed numerical rating scale pain score at 1 month (*P* = 0.003) and 3 months (*P* = 0.003).

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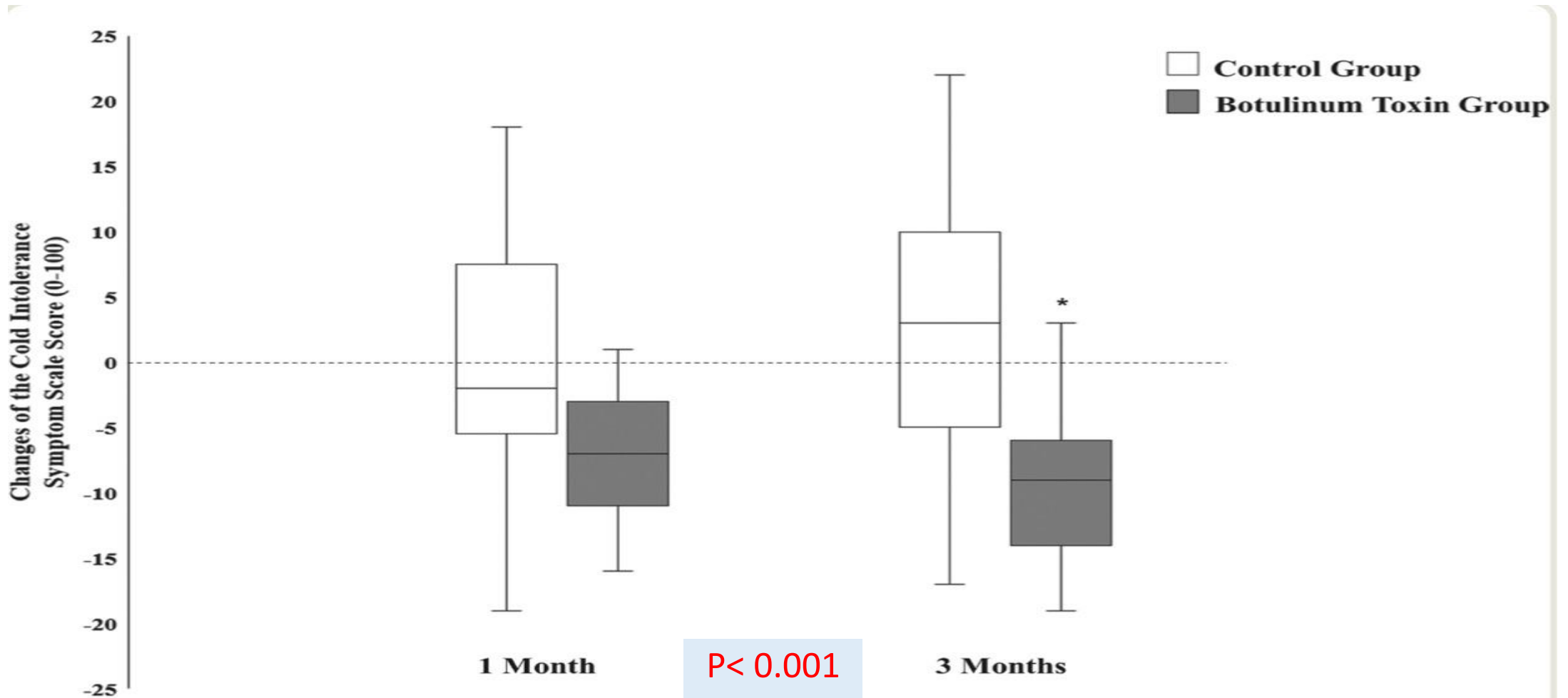
Fig. 4. Changes of the cold intolerance symptom severity score from baseline. The *asterisk* indicates a significant between-group difference in the change of the cold intolerance symptom severity score at 3 months (*P* < 0.001).

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

At 3 month

Botox : ΔT 1.1 °C ± 0.8   **VS   control :** ΔT -0.2 °C ± 1.2

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Pain score at 1 month [Botox : **-2.1** ± 1.0   VS   control : **-1** ± 1.6]

Pain score at 3 month [Botox : **-2.0** ± 1.0   VS   control : **-0.6** ± 1.6]

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Returned to baseline levels at 1 and 3 months **[Non-significant]**

Frequencies of symptoms in the cold intolerance questionnaire
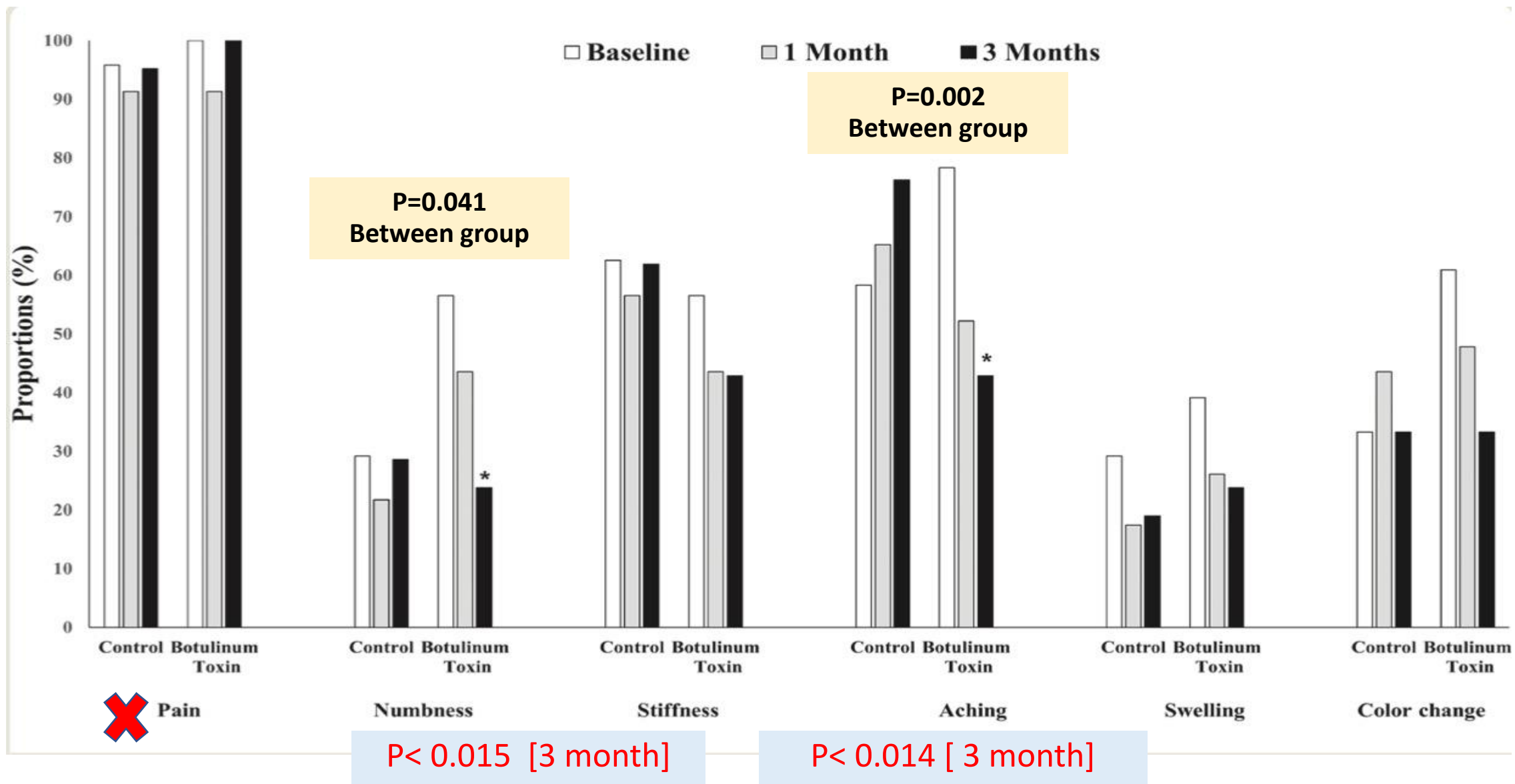
Result

- Patient's global impression change : (78% VS 54% , P=0.081 at 1 month)

  (70% VS 46% , P=0.1 at 3 month)

- Positive correlations between the initial & postprocedural immediate peak systolic velocities

  (r=0.64, P<0.001)

- Patient with higher baseline peak systolic velocity presented a greater improvement in cold tolerance after LSB

- Safety ; mild post procedure dizziness , back pain , no genitofemoral neuralgia

Result
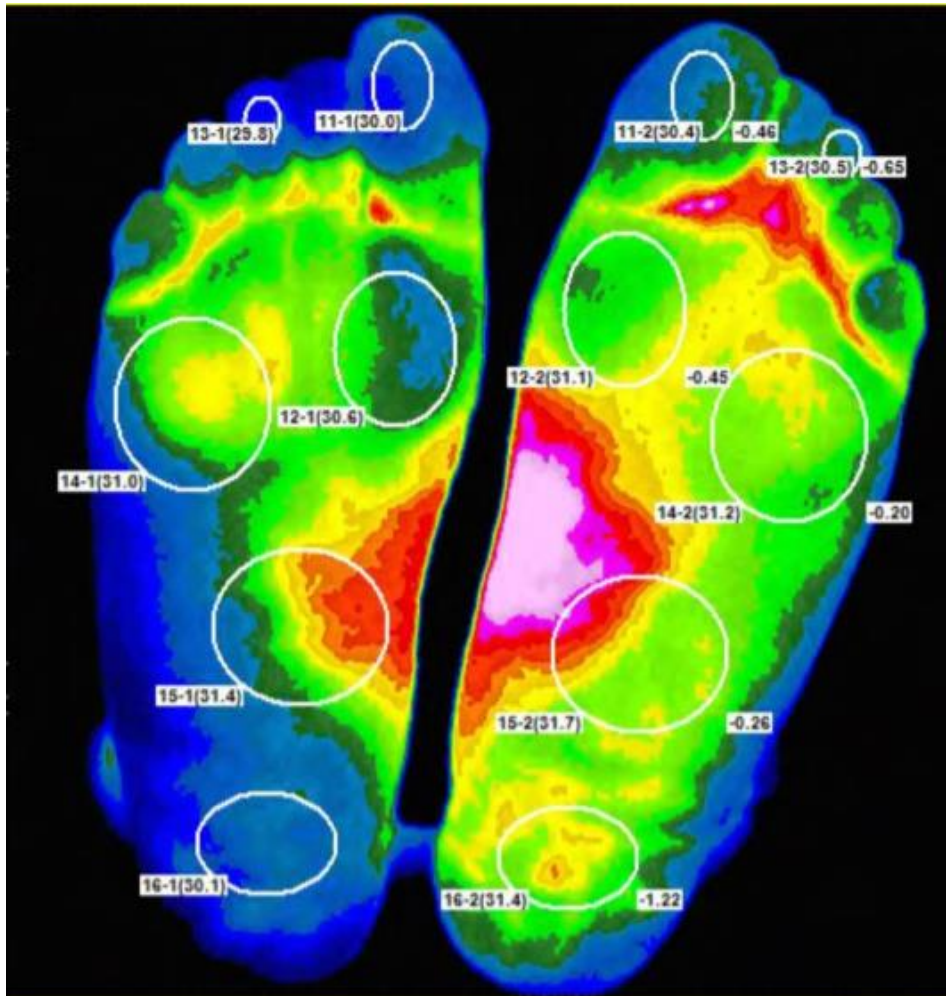
No correlations between the temperature increase and a reduction of the NRS at any time point

(r=-0.16,P=0.032 at 1 month ; r=-0.21,P=0.194 at 3 month)

Discussion

- Botulinum toxin A dissolves the synaptosomal associated protein 25, membrane fusion with synaptic vesicle

- Suppress the exocytosis of Ach & neurotransmitters in autonomic cholinergic synapse, NMJ, sensory neuron

- Sympathetic overflow is possible CRPS pathophysiology

- Botulinum injection onto LSB, which *enhance peripheral microcirculation with subsequent temperature increase in ipsilateral foot*

Discussion

- This is 1st RCT study on clinical effect of *botulinum toxin A to confirm prolonged temperature increase & pain reduction in CRPS*

- Primary outcome was ΔT rather than pain reduction

(CRPS do not always respond to LSB; rather, most patients present temperature increase after LSB)

- Their patients had chronic and highly refractory CRPS, small differences in pain reduction between group

- Initial peak systolic velocity represent vascular integrity, were *strongly correlated with reduced cold intolerance symptom*

Suggestion

- Small-scale study reported that subcutaneous or IM botulinum toxin injections improved pain intensity in CRPS

- Our results added botulinum toxin A onto LSB improved sensory symptoms; arching, numbness

- Further study ; investigate whether improve multiple symptom domains in CRPS or most effective route and site of injection for pain reduction

limitations

- Single center small-scale trial ; patients had highly intractable CRPS which required visit 3rd hospital

- RCT didn't include a placebo group (NSS injection instead of LA)

- Need for studies with a longer follow up to investigate the more prolonged effect of botulinum toxin A

- Didn't examine inflammatory cytokines or electrophysiologic tests for verifying changes in sensory symptom

- 75 IU of botulinum toxin A may not be sufficient for exerting its full effectiveness for LSB

  (compared to previous study , dose dependent blocking effect)

Critical Appraisal : RCT

Does this study address a clear question?

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical Appraisal : RCT

- Are the results of this single trial valid?

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?	✓		
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical Appraisal : RCT

• Are the results of this single trial valid?

	Yes	Can't tell	No
6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	✓		
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

- What were the results?

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	no
10. How precise were the results? Were the results presented with confidence intervals?	yes

Critical Appraisal : RCT

- Can I apply these valid, important results to my patients?

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?		✓ ✓	
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?	✓ ✓		