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# 보툴리눔 A 독소 주사를 이용한 레이노 환자의 겨울나기

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# Botulinum A Toxin Injection as an Adjuvant Wintering Therapy in Patients with Raynaud's Syndrome

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**Purpose:** Patients with secondary Raynaud's syndrome experience severe pain and even ulceration of the fingertips, particularly during the winter season. The aim of this retrospective review was to evaluate whether botulinum A toxin injection before the winter season could prevent severe pain and complications in patients with secondary Raynaud's syndrome.

**Methods:** Patients (n=10) were injected with botulinum A toxin (25 U) at 14 points on each hand. Sex, age, number of treatments, underlying diseases, pre- and post-injection pain intensity and frequency, satisfaction with the injection, and complications were evaluated. Statistical analyses were performed using the Wilcoxon signed-rank test.

**Results:** All patients had secondary Raynaud's syndrome and were female, with mean age of 50.1 years. All patients showed an improvement in pain intensity after the injection. The frequency of pain per week improved after the injection in seven patients and remained the same in three patients. The mean satisfaction rating was 7.0 out of 10 points. Eight patients were willing to reinject; however, two patients refused reinjection due to injectional pain. Two patients had temporary weakness of the hand. Seven patients showed an improvement in cyanosis. Nine patients showed an protectiv effects in fingertip ulcerations.

**Conclusion:** Botulinum A toxin injection in patients with secondary Raynaud's syndrome before the winter season may provide substantial improvements in pain and ulceration, as the pain increases during the cold season. Furthermore, the protective effect of botulinum A toxin may also be helpful in preventing additional surgery.

**Key Words:** Raynaud disease, Peripheral vascular diseases, Botulinum toxins, type A, Vasoconstriction

## INTRODUCTION

Raynaud's syndrome is associated with digital artery vasospasm, which induces ischemia of the fingertips and causes pain, ulcerations, and disuse. Raynaud's syndrome can be aggravated by many factors, particularly cold conditions[1]. After a precipitating vasoconstricting stimulus induced by coldness, small-caliber digital arter-

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ies undergo vasospasm[2]. The digits turn blue or pale, then they finally turn red due to reperfusion, and some areas of the digits may become damaged[3]. If the symptoms of Raynaud's syndrome are not controlled properly, amputation may be required[4,5]. Digital sympathectomy with pharmacologic treatment was introduced for the management of Raynaud's syndrome, but this has limited benefit in controlling the pain experienced by the patients daily, especially in cold conditions[6-8]. More aggressive surgical interventions, such as digital artery grafting, are often associated with surgical morbidity, especially in patients with prior surgical interventions[2]. Furthermore, it is difficult for surgeons to perform repetitive surgical interventions, which may result in exhaustion and more severe surgical complications, reducing the general condition of the patient[9,10]. Many pharmacologic treatments and lifestyle modifications are currently under development; however, these procedures are inadequate to quell the daily pain experienced by these patients, especially during the winter season[1].

The uses and mechanisms of botulinum A toxin in curative medicine are still being discovered. Botulinum A toxin is thought to affect the smooth muscle of the vessel wall[2,11-13], resulting in pain relief and increased perfusion of the fingertips immediately after injection[11]. Its effects last for months to years, and even permanent relief can occur[7]. The symptoms of Raynaud's syndrome become aggravated during winter, causing suffering and potentially precipitating additional surgery. However, the effects of preventive botulinum A toxin injection administered during the fall season should last through the winter season. Surgical intervention of vascular occlusion in patients with Raynaud's syndrome is helpful but it is not a complete cure because Raynaud's syndrome is a systemic disease. Prior injection of botulinum A toxin may help control symptoms from aggravating during the winter season in patients who have undergone prior surgery due to peripheral vascular occlusion of Raynaud's syndrome. Especially in South Korea, which has four distinct seasons, administering botulinum A toxin during fall may not be difficult.

The purpose of this study is to evaluate whether botulinum A toxin injection before the winter season could prevent severe pain and complications in patients with secondary Raynaud's syndrome.

## MATERIALS AND METHODS

### 1. Study population

A retrospective chart review was conducted between November 2016 and April 2018 of 10 consecutive patients with Raynaud's syndrome injected with botulinum A toxin for the treatment of ischemic pain of the digits of the hand prior to the winter season. The injection was performed in patients with prior surgery for the treatment of Raynaud's syndrome, such as a vessel graft or sympathectomy. Patients with a history of an allergic reaction to botulinum A toxin were excluded. Patients with mixed connective tissue disease were included. Informed consent was obtained from all patients prior to the botulinum A toxin injection. Our Institutional Review Board approved this study (IRB No. HYUH 2018-05-008-003).

### 2. Botulinum A toxin injection technique

Fifty units of botulinum A toxin (Botox; Allergan Inc., Irvine, CA, USA) were reconstituted with 0.9% sodium chloride and a preservative, at a dilution of 2 mL per 50-U vial. The botulinum A toxin was injected into both hands (25 U of botulinum A toxin in each hand) at 14 points (Fig. 1). In our protocol, we inject all of the fin-

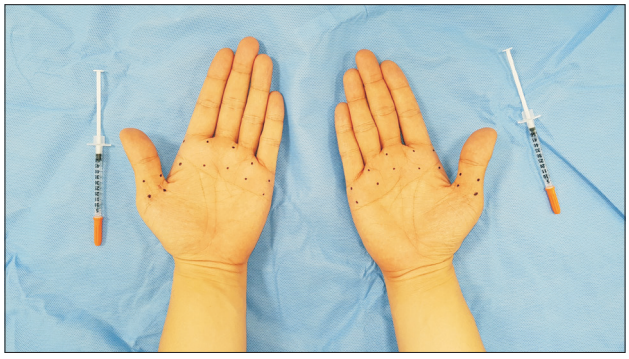

Fig. 1. Botulinum A toxin (25 U) was injected in each hand at 14 points (black dots) based on the digit injection pattern.

gers at the metacarpophalangeal joint, with two injection sites each. All patients were injected between October and early December, which is the first month of winter. The targeted anatomy was the common digital arteries. A 1-mL insulin syringe was used to infiltrate the soft tissues around the arteries with the botulinum A toxin solution. The injection was performed with the needle perpendicular to the hand and deep to the palmar fascia. The goal was to inject adjacent to the vessels, without injuring them. After the injection, the palms and the base of the digits were squeezed for 60 seconds by the patient to help distribute the botulinum A toxin throughout the injection region.

## 3. Outcome measures

All patients completed a questionnaire when visiting outpatient department or if not visited, telephone questionnaire, during the month of February, administered by the first author. The questionnaire is outlined in Fig. 2. The following data were collected: the patient's name, date of the survey, pain intensity (assessed using a visual analogue scale [VAS]), number of fingertip ulcerations during winters (before and after the injection), frequency of pain, post-injectional pain-free duration, number of cyanosis attack per week, satisfaction score, willingness to reinject, and complications.

| | | |
|---|---|---|
| Patient name | | |
| Date | | |
| Pain intensity scale score (VAS, 0-10) | Pre | Post |
| Number of fingertip ulceration after wintering therapy | Pre | Post |
| Frequency of pain attack per week | Pre | Post |
| Post-injectional pain-free duration | | |
| Improvement of cyanosis (cyanosis attack per week) | Pre | Post |
| Satisfaction after injection (0-10) | | |
| Willing to undergo reinjection (if rejected to reinject, state the reason) | | |
| Complication(s) | | |

**Fig. 2.** Questionnaire. VAS: visual analogue scale.

Four of the ten patients also underwent a thermoscan, as the authors recognized the need of a thermoscan after the first six patients were treated with the botulinum A toxin. The thermoscan was performed after the patients rested for one hour in a room with constant ambient temperature (Fig. 3).

## 4. Statistical analyses

Summary data are presented as number and percentages for categorical variables and as means with standard deviations for continuous variables. Patient characteristics of pain intensity and pain frequency per week at baseline and post-injection were compared using the Wilcoxon signed-rank test. All tests were two-tailed, and statistical significance was set at $p<0.05$. All analyses were performed using Stata version 12.0 (StataCorp. LP, College Station, TX, USA).

# RESULTS

## 1. Patient characteristics at baseline

All patients (n=10) were female, with an age range of 36 to 73 years. Three patients were treated with botulinum A toxin twice; the remaining seven patients were treated with botulinum A toxin once. All patients were

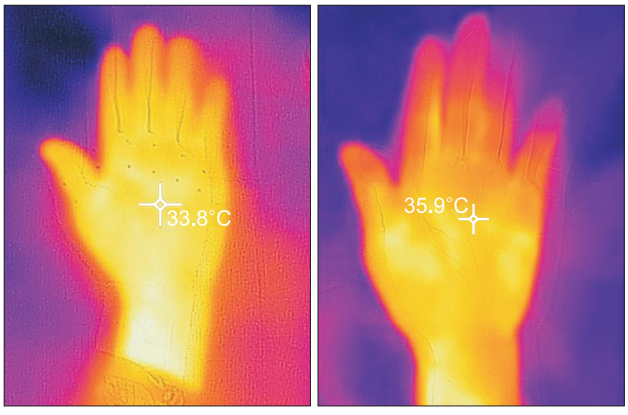


**Fig. 3.** The thermoscan images show a patient (left) at pre-injection and (right) at follow-up, 3 months after botulinum A toxin injection.

**Table 1.** Patients demographics

| Patient No. | Age (yr) | Sex | No. of injection | Underlying disease | Vessel reconstruction | Sympathectomy |
|---|---|---|---|---|---|---|
| 1 | 44 | Female | 2 | Systemic sclerosis | Digital artery | + |
| 2 | 64 | Female | 1 | Sjogren disease | Ulnar artery | + |
| 3 | 40 | Female | 1 | Systemic lupus erythematosus | Ulnar artery | + |
| 4 | 48 | Female | 1 | Systemic lupus erythematosus | Ulnar artery | + |
| 5 | 73 | Female | 2 | Mixed connective tissue disease | Ulnar artery | + |
| 6 | 42 | Female | 1 | Systemic lupus erythematosus | Ulnar artery | + |
| 7 | 36 | Female | 1 | Systemic sclerosis | Ulnar artery | + |
| 8 | 41 | Female | 1 | Systemic lupus erythematosus | Radial artery | + |
| 9 | 59 | Female | 1 | Systemic sclerosis | Digital artery | – |
| 10 | 64 | Female | 2 | Systemic sclerosis | Ulnar artery | + |

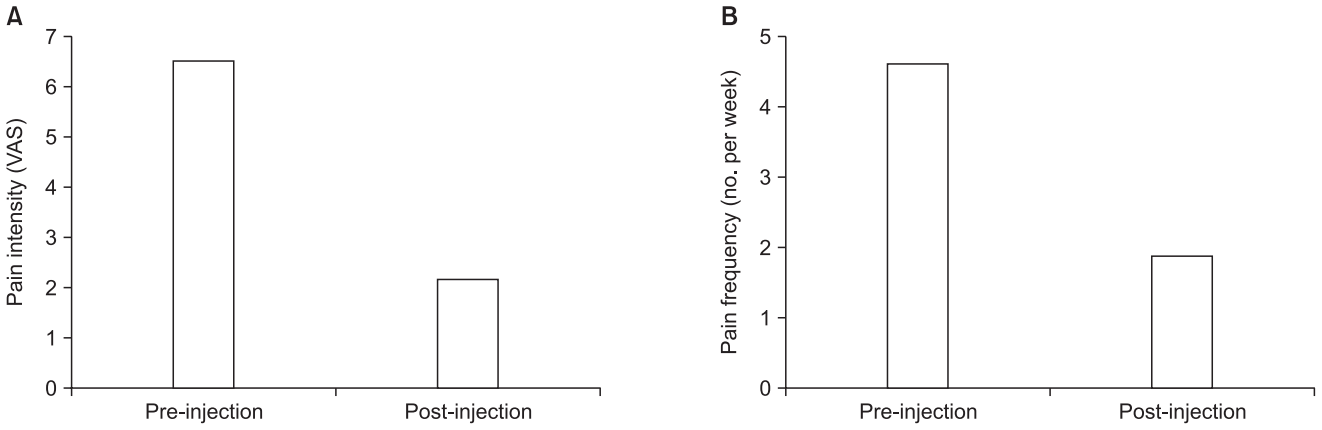


**Fig. 4.** (A) The graphs show the pain intensity visual analogue scale (VAS). Mean±standard deviation (SD) of pain intensity, pre- and post-injection ($p<0.05$). (B) The graphs show the pain frequency. Mean±SD of pain frequency, pre- and post-injection ($p<0.05$).

diagnosed with connective tissue disease or autoimmune disease. The underlying diseases included systemic sclerosis, lupus, Sjogren disease, and mixed connective tissue disease (Table 1).

## 2. Effects of the botulinum A toxin injection

Baseline VAS score of pain intensity and pain frequency per week improved and each after the botulinum A toxin injection. Intensity of pain improve all cases (6.5±1.5 vs. 2.2±1.2, $p<0.05$; Fig. 4A). The frequency of pain per week was also improved in seven patients (4.6±1.6 vs. 1.9±1.2, $p<0.05$; Fig. 4B).

In three patients had comparable pain frequency before and after the injection not changed. None of patients showed an aggravation of pain frequency after the botulinum A toxin injection.

The mean satisfaction score was 7.0 (out of 10 points). Eight patients were willing to reinject botulinum A toxin in the coming winter. Two patients refused reinjection because of intense pain during the injection. Seven patients showed improvement in cyanotic events during cold conditions. Nine patients showed a protective effect in fingertip ulcerations (Fig. 5). Two patients had a temporary weakness in grasping due to botulinum A toxin-induced paralysis (Table 2).

# DISCUSSION

Raynaud's syndrome is defined as a secondary sequela of mixed connective tissue disease[4-6]. In Raynaud's syndrome, patients experience pain, numbness, hand motion

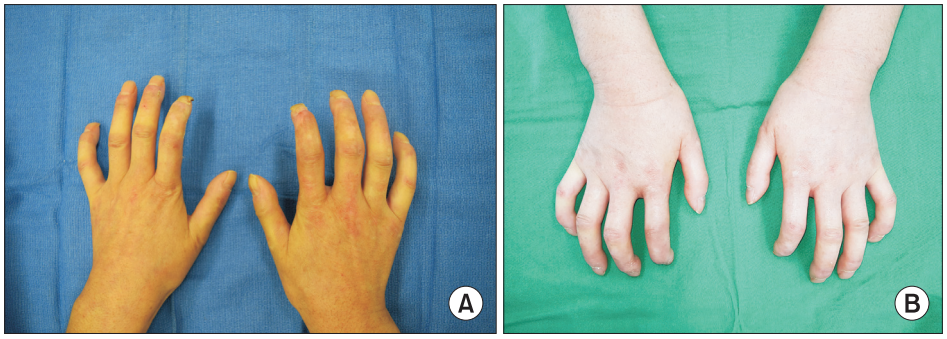


Fig. 5. The photographs show a patient (A) at pre-injection and (B) at follow-up, 6 months after botulinum A toxin injection.

Table 2. Post-injection evaluations

| Result | Score |
|---|---|
| Satisfaction (total: 10 points) | 7.0±0.9 |
| Willing to undergo reinjection | 80 |
| Temporary weakness | 20 |
| Improvement of cyanosis | 70 |
| Protective effect in fingertip ulceration | 90 |

Values are presented as mean±standard deviation or percentages.

limitations, and even necrosis of the fingertips, leading to the amputation of the digits. Lifestyle modification and pharmacologic management have limited effect on patients with Raynaud's syndrome, as they only target symptom control. Surgical interventions such as vascular reconstructions also prevent necrosis of the fingertips. No obvious fundamental treatment of Raynaud's syndrome has been discovered yet.

Botulinum A toxin may be useful in both primary and secondary Raynaud's syndrome. The mechanism of botulinum A toxin in treating the chronic ischemia and pain of Raynaud's syndrome is still under investigation; however, botulinum A toxin may affect several pain-related neurotransmitters, including norepinephrine, substance P, glutamate, and calcitonin gene-related proteins[6,14]. This provides patients with immediate tolerance to coldness. Therefore, administrating botulinum A toxin before winter may be helpful to patients with Raynaud's syndrome. Patients who have undergone prior surgery, who may be unwilling to undergo additional surgery, might benefit from this procedure.

In the present study, patients with Raynaud's syndrome and prior surgery, who may expect a great amount of pain during the winter, were treated with botulinum A toxin. All patients showed an improvement in pain during cold conditions, and most of the patients also showed an improvement in pain frequency. This pain relief was achieved immediately after the botulinum A toxin injection. The effects of botulinum A toxin not only prevents vasoconstriction of peripheral vessel but may also blocks digital sensory nerve. Although the weather became colder after the botulinum injection (minimum temperature: –16°C), all patients had gained better tolerance to the cold conditions. Numerous vascular studies have already shown the value of botulinum toxin in inducing vasodilatation or preventing thrombosis as well as in improving tissue viability[15]. Thus, botulinum A toxin could be applied, not only for therapeutic purposes, but also as a preventive procedure before winter in patients with Raynaud's syndrome.

In the present study, all patients had a subjective increase in finger warmth. In addition, thermoscans of the fingertip showed an average increase in temperature of 0.1°C to 2.2°C in four of patients evaluated. Although not all patients underwent thermoscans, this result indirectly shows the vasodilating effect of botulinum A toxin, which allows warm blood to circulate to the periphery. This may provide the periphery with more resistance to cold conditions. In prior winter seasons, all patients experienced ulcerations of the fingertip. However, in patients with pre-injection ulcerations of the fingertips, the ulcerations were improved or remained consistent. None of patients showed an aggravation of the ulcerations in the fingertips. Thus, the results of the present study demonstrate not only the therapeutic effect of botulinum A toxin but also its protective effect during cold conditions.

Patients' satisfaction with pre-winter botulinum A toxin

injection as a preventive therapy was acceptable. Because effects of botulinum A toxin last for few month, patients has to reinject every year. With the exception of severe pain during the injection, patients indicated that the botulinum A toxin injection was worth the effort. Transient weakness in grasping was observed in two patients due to botulinum A toxin-induced paralysis. However, the weakness was not severe, and patients were hardly aware of this complication. In the present study, patients were injected with 25 U of botulinum A toxin in each hand to avoid intrinsic muscle paralysis. The dose (25 U) may be adequate for the protective effects of botulinum A toxin if fine and precise injections toward the common digital arteries are made. Furthermore, persistent atrophy, which is a rare complication, did not occur[16]. A previous study suggested that avoiding the middle palm and injecting botulinum A toxin as close as possible to the webspace could prevent intrinsic weakness[2].

The present study has several limitations. First, the protective effect of botulinum A toxin was proven objectively by comparing the incidence of fingertip necrosis before and after the injection; however, a prospective study is necessary, as a placebo effect might exist, especially in a questionnaire study. Prior to injecting the botulinum A toxin, it is important that the proximal vascular inflow is sufficient[10]. Meticulous pre-injectional examination of the patient is required; if the proximal vascular inflow is insufficient, the anticipated effect will not occur. The present study only had 10 patients, which is due to the cost of the botulinum A toxin injection. Patient insurance in the Republic of Korea does not cover botulinum A toxin usage in the hand. Furthermore, not all patients underwent with thermoscan imaging; however, there was an increase in fingertip temperature in the evaluated patients. Furthermore, the authors were unable to determine an appropriate painless injection method on the hand. In the application of botulinum A toxin to the face, there are several methods for a painless injection, including the use of an ice roller massage or a eutectic mixture of local anesthetics. A few patients refused reinjection because of injectional pain. A simple method to anesthetize the palm should be determined.

Even with these limitations, the present study still has value. Patients cannot undergo repeated year-round injections of botulinum A toxin because of its complications, injectional pain, and expenses. The present study suggests an appropriate schedule for botulinum A toxin injections in patients with Raynaud's syndrome that may prevent pain, ulcerations of the fingertips, and amputation of the digits in a cost-effective manner.

## CONCLUSION

The present study demonstrated that a pre-winter injection of botulinum A toxin as a preventative therapy could provide patients with substantial improvements in pain and ulcerations, as the suffering of patients with Raynaud's syndrome increases during the cold season. Administrating botulinum A toxin may not also aid patients who are hard to perform additional surgical intervention, but also be helpful in preventing additional surgery.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

## ACKNOWLEDGEMENTS

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# 보툴리눔 A 독소 주사를 이용한 레이노 환자의 겨울나기

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**목적:** 이차성 레이노 증후군을 앓고 있는 환자들은 낮은 온도의 날씨에 심한 통증을 호소하며, 수지 말단부에 궤양이 생기기도 한다. 본 연구를 통하여 보툴리눔 A 독소를 주사하는 치료가 이차성 레이노 증후군 환자의 겨울을 지내는 데 있어 통증 및 합병증을 예방할 수 있는지 평가하였다.

**방법:** 총 10명의 환자들은 각각의 손 14지점에 보툴리눔 A 독소를 주사하였다. 성별, 나이, 주사 횟수, 기저질환, 주사 전후의 통증 강도나 빈도, 주사 후 만족도, 합병증을 평가하였다.

**결과:** 본 연구에서 이차성 레이노 증후군을 앓고 있는 환자는 총 10명으로 모든 환자는 보툴리눔 독소 주사 후 통증 강도 및 주간 통증 빈도에 유의한 호전을 보였다. 8명의 환자는 재주사를 희망하였고, 2명의 환자는 주사 시 통증으로 재주사를 원치 않았다. 2명의 환자는 일시적인 악력의 약화를 경험하였다. 7명의 환자는 청색증에 호전을 보였다. 9명의 환자는 수지말단의 궤양에 예방적인 효과를 보였다.

**결론:** 이차성 레이노 증후군 환자에 있어 겨울이 되기 전에 보툴리눔 독소를 주사하는 것은 통증의 악화와 수지 말단 궤양의 발생을 예방하는 효과가 있다. 또한, 이전에 이차성 레이노 증후군으로 인하여 수술을 받은 환자는 보툴리눔 독소를 주사하여 추가적인 수술을 방지할 수 있다.

**색인단어:** 레이노병, 말초 혈관 질환, 보툴리눔 독소, A형, 혈관수축

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