

The Tourniquet Ischemia Test Effectively Predicts the Efficacy of Lumbar Sympathetic Block in Patients with Lower Extremity Complex Regional Pain Syndrome Type I

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Background: Neuropathic pain is the most common clinical sign of complex regional pain syndrome (CRPS). Currently, lumbar sympathetic block (LSB) is commonly utilized in lower extremity CRPS that has failed to respond to medication therapy and physical therapy, but its effectiveness is unknown. The tourniquet ischemia test (IT) can distinguish between two types of CRPS: IT-positive CRPS and IT-negative CRPS.

Objective: The aim of the study was to investigate whether LSB improves pain scores in patients with lower extremity CRPS-1 and to screen factors to predict its efficacy.

Study Design: Prospective clinical observational study.

Setting: Pain management center.

Subjects: Forty-three patients diagnosed with lower extremity CRPS-1 using the Budapest criteria were included as participants.

Methods: Forty-three CRPS-1 patients were treated with LSB therapy, and all of them underwent a tourniquet ischemia test (IT) before undergoing LSB therapy. LSB therapy was performed using a combination of ultrasonography and fluoroscopy. Then, numeric rating scale (NRS) scores and the symptom relief rates of patients were evaluated at 1, 4, and 12 weeks. Finally, peripheral blood inflammatory cytokine samples were collected before and after the LSB treatment.

Results: At 4 weeks after the treatment, the total effective symptom relief rate of LSB on CRPS-1 was 25.6% (11/43), with 52.6% (10/19) of IT(+) patients and 4.2% (1/24) of IT(-) patients. There was a significant difference between the IT(-) and IT(+) groups ($P = 0.001$). The multivariate binary logistic regression analysis revealed that the response to the tourniquet IT was the only significant independent predictor of sympathetic block success ($p = 0.007$).

Conclusion: Tourniquet IT is a simple, safe and effective test to distinguish patients with lower extremity CRPS-1. The response to the tourniquet IT is a reliable predictor of LSB effectiveness in lower extremity CRPS-1 patients.

Keywords: complex regional pain syndrome, lumbar sympathetic block, tourniquet ischemia test, predict

Introduction

Complex regional pain syndrome (CRPS) is a painful condition that develops after a noxious event such as a fracture, trauma, or surgery. Pain, sensory, sudomotor, and vasomotor disturbances, trophic alterations, and impaired motor function are typical clinical characteristics of CRPS.¹ The estimated overall incidence rate of CRPS is 26.2 per

100,000 person-years, and its most prominent clinical manifestation is refractory neuropathic pain.² The majority of therapies are ineffective in providing patients with long-term pain alleviation.^{3,4} CRPS usually requires a multidisciplinary treatment that combines pharmaceutical therapy, physical therapy, psychotherapy, and interventional therapy to restore a patient's quality of life.³⁻⁶ However, CRPS has not yet been successfully managed; thus, a more reasonable treatment protocol is needed.

The mechanism of CRPS is related to sympathetic nervous system dysfunction.⁷ There is strong evidence that the sympathetic nervous system and inflammatory mediators (TNF- α , IL-1 β , IL-2, IL-4, IL-6, IL-10, etc.) interact in CRPS, contributing to the pathophysiology and clinical manifestations of the disease.⁸ Sympathetic nerve interventional therapy is used widely and has been found to be beneficial in reducing sympathetically-mediated pain symptoms such as CRPS symptoms, phantom pain, headaches, and facial discomfort.⁹ However, effective sympathetic interventional therapy for CRPS is still limited, and not all CRPS patients obtain ideal results.¹⁰ Only if a diagnostic tool that can identify the potential pathophysiological mechanism of CRPS is developed would mechanism-based therapy be practicable. If we can predict which kind of patients will benefit from sympathetic block, we will be able to identify suitable patients and decrease the number of unsuccessful invasive procedures, as well as potential consequences and costs.

The tourniquet ischemia test (IT) has been performed in individuals with sympathetic dysfunction. Early research has demonstrated that the tourniquet IT can easily block clinical signs in individuals suffering from sympathetic discomfort.¹¹ Specifically, wrapping a bandage over the injured limb's distal end can greatly reduce pain in most cases.¹² In another study, the tourniquet IT was applied as a screening tool for individuals who experienced limb discomfort that was either unresponsive or unexplained in clinical practice.¹³ There is currently no prospective clinical trial investigating the tourniquet ischemia test as a predictor of the lumbar sympathetic block (LSB) efficacy in lower extremity CRPS.

In this study, we attempted to identify CRPS-1 patients who would benefit from sympathetic block treatment. We analyzed the prognostic value of tourniquet ischemia status and clinical characteristics in 43 CRPS-1 patients who were treated at our center.

Methods

This study was designed as a prospective observational study. The research population was chosen from a group of 55 newly diagnosed lower extremity CRPS-1 patients at Shanghai Sixth People's Hospital's Department of Pain Management from September 2020 to May 2021. For this research, all patients were diagnosed with CRPS-1 using the Budapest standards. Of these participants, only 43 were selected for this study (Figure 1). The inclusion criteria were as follows: newly diagnosed patients with unilateral lower extremity CRPS-1 following a fracture, trauma, or surgery; patients with NRS score of 4 or more on a scale of 0–10 (with 0 indicating no pain and 10 indicating the worst

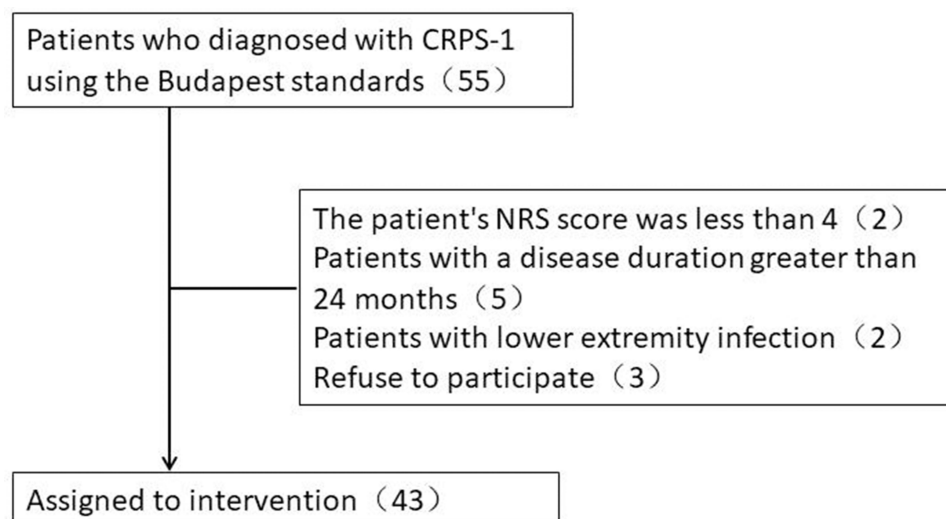


Figure 1 Flow chart.

imaginable pain); patients with a disease duration greater than 3 months but less than 24 months after the initial trauma; and patients aged from 20–80 years. The exclusion criteria were as follows: patients with multiorgan trauma; patients who were pregnant; patients with coagulation abnormalities; patients with infection; and patients with any other condition that may cause signs and symptoms that are similar to CRPS.

This trial (No. 2019–119) was approved by the Shanghai Sixth People's Hospital's Ethics Committee and was registered in the Chinese Clinical Trial Registry with registration number ChiCTR2000037755. The trial was registered at <https://www.chictr.org.cn/on> September 4, 2020. All procedures involving individuals were carried out in accordance with the ethical guidelines set out by the National Research Council. All patients signed a written informed consent form.

Treatment Protocols

All of the participating patients underwent a tourniquet IT before starting LSB therapy. First, the affected extremity was raised for a few minutes, and then the blood pressure cuff was attached to the limb's proximal end. Next, a tight elastic bandage was periodically applied across the affected extremity until exsanguination was achieved. Finally, the bandage was removed, and the affected limb was placed in a horizontal position for 10 minutes after inflating the blood pressure cuff to 300 mmHg. All changes in the severity of pain were recorded during the trial. Pain decreasing by more than 50% during ischemia was considered a positive response. The rating was negative in all other situations.

Each patient received LSB treatment in accordance with our standard protocol. The patients were constantly monitored by pulse oximetry and an automated noninvasive blood pressure monitor during the procedure and for at least 30 min after the procedure. An intravenous line was established for safety reasons just before LSB was conducted. One physician performed the LSB procedure for all of the CRPS participants in the trial. Each patient was positioned in a lateral position.¹⁴ The LSB target was located in the lower third of the L2 vertebra or the upper third of the L3 vertebra using a combination of ultrasonography and fluoroscopy. Following local disinfection, the skin was anesthetized with 1% lidocaine, and a 15-cm, 20-gauge needle was inserted with real-time ultrasound guidance until the anterolateral side of the vertebra was reached. The ultrasound was guided medially over the transverse process of the lumbar spine to penetrate the anterior fascia of the psoas major muscle. The needle tip, which was placed anteriorly and medially, was aimed at the psoas major muscle on the anterolateral side of the lumbar vertebral body. Color Doppler was applied to avoid damaging the vascular structure and design the needle trajectory. The kidney was examined before inserting the needle to verify that it would not obstruct the needle path. The needle was introduced from the lateral to the medial direction using an in-plane technique (Figure 2). Subsequently, the

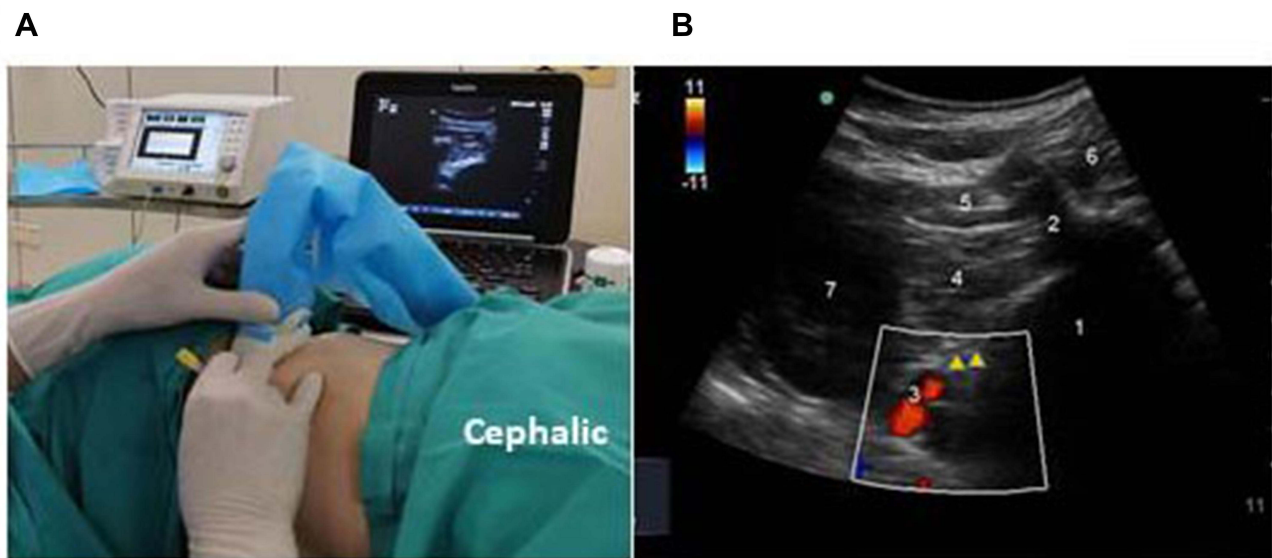


Figure 2 Ultrasound-guided lumbar sympathetic block. (A) An ultrasound probe was used to scan the lumbar sympathetic nerve of the patient while in the lateral position. (B) Ultrasonic image of the lumbar paravertebral region at the L3 vertebral level. 1, lumbar vertebra; 2, lumbar transverse process; 3, abdominal aorta; 4, psoas major; 5, psoas quadratus muscle; 6, erector spinalis muscle; 7, kidney. Arrowheads point to the anterior fascia of the psoas quadratus muscle.

injection of 2–3 mL contrast agent was observed with the C-arm in the anterior posterior (AP) projection and lateral projection after verifying the final position of the needle tip. The sympathetic diffusion pattern of the contrast agent in a successful LSB was linear along the longitudinal axis, with very little lateral or posterior expansion and no significant psoas shadow. Finally, sympathetic diffusion of the contrast dye was confirmed, and 15 mL of 1% lidocaine was administered (Figure 3).

Data Recording

Baseline characteristics, including age, sex, body mass index (BMI), disease duration, baseline NRS score, baseline foot skin temperature of the affected side, baseline peripheral blood inflammatory cytokine levels, and tourniquet IT results (IT+/IT-), were collected from the patients' medical records. The NRS score was used to assess the severity of limb pain, which ranged from 0 (no pain) to 10 (severe pain). To evaluate the effectiveness of the LSB procedure, telephone interviews were conducted with the patients after the procedure. The symptom relief rates was evaluated 1, 4, and 12 weeks after the LSB procedure, according to the following formula: $(\text{NRS base score} - \text{NRS score after block}) / \text{NRS base score} \times 100\%$. The procedure was considered clinically successful if the patients showed more than 50% relief in their NRS score, and the effective symptom relief rates were calculated for each group. The patients were followed-up at the outpatient department at the 4th week to retest their peripheral blood cytokine level. All adverse effects (eg, abnormal increased pain, numbness, paresthesia, back pain, and motor weakness) were recorded during the procedure.

Statistical Analysis

Normally distributed continuous data on patient demographics are reported as the mean $\pm$ standard deviation (SD), while nonnormally distributed continuous data are expressed as the median (interquartile range). Student's *t* test was used to assess the effects of baseline demographics and clinical symptoms on the response to the IT, while Pearson's chi-square test was used to compare categorical variables. The paired Wilcoxon test or signed rank-sum test was used to compare

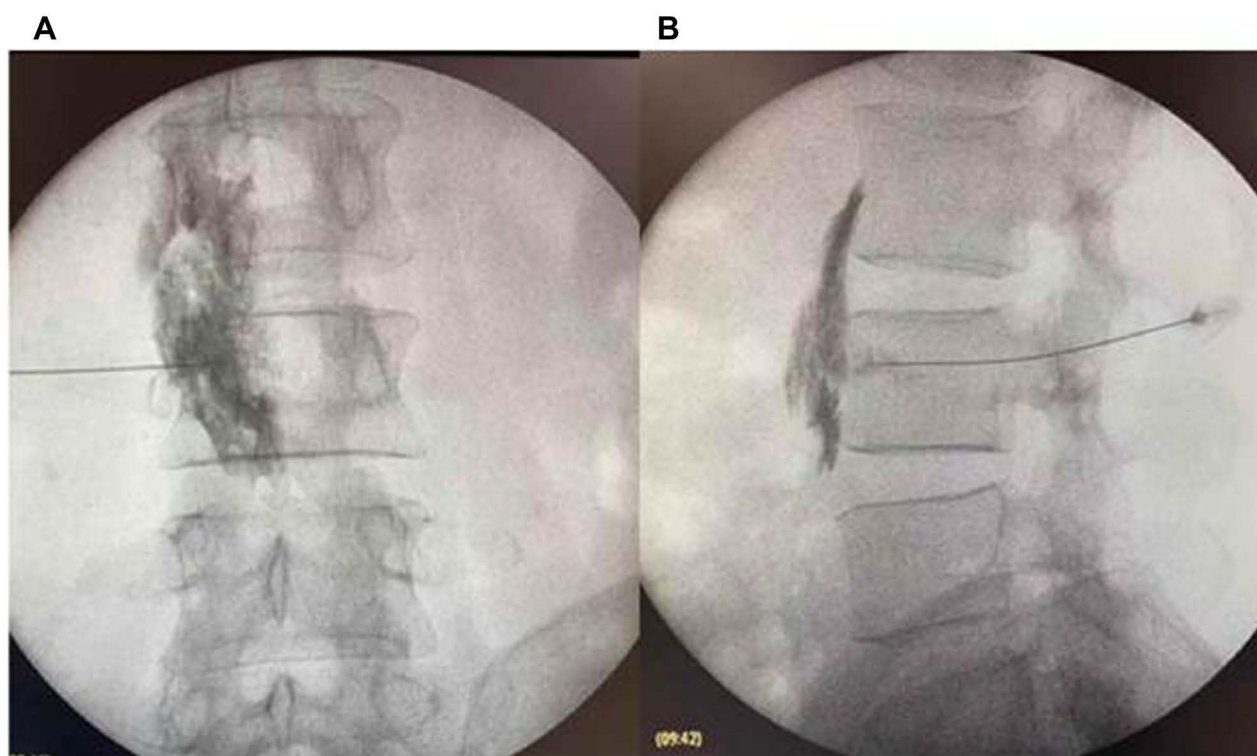


Figure 3 Location of the needle tip and contrast under AP/lateral fluoroscopy. **(A)** The needle tip should lie medial to the lateral margin of the vertebral body in the AP projection, and the contrast spreads over the surface of the vertebral body. **(B)** The needle tip should be positioned over the anterior one-third of the vertebral body in the lateral position, and the contrast spreads over the surface of the vertebral body.

the changes in NRS scores and inflammatory cytokines before and after LSB. A generalized linear mixed model (GLMM) was performed to evaluate changes in symptom relief rate over repeated measurements. If the repeated measures demonstrated a statistically significant time interaction, multiple comparison result was performed by contrast as Bonferroni correction.

Binomial logistic regression analysis was used to determine covariates that were associated with the effect of LSB. Univariate regressions were run first, using one covariate at a time. Next, the covariates that were significant predictors at a level of $P < 0.2$ were considered together in the multivariate regression model to rule out any confounder effects.

All statistical analyses were performed with SPSS software (version 22.0 IBM, USA). $P < 0.05$ was considered statistically significant.

Results

Demographic Characteristics

This study enrolled a total of 43 participants (Table 1). Between men and women, there were no significant differences in age, BMI, disease duration, IT response, baseline foot skin temperature, baseline NRS scores, or baseline inflammatory cytokine levels ($P > 0.05$, Table 1); however, the disease duration was longer in men than in women ($P = 0.015$, Table 1).

Between the IT(-) and IT(+) groups, there were no significant differences in BMI, disease duration, sex, baseline NRS score, or baseline inflammatory cytokine levels ($P > 0.05$, Table 2). However, there were significant differences in age and baseline foot skin temperature between the two groups ($P = 0.032$ and $P = 0.004$, respectively) (Table 2).

Some CRPS characteristics according to the Budapest criteria were observed in the two groups. Between the IT(-) and IT(+) groups, no significant differences were observed in the subjective categories of sensory, vasomotor, and motor/trophic disturbances ($P = 1.000$, $P = 0.373$ and $P = 0.432$, respectively; Table 3), except for sudomotor disturbances/edema ($P = 0.024$; Table 3).

The Effectiveness of LSB

The clinical success of LSB was well achieved at a week after the treatment, with the symptom relief rates are 63.2% and 29.2% in the IT(+) and IT(-) patients respectively ($P=0.066$, Figure 4). This successful pain reduction remains in the IT(+) patients, 52.6% (10/19), but not in the IT(-) patients, 4.2% (1/24) at 4 weeks after the treatment with a significant difference between the two groups ($P<0.001$, Figure 4). At the end of follow-up period, 12 weeks after LSB, 47.4% IT(+) patients got sustained relief, but none of IT(-) patient relieved pain ($P<0.001$, Figure 4). There were no significant differences in changes in TNF- α and IL-1 β levels between the two groups after LSB, while there were substantial variations in NRS scores and IL-8 changes between the two groups ($P = 0.000$ and $P = 0.006$, respectively; Table 4).

Factors Influencing the Effectiveness of LSB

The response to the IT and baseline foot skin temperature were shown to be predictors of sympathetic block success in the univariate logistic regression analyses ($p < 0.2$, Table S1). Together with the baseline IL-8 concentration,

Table 1 Demographic Characteristics

Number of Patients	All (n = 43)	Men (n = 13)	Women (n = 30)	P
Age (years)	47.44 $\pm$ 13.43	42.62 $\pm$ 14.43	49.53 $\pm$ 12.65	0.122
BMI (kg/m ²)	20.61 $\pm$ 2.70	21.47 $\pm$ 2.94	20.24 $\pm$ 2.56	0.175
Duration (months)	9.53 $\pm$ 5.00	12.69 $\pm$ 5.47	8.17 $\pm$ 4.14	0.015*
Base temperature (°C)	35.21 $\pm$ 0.47	35.21 $\pm$ 0.44	35.21 $\pm$ 0.49	0.989
IT-/IT+	24/19	8/5	16/14	0.619
NRS base score	7.00 (2.00)	7.00 (3.00)	6.50 (2.00)	0.280
TNF- α base level (pg/mL)	13.60 (21.90)	20.0 (27.95)	11.80 (14.05)	0.240
IL-1 β base level (pg/mL)	9.10 (8.80)	8.90 (14.80)	9.17 (7.97)	0.970
IL-8 base level (pg/mL)	27.46 (54.50)	144.17 (254.50)	25.45 (31.06)	0.340

Notes: * $P<0.05$, women vs men.

Table 2 Demographics for Patients Undergoing the Tourniquet IT

	IT- (n = 24)	IT+ (n = 19)	P
Age (years)	43.60 ± 13.56	52.32 ± 11.88	0.032*
Sex (female/male)	16/9	14/4	0.619
BMI (kg/m ²)	20.90 ± 2.81	20.25 ± 2.59	0.443
Duration (months)	8.96 ± 4.80	10.26 ± 5.24	0.400
Base temperature (°C)	35.39 ± 0.38	34.98 ± 0.49	0.004*
NRS base score	6.00 (1.00)	7.00 (2.00)	0.060
TNF- α base level (pg/mL)	14.40 (20.40)	12.40 (28.40)	0.720
IL-1 β base level (pg/mL)	9.00 (15.73)	9.10 (4.10)	0.830
IL-8 base level (pg/mL)	22.95 (41.80)	34.60 (218.60)	0.060

Notes: *P<0.05, IT(+) vs IT(-).

Table 3 Budapest Criteria (Symptoms) for CRPS Patients with Different Tourniquet IT Results

	IT- (n = 24)	IT+ (n = 19)	P
Sensory	22(91.7%)	18(94.7%)	1.000
Vasomotor	16 (66.7%)	15(78.9%)	0.373
Sudomotor/edema	14(58.3%)	17(89.5%)	0.024*
Motor/trophic	13 (54.1%)	8(42.1%)	0.432

Notes: *P<0.05, IT(+) vs IT(-).

these three factors were included in the multivariate binary logistic regression analysis; the results revealed that the response to the IT was the only significant independent predictor of sympathetic block success ($p = 0.007$, OR: 0.043, 95% CI: 0.004–0.429, Table 5).

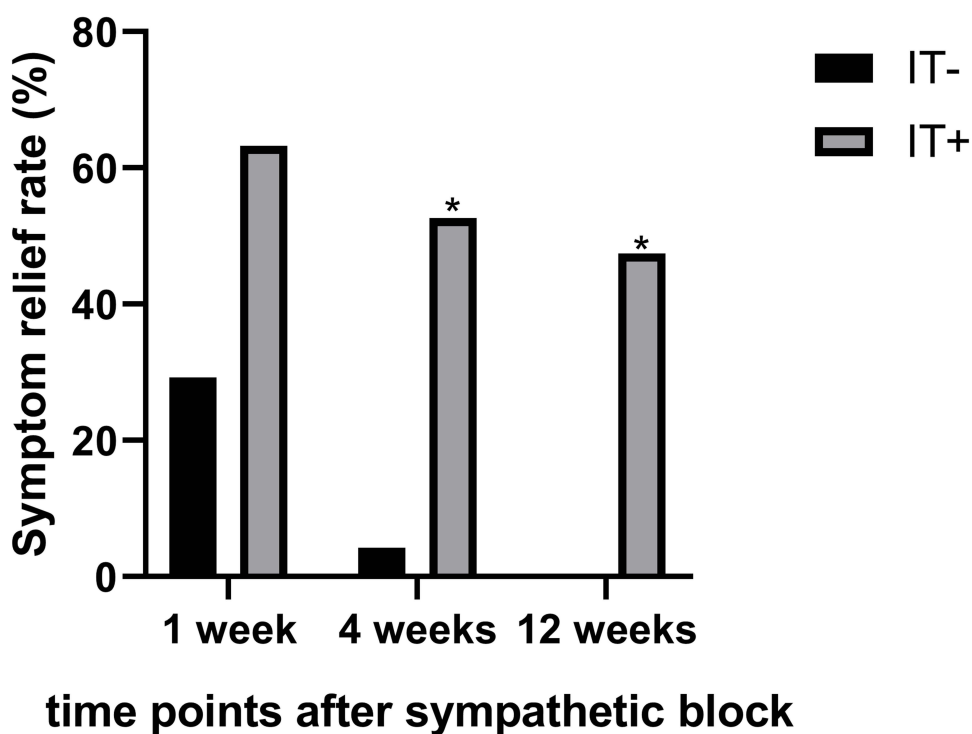
**Figure 4** Illustration of clinical success rates at different time points after the injection. IT-: IT(-) group, IT+: IT(+) group. * P<0.05, compared with IT(-) group.

Table 4 Clinical Effects in CRPS Patients with Different Tourniquet IT Results

	IT- (n = 24)	IT+ (n = 19)	P
Positive/negative	1/23	10/9	0.001*
Change in NRS score	2.00 (2.00)	3.00 (1.00)	0.000*
Change in TNF- α level	4.20 (6.50)	8.30 (24.10)	0.094
Change in IL-1 β level	4.25 (6.85)	5.70 (5.10)	0.159
Change in IL-8 level	10.15 (21.70)	20.00 (176.80)	0.006*

Notes: *P<0.05, IT(+) vs IT(-).

Table 5 Multivariate Logistic Regression Analysis of Independent Predictors of Sympathetic Block

Variables	β value	OR	95% CI	P
IT test result	-3.14	0.043	0.004–0.429	0.007*
Base temperature	-0.276	0.759	0.126–4.564	0.763
IL-8 base level	0.002	1.002	0.920–1.092	0.955

Notes: *P<0.2, OR=odds ratio; 95% CI =95% confidence intervals.

Discussion

The development and progression of CRPS can be caused by a variety of mechanisms.¹⁵ Trauma is now thought to be linked to the activation of the immune system and the production of a series of inflammatory cytokines.¹⁶ Chronic pain and neurogenic inflammation emerge from the ongoing disturbance of nervous system-related inflammatory processes induced by the generation of a large number of inflammatory cytokines, which contributes to the clinical symptoms of acute CRPS.^{9,16,17}

A tourniquet IT is a simple procedure that can be performed in an outpatient clinic, is quick and inexpensive, and causes little harm to health. Clinically, deep and diffuse distal pain in CRPS patients indicated microcirculation abnormalities. Although the mechanism of IT(+) is not clear, changes in microcirculation are involved and may be related to sympathetic dysfunction. In our study, the lower extremity tourniquet IT result was used to separate the patients into two groups: IT(+) and IT(-) groups. In both groups, age, sex, BMI, disease duration, baseline foot skin temperature, baseline NRS scores, and baseline peripheral blood cytokine levels (IL-1, IL-8, and TNF- α) were analyzed. The baseline skin temperature of the affected foot in the IT(-) group was substantially higher than that in the IT(+) group (Table 2). According to Bruehl,¹⁸ the potential mechanism of CRPS may vary among individuals and even between stages of CRPS across time, particularly during the transition from the acute stage of “warm CRPS” to the chronic stage of “cold CRPS”. In theory, sympathetic nerve system (SNS) activity is diminished in early CRPS, and the consequent excessive vasodilation causes acute-stage CRPS, which is typically associated with warm and red limbs. However, many patients in our study had “cold CRPS” from the beginning of their symptoms, which is similarly as previous study.¹⁹ It is not clear whether the internal explanation is linked to the tourniquet IT results. We investigated whether a patient’s baseline foot skin temperature could predict the outcome of sympathetic block treatment. According to the study, there are no differences in the cytokine levels between individuals with cold CRPS, intermediate CRPS, and warm CRPS.²⁰ Thus, we believe that the difference in baseline foot skin temperature between the two groups seemed to have no impact on cytokine alterations. It is also worth mentioning that, according to the Budapest criteria, sweating/edema, a CRPS symptom, was more prevalent in the IT (+) group. No significant difference was observed in the subjective category of the other symptoms (Table 3).

The overall effective symptom relief rate at the fourth week in our study of LSB for unilateral lower limb CRPS-I was 25.6% (11/43), with 52.6% (10/19) of IT(+) patients having an effective symptom relief rate of more than 50%, while that of IT(-) patients was only 4.2% (1/24) (Table 4). These results disprove the prevalent notion that LSB has a low effective pain reduction rate in treating CRPS.^{21,22} Simultaneously, our research revealed that an IT(+) result predicted a good response to LSB in CRPS-I patients. This is the first time that the response to a tourniquet IT was used as a novel predictor of prognosis in patients with lower extremity CRPS-I utilizing LSB, although all CRPS-I patients

had the condition for less than 24 months in this study. According to the majority of previous studies, only approximately one-third of CRPS-1 patients have a short alleviation of pain symptoms after a sympathetic block.²³ The effective symptom relief rate in the CRPS-1 patients with IT(+) results in our study was over 50% at 4 weeks after LSB treatment, and 47.4% of them sustained the pain alleviation lasting for 12 weeks (Figure 4), which is much higher and longer than that reported in other studies.^{21,24,25} These findings demonstrate that treating CRPS-1 patients who respond to LSB improves treatment accuracy while preventing unnecessary procedures for unresponsive CRPS-1 patients and saving societal medical resources. Furthermore, the analysis revealed that CRPS-1 patients can achieve a satisfactory analgesic effect for a long period of time and endure physical rehabilitation therapies.

The fact that the sympathetic block may not be successful in all cases of CRPS suggests that the link between the sympathetic nervous system and pain in CRPS is complex.²⁴ Considering much evidence showing that inflammation and sympathetic dysfunction play a role in the pathogenesis and clinical symptoms of CRPS,^{18,26} it is critical to determine what parameters may be used in patients who respond well to sympathetic block. According to the findings from our study, the levels of several peripheral blood proinflammatory cytokines, including IL-1 β , IL-8, and TNF- α , were significantly higher in patients with CRPS than in normal healthy persons before intervention. This conclusion is comparable to that from Schinkel et al,²⁷ who found that IL-8 (but not IL-6) levels were significantly higher in the peripheral blood of CRPS patients. We included these cytokines in the posttreatment observation period to examine whether changes in the levels of these cytokines could predict the success of the intervention therapy. We found that the baseline values of these three cytokines were not significantly different between the CRPS patients with IT(+) results and those with IT(-) results, indicating that the inflammatory response to CRPS was similar in both groups (Table 2). While the changes in the IL-8 level differed significantly between the two groups (Table 4), the baseline IL-8 level was found to be an independent predictor of successful sympathetic block in the univariate logistic regression analysis (supplementary Table 1). However, multivariate regression analysis was also performed. After the mixed factors were removed, the baseline level of IL-8 no longer had a predictive effect (Table 5). Although previous studies²⁸ identified high levels of IL-8 and TNF- α receptors in the peripheral blood during the acute phase of CRPS, it is still uncertain whether the enhanced inflammatory response is a key factor in disease progression. Our findings suggest that these cytokine alterations are unable to predict whether LSB will be successful.

Blumberg et al¹² designed the tourniquet IT, which became the prototype. Specifically, the cuff is fixed to the affected limb and compressed during the systolic period to interrupt distal circulation and examine whether it affects pain. In most cases, there is significant pain inhibition immediately after the cuff is applied. According to Johann Lambeck et al,¹³ who retrospectively analyzed the clinical significance of the tourniquet IT that was routinely used in individuals with suspected CRPS, the test had a low sensitivity (49.8%). It has not been reported whether the response to the tourniquet IT can predict the efficacy of sympathetic block in patients with CRPS. In our study, we screened out three potential predictors after the univariate logistic regression analysis and then included the potential predictors in the multivariate binary logistic regression analysis. Ultimately, the only factor that remained a significant predictor of successful sympathetic block was the response to the tourniquet IT.

Conclusion

Patients with lower extremity CRPS-1 may benefit from LSB. The tourniquet IT response of patients with lower extremity CRPS-1 may be a reliable predictor of LSB effectiveness. We suggest that the tourniquet IT is an effective, safe, and quick prediction tool for determining if LSB will be effective for lower extremity CRPS-1.

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Disclosure

All authors report no conflicts of interest in this work.

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