ANESTHESIOLOGY

Outcomes of Sympathetic Blocks in the Management of Complex Regional Pain Syndrome

A Retrospective Cohort Study

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ABSTRACT

Background: Sympathetic dysfunction may be present in complex regional pain syndrome, and sympathetic blocks are routinely performed in practice. To investigate the therapeutic and predictive values of sympathetic blocks, the authors test the hypotheses that sympathetic blocks provide analgesic effects that may be associated with the temperature differences between the two extremities before and after the blocks and that the effects of sympathetic blocks may predict the success (defined as achieving more than 50% pain reduction) of spinal cord stimulation trials.

Methods: The authors performed a retrospective study of 318 patients who underwent sympathetic blocks in a major academic center (2009 to 2016) to assess the association between pain reduction and preprocedure temperature difference between the involved and contralateral limbs. The primary outcome was pain improvement by more than 50%, and the secondary outcome was duration of more than 50% pain reduction per patient report. The authors assessed the association between pain reduction and the success rate of spinal cord stimulation trials.

Results: Among the 318 patients, 255 were diagnosed with complex regional pain syndrome and others with various sympathetically related disorders. Successful pain reduction (more than 50%) was observed in 155 patients with complex regional pain syndrome (155 of 255, 61%). The majority of patients (132 of 155, 85%) experienced more than 50% pain relief for 1 to 4 weeks or longer. The degree and duration of pain relief were not associated with preprocedure temperature parameters with estimated odds ratio of 1.03 (97.5% CI, 0.95–1.11) or 1.01 (97.5% CI, 0.96–1.06) for one degree decrease ($P = 0.459$ or 0.809). There was no difference in the success rate of spinal cord stimulation trials between patients with or without more than 50% pain relief after sympathetic blocks (35 of 40, 88% *vs.* 26 of 29, 90%, $P > 0.990$).

Conclusions: The authors conclude that sympathetic blocks may be therapeutic in patients with complex regional pain syndrome regardless of preprocedure limb temperatures. The effects of sympathetic blocks do not predict the success of spinal cord stimulation.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Sympathetic blocks are used in the diagnosis and treatment planning of patients with complex regional pain syndrome
- It is unclear whether the response to sympathetic blocks is associated with spinal cord stimulation trial success

What This Article Tells Us That Is New

- In patients with complex regional pain syndrome, skin temperature change is not associated with sympathetic block pain reduction
- The short- and long-term effects of sympathetic blocks are not associated with spinal cord stimulation outcomes

Complex regional pain syndrome is mechanistically complex and clinically challenging. Disturbance of the sympathetic nervous system is a distinct mechanism for the manifestations observed in this syndrome.[1–5] Sympathetic blocks have been a well-accepted component of clinical management for patients with complex regional pain syndrome.[4,6–11] However, there is limited evidence regarding the analgesic effects of sympathetic blocks in the short and long terms.[12,13] Two very small, randomized, crossover studies showed modest benefits 2 days after a local anesthetic sympathetic block. However, benefits of sympathetic block over weeks or months have not been evaluated in randomized, controlled trials. The effectiveness of sympathetic block is reported to be less than 50% in a few small-sample studies, and the duration of its therapeutic effects is limited.[7,11,14] A case series of 25 subjects who had three stellate ganglion blocks at weekly intervals for upper extremity complex regional pain syndrome reported that 40% of the

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patients had complete pain relief, 36% had partial pain relief, and 24% had no pain relief over a 6-month observation period.[11] It appears that sympathetic block is most effective in decreasing allodynia.[6] Better patient selection for this procedure may help increase its cost-effectiveness by reducing the number of ineffective blocks based on prognostic factors.

Predictors of outcomes of sympathetic blocks have been evaluated in few prospective non-controlled open label trials.[6,7] One study of 49 patients found that the presence of allodynia was a negative predictor of desired outcomes,[7] whereas a second study of 20 patients indicated that the presence of anxiety and active litigation was associated with poor outcomes of the procedure.[6] There has been considerable interest in using baseline temperature and change of temperature after sympathetic block as predictors of clinical outcomes given that sympathetic block is mostly proposed to be effective for cold complex regional pain syndrome.[7,15,16] The predictive value of these parameters was investigated in a small-sample-size study, but no association was found between these parameters and clinical outcomes after sympathetic blocks, which seemed to contradict conventional wisdom.[7] Another important matter focuses on the predictive value of sympathetic blocks and other clinical parameters in the selection of patients for spinal cord stimulation,[17,18] which is an option for long-term effective management of complex regional pain syndrome. A study of 23 patients evaluated the predictive value of sympathetic block for the success of spinal cord stimulation and suggested that patients with a good response to sympathetic block before spinal cord stimulation are more likely to have a positive response during their spinal cord stimulation trial and long-term pain relief after placement of permanent spinal cord stimulation device.[17] These observations are clinically relevant and deserve further investigation with larger sample sizes.

We hypothesized that sympathetic blocks provide analgesic effects that may be predicted by the temperature differences between the two extremities before and after the blocks in patients with complex regional pain syndrome. We further hypothesized that the responses to sympathetic blocks may predict the success or failure of spinal cord stimulation trials in patients with complex regional pain syndrome. We tested these hypotheses in this retrospective, single-center, observational study.

Materials and Methods

Study Design

This is a retrospective observational investigation specifically designed to test our hypotheses. The study hypotheses, outcomes measures, and protocols were registered, recorded, and approved by the Research Advisory Committee of the Anesthesiology Institute of Cleveland Clinic, Cleveland, Ohio. Statistical analysis was planned before data collection as part of the requirements in the approval process by the Research Advisory Committee. The Institutional Review Board of Cleveland Clinic, Cleveland, Ohio, which granted exception for requiring written informed consent, further approved the research protocol. Our study was designed to achieve three aims. First, we evaluated the analgesic effects of sympathetic blocks for complex regional pain syndrome and other chronic pain conditions. Second, we analyzed the association between pain reduction after the block and the preprocedure temperature parameters of the two extremities. Third, we examined the predictive value of sympathetic block in the selection of patients for spinal cord stimulation.

Setting

This investigation was conducted in the Cleveland Clinic main campus location of the Cleveland Clinic Pain Management Department, a major academic center in the United States. Data of patients who underwent sympathetic blocks in routine clinical care between January 1, 2009 and January 1, 2016 were extracted from the electronic medical records in the Epic system of the Cleveland Clinic by our research and clinical fellows in the Anesthesiology Institute. The blocks were performed by 10 experienced attending physicians in the department. Patients' responses to the blocks were evaluated and documented in their follow-up visits, with durations ranging from 10 months to 8 yr as part of their routine care. Two statisticians in our institute worked together with the rest of the research team to perform the statistical analysis.

Patients

We identified all patients (647) with sympathetic blocks using billing codes (CPT 64510, 64520) and diagnosis codes (ICD-10 CM, G90.511, G90.512, G90.513, G90.522, G90.523; ICD-9CM 337.21; ICD-9CM 337.22) in our Epic system between January 1, 2009 and January 1, 2016 through computer algorithms per informatics personnel in our institute. We reviewed and extracted data from the electronic medical records of all patients who underwent sympathetic blocks (lumbar sympathetic block, stellate ganglion block, and thoracic sympathetic block) primarily for care of complex regional pain syndrome.

Diagnosis of Complex Regional Pain Syndrome Types I and II

The diagnoses were established according to the Budapest criteria and documented in Epic.[19] In our practice, we used a template in Epic containing the Budapest criteria for patient care, teaching, and research purposes. This practice helps minimize variability in patient care and ensure proper documentation in all patient encounters with rare exceptions. The symptoms were assessed by history taking, and the signs were objectively measured and observed by the attending physicians (see Supplemental Digital Content for details, http://links.lww.com/ALN/C20).

Exclusion Criteria

We excluded patients who had bilateral procedures, unsuccessful blocks defined as postprocedure temperature rise less than 1.5°C or missing temperature recording after the procedure, and insufficient data about temperature measurement or postprocedure pain follow-up pain scores (fig. 1).

We extracted data regarding age and sex; laterality of the procedure; diagnosis for which the procedure was performed; spinal cord stimulator trial or implant; comorbid conditions including fibromyalgia, diabetes mellitus, body mass index greater than 35, depression or anxiety, and other chronic pain conditions. All the chronic comorbid conditions were diagnosed with accepted definitions and criteria by respective specialists in the Cleveland Clinic and documented in their electronic medical records.

Data were tabulated manually by three clinical and research fellows who were not blinded to the clinical outcomes. Our main outcome measures were documented as *percent pain relief* and *duration of pain relief*. Other parameters, such as temperature, were direct and objective measurements. All parameters were extracted directly from the medical records and none required subjective rating by individual investigators. Data extraction for each patient was performed only once. However, at the beginning of the data collection process, two investigators extracted data from the same first five patients. We compared the extracted data by the two investigators and did not find any substantial interrater variability.

Our exposures of interest were (1) preprocedure temperature of the involved extremity and (2) difference in preprocedure temperature between the two extremities, defined as involved extremity preprocedure temperature minus contralateral extremity preprocedure temperature. The pain scores were derived from a numerical rating scale of 0 to 10, assessed at baseline immediately before the block, at 30 min after the block, and subsequent follow-up visits or phone encounters and documented in electronic health records. The question was: "On a scale of 0 to 10, 0 being no pain and 10 being the worst pain you can imagine, what is your pain score now?"

Our primary outcome was improvement of pain by at least 50%, as reported by the patient during follow-up visits or phone encounters. Our secondary outcome was duration of satisfactory pain control defined by more than 50% reduction in pain intensity for periods of less than 1 week (1 to 7 days), 1 to 4 weeks (8 to 30 days), 1 to 3 months (31 to 90 days), 3 to 6 months (91 to 180 days), and more than 6 months (more than 180 days). We then assessed the relationship between the exposures and outcomes in patients with or without complex regional pain syndrome. Finally, we assessed whether pain improvement after sympathetic blocks was associated with an increased success rate of spinal cord stimulation trials measured by the ratio of spinal cord stimulation implant-to-trial (number of patients who had an implant after a successful trial over the total number of patients who underwent spinal cord stimulation trials). Successful spinal cord stimulation trial is defined as patient reported more than 50% pain reduction and functional improvement in the spinal cord stimulation trial period (typically 7 to 14 days) and an implant was subsequently performed based on a decision made collaboratively between the patient and the attending physician and his or her team.

Sympathetic Block Procedures

All procedures were performed by a team consisting of a pain medicine fellow in training and an experienced academic

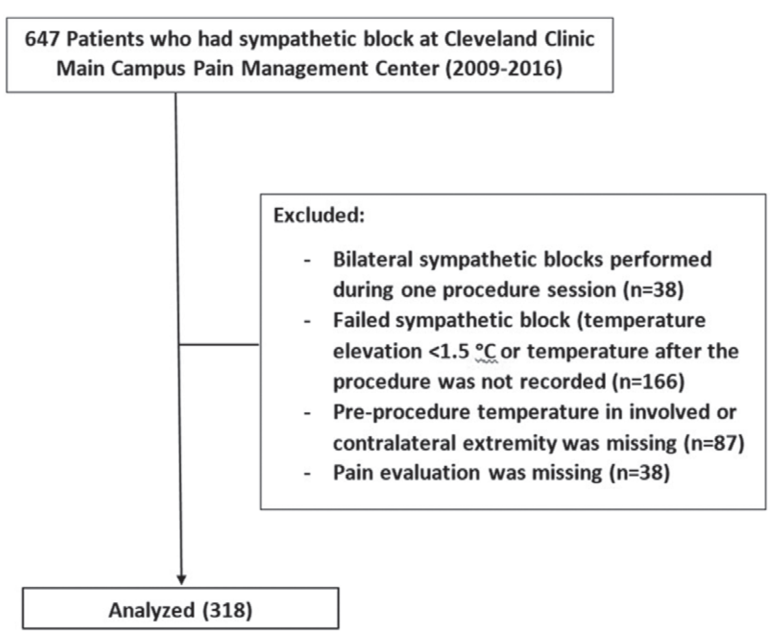

Fig. 1. Flow chart of patient inclusion.

attending physician under fluoroscopic guidance or ultrasound guidance (in some cases of stellate ganglion block). A total of 10 seasoned attending physicians were responsible for patient selection and supervision or execution of the procedure. All procedures were performed under fluoroscopic guidance and under sterile conditions. A 22g or 25g spinal need with a 15 degree curve for spinal anesthesia was used. The injectate included 5 ml to 20 ml of 1% lidocaine or 0.25% bupivacaine depending on the types of sympathetic blocks and at the attending physicians' discretion. Triamcinolone of 40 mg or dexamethasone 10 mg was commonly used unless it was contraindicated. Lumbar sympathetic block was typically performed at the waist of the lumbar 3 vertebral body level. Stellate ganglion block was performed at the vertebral level C6–C7 using the anterior paratracheal approach.[20] Thoracic sympathetic block was performed at the T2–T3 level.

Sympathetic blocks were considered correctly performed when there was radioscopically confirmed craniocaudal contrast dye outline over the prevertebral sympathetic chain at the C6–T1 level for stellate ganglion blocks, T1–T3 for the thoracic sympathetic blocks, and L2–L4 for lumbar sympathetic blocks. Injection was given only after radiologic confirmation of satisfactory contrast spread. An increase of more than 1.5°C from baseline indicated that the block was successful.[21]

Skin temperature was measured in degrees Celsius (°C) using a LS-1400D Dual Display Temperature Monitor with skin Temperature Sensor 400 Series (NovaMed, Elmsford, NY, USA) for continuous, noninvasive measurement to reflect any temperature change. Measurements were made at the affected and contralateral extremities. The plantar aspects of the feet or hands were assessed at standardized points (thumbs for stellate ganglion blocks and upper thoracic sympathetic blocks or big toes for lumbar sympathetic blocks). Temperature measurements were performed at the outpatient clinic. They were monitored continuously and measurements were taken and recorded at baseline before the sympathetic block and 30 min after the block. This allowed us to measure the relative increase in skin temperature as a measure of completeness of the sympathetic block.[22]

Statistical Analysis

Patient characteristics were summarized using number (percentage) for categorical variables, mean ± SD for normally distributed continuous variables, and median [Q1, Q3] for nonnormally distributed continuous variables.

For this observational study, patients with missing preprocedure temperature (exposure) or postprocedure pain evaluation (outcome) data in their records either attributable to missing follow-up information or to incomplete documentation were excluded from statistical analysis, because these conditions preclude them from any meaningful analysis (fig. 1). The decision on exclusion of patients with missing data from the analysis was preplanned.

Primary Analysis. We assessed the association between successful pain reduction after sympathetic block procedure (*i.e.*, more than 50%) and (1) preprocedure temperature of the involved extremity as well as (2) preprocedure temperature difference between the involved and the contralateral extremities, each using a multivariable logistic regression. We adjusted for age, sex, body mass index, type of procedure, laterality of procedure, diagnosis, fibromyalgia, diabetes, depression, and other chronic pain conditions. The Hosmer–Lemeshow test was used to assess the goodness of fit. In addition, we performed a sensitivity analysis in which we assessed the pain reduction as an ordinal outcome (*i.e.*, less than 25%, 25 to 50%, 50 to 75%, and more than 75%) using a proportional odds logistic regression model. This model takes into account the ordinal nature of the response variable (*i.e.*, more than 75% better than 50 to 75% better, than 25 to 50% better, than less than 25%). The resulting odds ratio estimates the relative odds of achieving a better pain reduction category. Bonferroni correction was used to adjust for multiple primary analyses; 97.5% CIs were reported and the significance criterion for the two primary analyses was $P < 0.025$ (*i.e.*, 0.05/2). Two-tailed testing was used. Although the duration of more than 50% pain relief varied widely between individual patients, none of them were considered outliers because this variability has been a known fact in clinical practice.

Secondary Analysis. We assessed whether the association between successful pain reduction and preprocedure temperature of the involved extremity as well as preprocedure temperature difference between the involved and the contralateral extremities depended on a diagnosis of complex regional pain syndrome in an analogous logistic model with an exposure-by-diagnosis interaction test. Interactions were considered significant if $P < 0.10$. For informational purposes, we reported the associations separately for patients undergoing sympathetic blocks with and without complex regional pain syndrome regardless of the significance of the exposure-by-diagnosis interaction. Finally, we assessed the association between duration of satisfactory pain control (more than 50% pain reduction) and (1) preprocedure temperature of the involved extremity as well as (2) preprocedure temperature difference between the involved and the contralateral extremity, each using a proportional odds logistic regression model to account for the ordinal nature of the outcome (*i.e.*, less than 1 week, 1 to 4 weeks, 1 to 3 months, and 3 to 6 months). The significance criterion for the two secondary analyses was $P < 0.025$ (*i.e.*, 0.05/2, Bonferroni correction).

Assessment of Assumptions. For each multivariable model, the variance inflation factor was used to assess multicollinearity among these predictors, with a cutoff point of less than 5 indicating multicollinearity. For all ordinal regressions, we used the likelihood-ratio test to check the proportional odds assumption. The test may be overly sensitive with large sample sizes, large predictors, or continuous predictors. Therefore, if the likelihood-ratio test was significant, we also examined the model using a set of separate binary logistic regressions to assess homogeneity of the estimated odds ratios across levels of the response variable (*i.e.*, dichotomizing the ordinal outcome to binary outcomes: more than 75% *vs.* three categories less than or equal to 75%, two categories more than 50% *vs.* two categories less than or equal to 50%, and three categories more than 25% *vs.* less than or equal to 25%).

Fisher exact tests were used to test differences in success rate of spinal cord stimulation trial between groups of patients with or without more than 50% pain reduction after sympathetic blocks. A successful trial was defined in patients as having more than 50% pain reduction, improved functionality, reduced analgesic requirement, and subsequently received spinal cord stimulation implant. These tests were performed for those who had spinal cord stimulation trials after sympathetic blocks and those who had spinal cord stimulation trials before sympathetic blocks.

Sample Size Considerations. We used data from all available patients who met our inclusion–exclusion criterion (a total of 318). We had an estimated 90% power to detect an odds ratio of 1.10 or more for one unit (°C) increase in preprocedure temperature of the involved extremity at the overall 0.05 significance level, assuming a mean temperature of 24°C with a SD of 4 and a 60% incidence of successful pain reduction (*i.e.*, more than 50%). SAS software version 9.4 (SAS Institute, USA) was used for all statistical analysis.

Results

We excluded patients who had bilateral procedures (38 of 647), unsuccessful blocks defined as postprocedure temperature rise less than 1.5°C or missing temperature recording after the procedure (166 of 647), and insufficient data about temperature measurement (87 of 647) or postprocedure pain follow-up pain scores (38 of 647; fig. 1). Data from a total of 318 patients were used and analyzed. Among the 318 patients, 26% were male with an average age of 43 yr (SD = 15 yr). Most patients were diagnosed with complex regional pain syndrome (255 of 318, 80%). An overwhelming majority of sympathetic blocks were lumbar sympathetic blocks (83%; table 1). A total of 185 patients (58%) had successful pain reduction (more than 50%) after the procedure, 155 of which (84%) were patients with complex regional pain syndrome (fig. 2). Among the patients with complex regional pain syndrome, the duration of more than 50% pain relief was fewer than 7 days in 23 patients (15%), 1 to 4 weeks in 110 patients (71%), 1 to 3 months in 14 patients (9%), and 3 to 6 months in 8 patients (5%).

We did not find a statistically significant association between preprocedure temperature in the involved extremity and successful pain reduction (table 2 and fig. 3A). The estimated odds ratio of having a successful pain reduction was 1.03 (97.5% CI, 0.95–1.11) for a one-degree decrease in the preprocedure temperature in the involved extremity, after adjusting for potential confounding factors ($P = 0.459$). Hosmer–Lemeshow test indicated no evidence of poor fit ($P = 0.787$), meaning that the observed data agree reasonably well with what the model predicts (*i.e.*, with the expected values from the model).

Table 1. Patient Characteristics

Variable	All Patients (N = 318)	Successful Pain (More Than 50%) Reduction (N = 185)	Unsuccessful Pain Reduction (N = 133)
Age, yr	43 ± 15	43 ± 14	41 ± 16
Sex (male), n (%)	82 (26%)	43 (23%)	39 (29%)
Fibromyalgia, n (%)	17 (5%)	12 (6%)	5 (4%)
Diabetes, n (%)	33 (10%)	20 (11%)	13 (10%)
Body mass index > 35 kg/m^2, n (%)	64 (20%)	36 (19%)	28 (21%)
Depression, n (%)	64 (20%)	42 (23%)	22 (17%)
Chronic pain, n (%)	174 (55%)	108 (58%)	66 (50%)
Procedures			
Lumbar sympathetic block	265 (83%)	148 (80%)	117 (88%)
Stellate ganglion block	52 (16%)	36 (19%)	16 (12%)
Thoracic sympathetic block	1 (0.3%)	1 (0.5%)	0 (0%)
Diagnosis, n (%)			
Complex regional pain syndrome	255 (80%)	155 (84%)	100 (75%)
Peripheral neuropathy	47 (15%)	19 (10%)	28 (21%)
Unhealing ulcer	7 (2%)	5 (2.7%)	2 (1.5%)
Ischemic pain	5 (2%)	3 (1.6%)	2 (1.5%)
Others (diabetes 3, hyperhidrosis 1)	4 (1%)	3 (1.6%)	1 (0.8%)
Lumbar sympathetic block (*vs.* others), n (%)	265 (83%)	148 (80%)	117 (88%)
Procedure side (right), n (%)	151 (47%)	91 (49%)	60 (45%)
Preprocedure pain score (0 to 10)	7 [6, 8]*	7 [5, 8]†	8 [6, 9]‡
Preprocedure temperature in involved extremity (°C)	23.0 [21.4, 25.4]	23.0 [21.2, 25.9]	22.8 [21.7, 25.0]
Preprocedure temperature difference between involved and contralateral extremity (°C)	0 [−0.6, 0.5]	0 [−0.6, 0.5]	0 [−0.4, 0.5]
Postprocedure temperature elevation (°C)	9.6 [6.0, 11.7]	10.0 [6.1, 12.0]	9.3 [5.5, 11.1]

Summary statistics are presented as number (%) of patients, mean ± SD, or median [Q1, Q3], respectively.

*,†,‡ represent 10, 6, and 4 missing points.

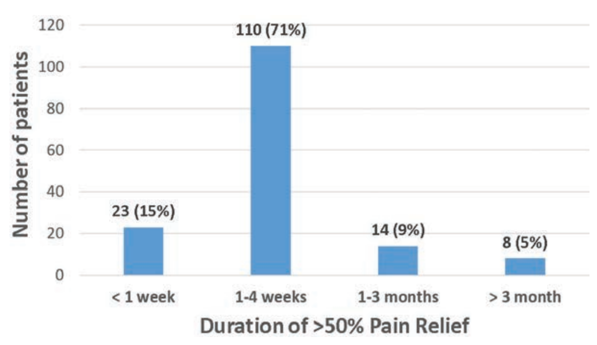

Fig. 2. Analgesic outcomes of sympathetic blocks in patients with complex regional pain syndrome.

Our sensitivity analyses, in which we assessed the pain reduction as an ordinal outcome (*i.e.*, less than 25%, 25 to 50%, 50 to 75%, and more than 75%), produced consistent results: the estimated odds ratio of having a better pain reduction (*i.e.*, more than 75% *vs*. three categories less than or equal to 75%, two categories more than 50% *vs*. two categories less than or equal to 50% and *etc*.) was 1.02 (0.97, 1.07) for a one-degree decrease in the preprocedure temperature in the involved extremity (P = 0.404). However, the proportional odds assumption of the ordinal regression was statistically violated (P < 0.001), suggesting that the relationship between exposure and outcome might not be consistent over the outcome categories. Nevertheless, inspection of the odds ratios from the separate binary logistic regressions (see Materials and Methods, Statistical Analysis section) showed that the ordinal proportional odds model was indeed reasonable, with odds ratios of 1.02 (0.92–1.12), 1.03 (0.94–1.13), 1.05 (0.95–1.15) for modeling the binary outcome of more than 75% *versus* less than or equal to 75%, more than 50% *versus* less than or equal to 50%, and more than 25% *versus* less than or equal to 25%, respectively.

Furthermore, the association between temperature and successful pain reduction was not different between patients diagnosed with and without complex regional pain syndrome (temperature-by-diagnosis interaction P = 0.770, table 2).

Similarly, preprocedure temperature difference between the involved and contralateral extremities was not associated with successful pain reduction (table 2 and fig. 3B). The estimated odds ratio of having successful pain reduction was 1.05 (97.5% CI, 0.93–1.19) for a one-degree decrease in the difference between involved and contralateral extremity, after adjusting for potential confounding factors (P = 0.417). Hosmer–Lemeshow test indicated no evidence of poor fit (P = 0.715). Our sensitivity analyses assessing pain reduction as an ordinal outcome (*i.e.*, less than 25%, 25 to 50%, 50 to 75%, and more than 75%) yielded consistent results: the estimated odds ratio of having a better pain reduction was 1.03 (0.95–1.11) for a one-degree decrease in the difference between extremities (P = 0.428). The proportional odds assumption of the ordinal regression was statistically violated (P < 0.001). From the separate binary logistic regressions, inspection of the separate odds ratios showed the ordinal proportional odds model was reasonable, with odds ratio of 1.05 (0.90–1.23), 1.05 (0.91–1.21), 1.05 (0.90–1.22) for modeling the binary outcome of more than 75% *versus* less than or equal to 75%, more than 50%

Table 2. Primary and Secondary Analyses

Exposure of Interest – Preprocedure Temperature	Estimated Odds Ratio* (97.5% CI)	*P* Value
Primary outcome – Successful pain reduction (>50%; multivariable logistic regression)		
Preprocedure temperature in involved extremity (°C)	1.03 (0.95–1.11) per decrease of 1°C	0.459
Temperature-by-diagnosis types interaction†		0.773
Diagnosis with CRPS	1.02 (0.92–1.14) per decrease of 1°C	0.622
Diagnosis without CRPS	1.05 (0.85–1.29) per decrease of 1°C	0.565
Preprocedure temperature difference: involved – contralateral extremity (°C)	1.05 (0.93–1.19) per decrease of 1°C	0.417
Temperature difference-by-diagnosis types interaction†		0.959
Diagnosis with CRPS	1.05 (0.87–1.26) per decrease of 1°C	0.554
Diagnosis without CRPS	1.05 (0.79–1.40) per decrease of 1°C	0.646
Secondary outcome - Duration of pain reduction (proportional odd logistic regression model) (1 week, 1 to 4 weeks, 4 weeks to 3 months, 3 to 6 months, categories treated as ordinal)		
Preprocedure temperature in involved extremity (°C)	1.01 (0.96–1.06)‡§ per decrease of 1°C	0.809
Preprocedure temperature difference: involved – contralateral extremity (°C)	1.06 (0.97–1.15)‡‖ per decrease of 1°C	0.122

N = 318. CRPS indicates complex regional pain syndrome.

*We adjusted for age (a continuous variable), sex (male *vs.* female), body mass index (more than 35 *vs.* less than or equal to 35), type of procedure (Lumbar Sympathetic Block *vs.* others), laterality of procedure (left *vs.* right side), diagnosis (CRPS, peripheral neuropathy, ulcer, ischemic pain, others), fibromyalgia (yes *vs.* no), diabetes (yes *vs.* no), depression (yes *vs.* no), and other chronic pain condition (yes *vs.* no).

†When checking interactions between exposures and diagnosis types, the diagnosis types were aggregated into two categories (with CRPS or not).

‡The estimated odds ratio of having a longer duration of pain reduction (*i.e.*, 3 to 6 months *vs.* three categories ≤ 3 months, two categories more than 4 weeks *vs.* two categories ≤ 4 weeks, *etc.*).

§The likelihood-ratio test P = 0.660.

‖P = 0.887, indicated no evidence of violation of the proportional odds assumption.

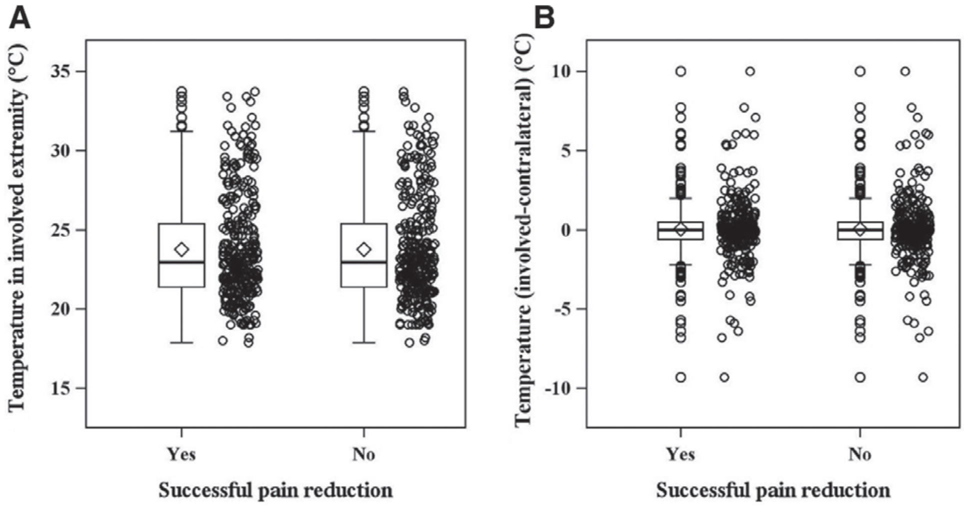

Fig. 3. Relationships between temperature parameters and effects of sympathetic blocks. Box plots and scatter plots of (*A*) preprocedure temperature in the involved extremity and (*B*) preprocedure temperature difference between the involved and contralateral extremity (involved limb temperature minus contralateral limb temperature) for patients who had successful (more than 50%) pain reduction after the procedure (n = 185) and patients who did not (n = 133). The first quartile, median, and third quartile comprise the boxes; the diamond symbol in the box represents the mean; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively; points outsides these whiskers are displayed individually.

versus less than or equal to 50%, and more than 25% *versus* less than or equal to 25% respectively.

In addition, no temperature-by-diagnosis interaction was found (P = 0.960), indicating the association between the temperature difference and successful pain reduction was not different between patients diagnosed with and without complex regional pain syndrome (table 2).

Among the 318 patients included in the analysis, 255 were diagnosed with complex regional pain syndrome. Successful pain reduction was observed in 155 patients with complex regional pain syndrome (155 of 255, 61%) as compared with 30 patients without complex regional pain syndrome (30 of 63, 48%). After adjusting for age, sex, body mass index, procedure type, fibromyalgia, diabetes mellitus, depression, and other chronic pain condition, the estimated odds ratio of having successful pain reduction was 1.89 times more likely (95% CI, 1.03–3.48) for patients with a diagnosis of complex regional pain syndrome *versus* patients without (P = 0.040). This was only marginally significant and would not be significant after Bonferroni correction.

The duration of pain reduction (*i.e.*, less than 1 week, 1 to 4 weeks, 4 weeks to 3 months, 3 to 6 months) was not associated with preprocedure temperature in the involved extremity or the difference between the involved and contralateral extremity. The proportional odds assumption was not violated in either model (*i.e.*, P = 0.660 and P = 0.887), indicating that a single odds ratio can be used to assess the relationship between the respective exposures and duration of pain reduction. The estimated odds ratio of having a longer duration of pain reduction (*i.e.*, 3 to 6 months *vs.* three categories less than or equal to 3 months, two categories more than 4 weeks *vs.* two categories less than or equal to 4 weeks, *etc.*) was 1.01 (0.96–1.06) for a one-degree decrease in the preprocedure temperature in the involved extremity (P = 0.809). The estimated odds ratio of having a longer duration of pain reduction was 1.06 (97.5% CI, 0.97–1.15) for a one-degree decrease in the difference (P = 0.122). For primary and secondary analyses, no multicollinearity among these predictors was found, with all variance inflation factor less than 2.

A total of 69 of the 255 patients with complex regional pain syndrome underwent spinal cord stimulation trial. Successful trials were achieved in 35 of 40 patients (87.5%) with more than 50% pain reduction after sympathetic blocks while successful trials were achieved in 26 of 29 patients (89.7%) with less than 50% pain reduction after sympathetic blocks. There was no difference in success rate of the spinal cord stimulation trial between the two groups (Fisher exact test, $P > 0.990$). Forty-nine patients received spinal cord stimulation trial after sympathetic blocks; 44 subsequently underwent implantation of spinal cord stimulation, resulting in an implant-to-trial ratio of 90%. The implant-to-trial ratio was 24 of 27 (89%) for patients who had more than 50% pain reduction and was 20 of 22 (91%) for patients who did not. There was no difference in success rate of the spinal cord stimulation trial between the two groups (Fisher exact test, $P > 0.990$). Twenty patients received a spinal cord stimulation trial before sympathetic blocks; 17 subsequently underwent implantation of a spinal cord stimulation system. The implant-to-trial ratio was 11 of 13 (85%) for patients who had more than 50% pain reduction and 6 of 7 (86%)

for patients who did not. There was no difference in success rate of the spinal cord stimulation trial between the two groups (Fisher exact test, $P > 0.990$).

Discussion

In this study of sympathetic nerve blocks for complex regional pain syndrome and other painful conditions, we found that 58% of this cohort of patients responded with more than 50% pain reduction. Among the patients with a diagnosis of complex regional pain syndrome, 61% responded with more than 50% pain reduction. The pain relief lasted 1 to 4 weeks in the large majority (71%) of patients with complex regional pain syndrome. There was an additional small population of patients (14%) who experienced significant pain relief for more than a month or 3 months after a single sympathetic block. These data help to bridge the gap related to the scarcity of published evidence to support or refute the use of sympathetic blocks for complex regional pain syndrome.[23] The more than 50% pain reduction rates of 58% to 61% in our study are slightly higher than the less than 50% response rates reported in other studies.[7,14]

Most of the previously published studies focused on short-term effects within hours or days.[14,24] Our investigation examined analgesic outcomes for durations up to 6 months and demonstrated that most patients (77%) with complex regional pain syndrome experienced therapeutic benefits for 1 to 4 weeks or longer. This range of duration of pain relief can be very meaningful for many patients, particularly those in the early phase of complex regional pain syndrome, by facilitating physical therapy and occupational therapy, maintaining range of motion, and improving daily activities. It is therefore an option, as well as a common clinical practice, for patients to periodically have repeat blocks to gain these benefits for longer pain relief.

The effects of sympathetic blocks may be mediated by several mechanisms. Dysfunction of the sympathetic nervous system in complex regional pain syndrome results in cool skin, increased sweating, and sympathetically-maintained pain. Although the norepinephrine level is lower in the complex regional pain syndrome–affected than the contralateral limb, sympathetic sprouting and upregulation of α-adrenoceptors may result in adrenergic supersensitivity.[25] Thus, blocking sympathetic nerves may reduce some of the sympathetically mediated symptoms of complex regional pain syndrome. In addition, complex regional pain syndrome is associated with signs of inflammation such as edema, increased skin temperature, skin color changes, and pain. It is accompanied by increased neurogenic inflammation, which depends mainly on calcitonin gene-related peptide, substance P, and proinflammatory cytokines.[26–30] The inflammatory processes and pain may be reduced by including a corticosteroid in the local anesthetic injectate, which by itself can be antiinflammatory,[31] in addition to its sodium channels blocking property.

It is critically important to identify parameters that can be used to identify the patient population who will respond favorably to sympathetic blocks. Our data has demonstrated the long term effects of sympathetic blockade (fig. 2) and the absence of relationships to preprocedure temperature (fig. 3A) or temperature difference between the involved and contralateral extremities (fig. 3B) in patients with complex regional pain syndrome (table 2). These results challenge the conventional notion that sympathetic blocks are mostly beneficial for patients with cold complex regional pain syndrome and suggest that these temperature parameters are not predictive of successful outcomes of the procedure. This is consistent with a previous report of a small sample of patients.[7] Furthermore, our results demonstrate that there was no association with duration of pain relief and temperature parameters. Thus, our results suggest that routine diagnostic skin temperature measurements cannot reliably predict degree or duration of pain relief for a subsequent sympathetic block.

Spinal cord stimulation is an option for long-term effective management of complex regional pain syndrome.[12,32–38] New advances have further improved the success rate, particularly with the introduction of dorsal root ganglion stimulation.[38,39] Previous studies have reported an association between response to sympathetic block and outcomes of spinal cord stimulation.[17] In our study, there were 49 patients with complex regional pain syndrome who underwent a spinal cord stimulation trial after sympathetic blocks, and there was no statistically significant difference in the likelihood of a successful trial in patients who responded to sympathetic blockade and those who did not. Additionally, there were 20 patients who had a spinal cord stimulation trial before sympathetic blocks, and there was no difference in the success rate of the spinal cord stimulation trials between patient groups with or without more than 50% pain reduction after sympathetic blocks. Contrary to a previous report,[17] we did not observe a relationship between response to sympathetic block and outcomes of spinal cord stimulation. Those who do not respond to sympathetic block may still be good candidates for spinal cord stimulation or dorsal root ganglion stimulation, but this must be further studied using prospective techniques.

There are a number of limitations of this study owing to its retrospective nature, such as the absence of a control group and data quality issues with nonblinding and missing data. Although statistical adjustments were made for a variety of variables, the results of this retrospective study could be clouded by unknown confounding factors. To minimize potential confounders, we excluded bilateral sympathetic blocks, failed sympathetic blocks, and patients with missing data in our analysis. The sympathetic blocks were mainly lumbar sympathetic blocks such that our conclusions are likely more relevant to complex regional pain syndrome in the lower extremity. In addition, there were substantial technical variations in performing the procedures, including selection of local anesthetics, volume of the injectate, and experience of operators (fellows *vs.* attending physicians), which may affect the outcomes of the blocks. Furthermore, the success of spinal cord stimulation was based on implant-to-trial ratio as a surrogate for spinal cord stimulation effect because of a lack of long-term follow-up data. These factors may have impacted the outcomes or conclusion but were not accounted for in the analyses. Even with all of these limitations, our data closely reflect the daily practice of pain medicine in large academic centers, thus the findings and conclusions from this study are applicable to real-world practice.

In conclusion, this study demonstrates that sympathetic blocks provided clinically significant pain reduction for 1 to 4 weeks or beyond in a majority of patients. There were no relationships between a patient's preprocedural extremity temperature and the degree or duration of pain relief after sympathetic blocks. In addition, the successful response to a sympathetic block was not associated with the success of spinal cord stimulation trials. These results suggest that the response to sympathetic blocks is independent of preprocedure temperature and that complex regional pain syndrome patients who fail to respond to sympathetic blocks may still have a successful spinal cord stimulation trial. Additional studies are warranted to further examine the factors that determine the degree and duration of pain relief after sympathetic block for the treatment of complex regional pain syndrome and other neuropathic pain conditions.

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Competing Interests

The authors declare no competing interests.

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Coupling Hoses then Coupling Pierrots with Pirouettes: William B. Kilbourne Peddles "Pain Stop" from Auburn, Maine

In 1877, William Bates Kilbourne (1850 to 1924) of Auburn, Maine, was granted United States Patent No. 189,941 for coupling threaded hoses. A dozen years later, Kilbourne's trade card advertised his namesake "Pain Stop" by coupling the image of a melancholic clown, the face-painted Pierrot, with the pirouetting Columbina (*upper image*). The clown was forever losing his love interest, Columbina, to the unpictured trickster, Harlequin. Although Kilbourne's panacea was "good for internal use in small doses, and excellent for external use," could even "Pain Stop" relieve Pierrot's pain? (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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