

# Predictors of Pain Relieving Response to Sympathetic Blockade in Complex Regional Pain Syndrome Type 1

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## ABSTRACT

**Background:** Sympathetic blockade with local anesthetics is used frequently in the management of complex regional pain syndrome type 1 (CRPS-1), with variable degrees of success in pain relief. The current study investigated which signs or symptoms of CRPS-1 could be predictive of outcome. The incidence of side effects and complications of sympathetic blockade also were determined prospectively.

**Methods:** A prospective observational study was done of 49 patients with CRPS-1 in one extremity only and for less than 1-yr duration who had severe pain and persistent functional impairment with no response to standard treatment with medication and physical therapy.

**Results:** Fifteen (31%) patients had good or moderate response. The response rate was not different in patient groups

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## What We Already Know about This Topic

- Complex regional pain syndrome exhibits some signs and symptoms that may indicate sympathetic autonomic dysfunction, yet sympathetic blockade produces inconsistent improvement in this condition

## What This Article Tells Us That Is New

- In a prospective series of patients with complex regional pain syndrome type 1, the success rate with sympathetic blockade was moderate (31%), and no signs or symptoms predicted block success

with cold or warm type CRPS-1 or in those with more or less than 1.5°C differential increase in skin temperature after sympathetic blockade. Allodynia and hypoesthesia were negative predictors for treatment success in CRPS-1. There were no symptoms or signs of CRPS-1 that positively predicted treatment success. A majority of patients (84%) experienced transient side effects such as headache, dysphagia, increased pain, backache, nausea, blurred vision, groin pain, hoarseness, and hematoma at the puncture site. No major complications were reported.

**Conclusions:** The presence of allodynia and hypoesthesia are negative predictors for treatment success. The selection of sympathetic blockade as treatment for CRPS-1 should be balanced carefully between potential success and side effect ratio. The procedure is as likely to cause a transient increase in pain as a decrease in pain. Patients should be informed accordingly.

**T**HE use of a sympathetic block (SB) for diagnostic and therapeutic purposes in the management of complex regional pain syndrome type one (CRPS-1) is based on previous

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hypotheses concerning the involvement of the sympathetic nervous system in the pathophysiologic mechanism of this disease.<sup>1</sup> The nociceptive afferent input was believed to cause hyperactive spinal neuron activity, which stimulated the sympathetic neurons to induce arterial spasms, ischemia, and edema.<sup>2</sup>

In certain cases of CRPS-1, the pain may be attributable to a sympathetically maintained form of pain that is classically defined as pain relieved by SB with local anesthetics.<sup>3,4</sup> Consequently, SB frequently is performed for the management of CRPS. Current treatment guidelines for CRPS-1 limit the role of SB to selected cases that are refractory to conservative treatment with pharmacologic therapy and physical rehabilitation.<sup>5,6</sup> When a single SB with a local anesthetic (diagnostic block) proves successful (50% or more pain reduction for the duration of action of the local anesthetic), repeated blocks or a more definitive sympathetic blockade using radiofrequency lesions may be considered.<sup>6,7</sup> A review of the literature shows that SB with a local anesthetic in patients with CRPS resulted in pain relief in approximately one third of patients.<sup>8</sup> Predicting which patients would benefit from SB would assist physicians in patient selection and reduce the number of unsuccessful invasive SB procedures, along with their potential complications and side effects. Signs such as mechanical allodynia, temperature asymmetry, and color changes have been related to a positive response to sympathetic blockade.<sup>7,9</sup> Dynamic mechanical allodynia predicted a pain relieving response to SB in one study<sup>9</sup> but failed to predict pain relief in another study.<sup>10</sup> Some authors think that patients with primarily cold CRPS-1 who do not have adequate response to vasodilating medication may be good candidates for percutaneous sympathetic blockade using local anesthetics, although this was not proven in a prospective study.<sup>11</sup> To investigate possible predictors of successful sympathetic blockade in CRPS-1, we conducted a prospective observational study in which we investigated if easily obtainable signs and symptoms such as hyperalgesia and allodynia, hypoesthesia and hyperesthesia, warm or cold subtype, abnormal skin coloring, abnormal extremity sweating, edema, and abnormal motor signs and symptoms could predict the pain-reducing effect of SB in patients with CRPS-1 of less than 1 yr duration. Although serious complications such as pneumothorax, convulsions and severe hypotension, and hypoventilation caused by subarachnoid block are known to occur occasionally,<sup>12</sup> there is a lack of studies assessing possible side effects.<sup>8</sup> Thus, the second aim of the study was to determine the number and type of adverse events after SBs with local anesthetics.

## Materials and Methods

### Patients

In this prospective observational study, we screened all consecutive patients with a possible diagnosis of CRPS who were referred to the pain management centers of Maastricht and Tilburg in the Netherlands. Patients were eligible for participation in the study if they had CRPS-1 according to the criteria established by the International Association for the Study of Pain (IASP), which are<sup>13</sup>: (1) the presence of con-

tinuous pain, allodynia, or hyperalgesia disproportional to the inciting event; (2) evidence at some time of edema, abnormal skin blood flow, and sudomotor abnormalities in the region of pain; and (3) other causes of pain or dysfunction are excluded.

Other inclusion criteria were: disease duration less than 1 yr after the initiating trauma; signs or symptoms in one extremity only; age 18 yr or older; able to follow written and verbal instructions; no pain reduction with persistent functional impairment after initial standard therapy (see below); mean numeric pain rating score of 5 or more on a scale of 0–10 (with 0 being no pain and 10 being the worst imaginable pain) assessed according to Jensen and McFarland.<sup>14</sup> Exclusion criteria were: pregnancy, coagulation disorders, general infection, fever or local infection at the puncture site, drug or alcohol abuse, diabetic polyneuropathy, or any other disease that may account for signs and symptoms mimicking CRPS. The study was approved by the medical ethics committees of the Maastricht University Medical Centre and the St. Elisabeth Hospital in Tilburg, the Netherlands. All patients gave written informed consent.

### Standard Therapy

Standard therapy was provided according to CRPS treatment guidelines,<sup>15</sup> and before SB was offered as a treatment, all patients received physical therapy aimed at active mobilization, according to a fixed protocol, which consisted of graded exercises aimed at restoring strength, mobility, and function of the affected extremity. Physical therapy was performed twice a week with a minimum duration of 30 min. Exercises were adjusted so that an increase of pain during and after exercise returned to pre-session levels within 24 h.<sup>16</sup> Topical application of the free radical scavenger dimethyl sulfoxide, 50%, three to five times daily was given as anti-inflammatory therapy. The physical therapy was supplemented with oral analgesic medication such as the nonsteroidal anti-inflammatory agents acetaminophen and tramadol. If insufficient pain relief was obtained after at least 3 weeks of the analgesic medication, gabapentin was given in doses as large as 1,800 mg daily. Insufficient pain relief was defined as an unchanged numeric pain rating score or maximal one-point numeric pain rating score improvement. If insufficient pain relief was obtained after at least 3 weeks of gabapentin, transcutaneous electrical nerve stimulation therapy was applied for at least 2 weeks. After this, if there still was insufficient pain relief, a sympathetic blockade (*i.e.*, stellate ganglion block for the upper extremity and lumbar SB for the lower extremity) was proposed.

### Sympathetic Blocks

During the procedure and for a period of at least 30 min after the procedure, patients were monitored continuously by pulse oximetry and an automated noninvasive blood pressure monitor. Just before the SB was performed, an intravenous line was placed for safety reasons. All SBs were performed

by staff anesthesiologists with at least 10 yr experience in interventional pain management. A gold standard for defining an adequate block remains undefined. Thus, we considered the SBs correctly performed if there was radioscopically confirmed adequate craniocaudal contrast dye outline over the prevertebral sympathetic chain at the C6–C7–Th1 level for the upper limb and over the prevertebral sympathetic chain at the L3–L4–L5 level for the lower limb. Injection of local anesthetic was given only after radiologic confirmation of this adequate craniocaudal contrast dye outline.

Stellate ganglion block on the cervical sympathetic chain was performed at the vertebral level C6–C7 using the anterior paratracheal approach with fluoroscopic guidance.<sup>6</sup> The patient was placed in supine position with the head slightly hyperextended. The height of C6–C7 was determined by fluoroscopy with the C-arm in anteroposterior position and adjusted until the vertebral end plates were viewed perpendicular. After local disinfection, the skin was anesthetized using lidocaine, 1%, and a 60-mm, 20-gauge radiocontrast needle was inserted at the junction of the processus transversus and the corresponding C6 or C7 corpus vertebralis. After the needle contacted the bone, oblique projection was used to check if the needle was anterior to the foramen intervertebrale. If the needle was past that level, no contact was made with the base of the processus transversus, and the needle was repositioned. Once the needle was in the correct position, a small amount (0.5–1 ml) of contrast dye was injected to visualize and prevent potential intravascular injection. After an adequate craniocaudal contrast dye spread was obtained, an injection of 10 ml bupivacaine, 0.25%, was given. This volume of local anesthetic was chosen because the objective was to test the standard SB technique, and this amount generally reflects common clinical practice.

Lumbar SB was performed with the patient in the prone position.<sup>6</sup> The C-arm fluoroscope was used to identify the level L2–L4 and adjusted until the vertebral end plates were viewed perpendicular. The C-arm was turned laterally until the distal end of the processus transversus projected in line with the lateral edge of the corresponding L2–L4 corpora vertebrae. After local disinfection, the skin was anesthetized using lidocaine, 1%, and a 15-cm, 20-gauge needle was inserted using tunnel view until the front of the vertebra was reached. The lateral projection was used to check if the needle did not pass the anterior side of the corpus vertebrae. The anterior posterior projection was used to check if the needle point projected over the facet joint of the spinal column. The truncus sympathicus was reached by a single-needle approach at the L3 corpus vertebrae. After an adequate craniocaudal contrast dye outline was obtained, 10 ml bupivacaine, 0.25%, was injected.

### Variables

The average week spontaneous pain scores were derived from a numerical rating scale of 0–10, assessed three times daily on

5 consecutive days, at home at baseline, immediately before SB, and at 30 min and 2, 4, 6, and 8 h after the SB and three times daily for a period of 1 week after SB.

Skin temperature was measured in degrees Celsius (°C) using a Genius First Temp infrared thermometer (Tyco Healthcare Group LP, Mansfield, MA) set on “surface” in a room maintained at 20°–22°C and after an adjustment period of 10 min. Measurements were made at the affected and contralateral extremity. The dorsal aspects of the hands or feet were assessed at five standardized points. The mean temperature was calculated of these five measurements. Temperature measurements were performed at the outpatient clinic, baseline before the SB, and 30 min after the SB. This allowed us to measure the relative increase in skin temperature as a measure of completeness of the SB.<sup>17</sup> Treatment success was defined as pain relief of  $\geq 50\%$  for at least 6 h. Patients who had pain reduction of 50% for at least 6 h or more were considered moderate responders. Patients who had pain relief of at least 50% for 2–7 days were considered good responders.

To make subgroup phenotype analysis possible, evaluations were performed according to a strict measurement protocol, distinguishing symptoms reported by patients and signs established by the investigators. Assessment of signs was performed in a clinical fashion (*i.e.*, left-right comparisons, palpation, provocation tests). The features were registered as dichotomous variables (present-absent).<sup>18</sup> A standardized symptom checklist was used at the outpatient clinic to register relevant signs and symptoms associated with CRPS-1 within one of the four different categories according to the factor structure proposed by Harden and Bruehl and colleagues. Patients with CRPS-1 may report symptoms or display signs in four different categories: sensory, vasomotor, sudomotor or edema, and motor or trophic.<sup>19,20</sup>

The symptoms were assessed by history taking, and the signs were objectively measured and observed by the physician. In the sensory category, hypoesthesia and hyperesthesia signs and allodynia were assessed by gently stroking the skin with a cotton swab. If this caused pain, the patient was considered to have allodynia. The sign of hyperalgesia was assessed by means of blunt pinprick. If this caused more pain than was seen on the contralateral side, hyperalgesia was considered present. In the vasomotor category, skin color asymmetry existence (blue or red discoloration) was observed and skin temperature asymmetry was assessed by infrared thermometry. In the edema or sudomotor category, the edema and sweating asymmetry were assessed by history taking and observation. In the motor or trophic category, the reduced range of motion, muscle weakness of the involved limb, tremor, myoclonus, bradykinesia, and trophic abnormalities (*i.e.*, of hair, skin and nails) were assessed by history taking and observation.

### Statistical Analysis

The frequency of occurrence at baseline of the different possible predictors of outcome was determined in the successfully (50%

pain relief) and in unsuccessfully treated groups. We performed an intention-to-treat analysis based on technically correctly performed SB as confirmed by C-arm radioscopy. We also did a subgroup analysis of patients who experienced a relative increase in skin temperature of at least 1.5°C compared with the contralateral side because some authors consider this amount of temperature increase sufficient evidence of a blockade of the sympathetic nervous system, although not all sympathetic function may be abolished.<sup>17,21,22</sup> In addition, we examined if a moderately important pain decrease of 30% or more for at least 2 days after the intervention would influence the predictor finding in subgroup analysis.<sup>23</sup> Change in skin temperature *versus* change in pain intensity was visualized with a scatter plot using different symbols to indicate the responder and nonresponder patients.

For each patient in the current study, the number of CRPS characteristics present was calculated within four sign and four symptom categories (sensory, vasomotor, sudomotor, mototrophic).<sup>24</sup> The frequency and duration (in days) of side effects was established and tabulated separately for stellate ganglion and lumbar sympathetic blockade.

Because of different total numbers of signs and symptoms in each category, standardized scores (Z-scores) for each of these eight categories were derived. These Z-scores were used in the univariate logistic regression analysis. The predictive performance of the four symptom and signs categories and age, gender, localization of the disease, precipitating event, disease duration, and all assessed symptoms and signs of CRPS-1 individually were evaluated with an univariate regression analysis or chi-square analysis. Two-tailed *P* values of <0.05 were considered significant.

The model building was done according to Hosmer and Lemeshow.<sup>25</sup> To judge the importance of the variables in the model, variables with a *P* value <0.10 were considered a candidate in a multivariate logistic regression model with a forward stepwise procedure. Compared with Hosmer and

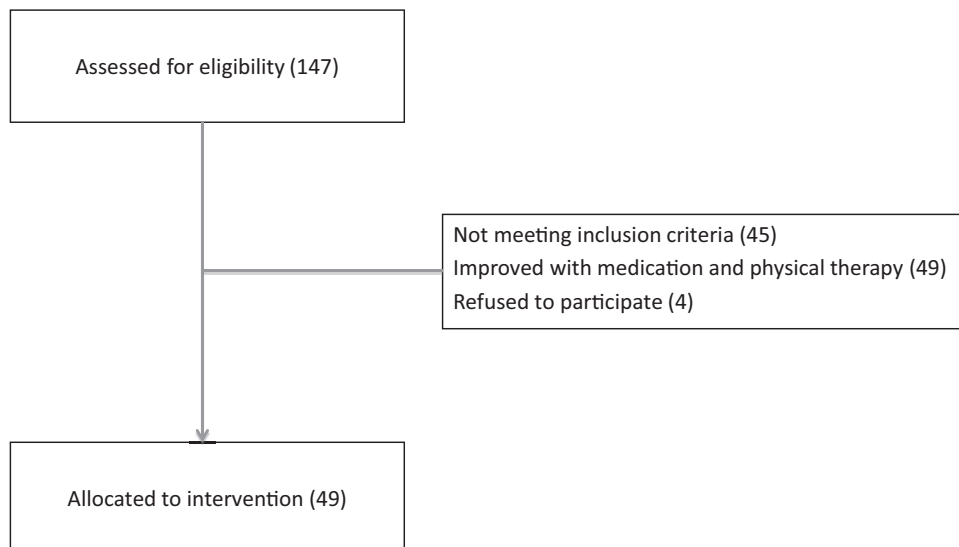
Lemeshow's suggestion (*P* value <0.25), this *P* value was chosen more conservatively because of the relative small sample size of responder patients. The multivariate logistic regression with forward stepwise procedure entered only variables with *P* values <0.05.

The predicted probability of the multivariate regression analysis was used to construct a receiver operating characteristic curve and calculate the area under the curve. The area under the curve is indicative for the discriminative ability where 0.5 indicates no discrimination and an area under the curve of 1.0 indicates perfect discrimination.<sup>26</sup> We used a bootstrapping procedure to adjust for overoptimism in model performance.<sup>26–28</sup> Bootstrap samples were drawn with replacement (*n* = 200) from the full data set, and the areas under the curve of these data sets were averaged. Analyses were performed with the Statistical Package for the Social Sciences, version 15 (SPSS Inc., Chicago, IL). The bootstrap procedure and univariate regression analysis were performed with STATA/SE version 11.1 (StataCorp LP, College Station, TX).

## Results

### Study Population

The source population was 147 patients with presumed CRPS referred between June 2005 and October 2008 to the pain management centers of Maastricht and Tilburg in the Netherlands. One hundred two patients fulfilled the inclusion criteria for this study. These patients had CRPS-1 in one extremity with disease duration of less than 12 months (mean duration, 17 weeks; range, 2–50 weeks). Of these 102 patients, 49 experienced improvement with medication and physical therapy, and 49 patients provided informed consent for the SB and completed the study. The 49 patients who experienced improvement with conservative treatment and 4 patients who refused SB were excluded from this study (fig.



**Fig. 1.** Flow chart.

**Table 1.** Baseline Demographics and Characteristics

Characteristics	N	%
Total	49	
Age, mean (SD) 44.9 (12.1)		
Disease duration in days, mean (SD) 233 (84)		
Male gender	12	24
CRPS-1 location		
Lower extremity	27	55
Upper extremity	22	45
Left side	26	53
Right side	23	47
Precipitating event		
None	13	26
Fracture, sprain	19	39
Surgery	14	29
Other	3	6
CRPS-1 criteria		
IASP	49	100
Budapest clinical I	44	90
Budapest research	37	76

CRPS-1 = complex regional pain syndrome type 1; IASP = International Association for the Study of Pain.

1). Table 1 shows the baseline variables of SB-treated patients. The mean age of the participants was 44.9 (SD 12.1) yr (range, 18–71 yr), and 75.5% were women. The mean time since CRPS onset (initial injury) and SB treatment was 233 (SD 84) days.

### Symptoms and Signs of CRPS-1

All patients fulfilled the IASP criteria, 90% the Budapest clinical criteria, and 76% the Budapest research criteria.<sup>19,20,29</sup>

### Outcome

The 49 evaluated patients had adequate craniocaudal contrast dye spread over the prevertebral sympathetic chain confirmed radiosopically. All of these SB were considered to be performed technically correctly. As shown in table 2, 15 patients (of 49, 31%) were treated successfully with SB. Of these, 10 patients were good responders and 5 were moderate responders. In 34 patients, the SB did not result in pain relief. Table 3 shows that 33 patients (of 49, 67%) had a relative skin temperature increase of at least 1.5°C after SB. Among the 33% who did not have a temperature increase, 37% were responders. The scatter plot, which visualizes change in skin temperature *versus* pain relief, shows that skin temperature increase after SB did not correlate with pain decrease in our study (fig. 2).

### Intention to Treat Analysis, Univariate Analysis, and Logistic Regression

Table 4 shows the results of the baseline symptom and sign assessment. These variables together with the baseline demographics and characteristics as shown in table 1 were used in an univariate logistic analysis to explore correlations between patient characteristics and success of SB treatment.

**Table 2.** Mean NRS (SD) in Responders and Nonresponders to Sympathetic Blockade before and after the Treatment

Outcome	0–7 Days		
	before SB NRS (SD)	2–48 h NRS (SD)	0–7 Days NRS (SD)
Responders (N = 15)	5.8 (1.2)	2.7 (1.1)	2.9 (1.2)
Good (N = 10)	5.9 (1.3)	2.5 (1.2)	2.5 (1.0)
Moderate (N = 5)	5.6 (1.1)	2.9 (0.9)	3.7 (1.1)
Nonresponders (N = 34)	6.8 (1.4)	5.9 (1.8)	6.1 (1.7)

NRS = numerical pain rating score.

Baseline demographics and characteristics (*e.g.*, disease duration;  $P = 0.44$ ) did not predict pain relief after SB in univariate analysis. The univariate analysis indicates that the absence or presence of cold asymmetries in the affected extremities did not predict SB outcome in our study (objectively measured cold asymmetry  $P = 0.87$ ; warm asymmetry  $P = 0.63$ ).

For model building, the symptoms allodynia ( $P = 0.03$ ), hypoesthesia ( $P = 0.04$ ), bradykinesia ( $P = 0.04$ ), tremor and/or myoclonus ( $P = 0.06$ ) and the sign bradykinesia ( $P = 0.06$ ), and the motor or trophic subgroup ( $P = 0.04$ ) were considered as potential predictors and were entered in a stepwise multivariate logistic regression model. The variable bradykinesia was measured as a sign and a symptom, and these proved to be collinear. Therefore, we performed the modeling procedure on two models.

In both procedures, allodynia ( $P = 0.02$ ) and hypoesthesia ( $P = 0.02$ ) were included in the final model.

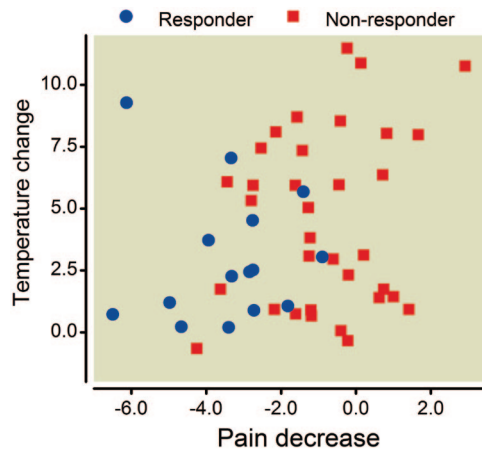
### Performance of the Model

Figure 3 shows the receiver operating characteristic curve with the area under the curve. The area under the curve was 0.82 (CI 0.70–0.95). In the models as generated by the bootstrap procedure, the rate of occurrence of hypoesthesia in the model was 84%, allodynia 75%, bradykinesia (sign as well as symptom) 37%, and the motor or trophic subgroup 22%. The average of the area under the curves of the receiver operating characteristic curves was 0.78 (CI 0.61–0.95).

**Table 3.** Responders after Sympathetic Block According to Relative Skin Temperature Increase

	SB > 1.5°C		Total
	No	Yes	
Nonresponders	10	24	34
Good and moderate responders	6	9	15
Total	16	33	49

SB = sympathetic block.



**Fig. 2.** Scatter plot of mean pain change versus skin temperature change after sympathetic blockade treatment in patients with (responder) and without (nonresponder) response to sympathetic blockade.

### Subgroup Analysis

As shown in table 3, the percentage of responders in our study was not significantly different in patients with or without a skin

temperature increase of more than 1.5°C after SB: 9 of 33 (27%) in the group with more than 1.5°C increase; 6 of 16 (37%) in the group with less than 1.5°C increase; chi-square  $P = 0.52$ . In the subgroup of CRPS-1 patients with more than 1.5°C skin temperature increase, we found no predictors of a positive pain relieving response to SB. Allodynia and hypoesthesia in this analysis also were predictors of a negative pain relieving response after the intervention.

We repeated the analysis with patients who had 30% or more pain decrease for at least 2 days after the intervention (21 of 49; 43%). In univariate analysis, we found predictors only for a negative response to SB (*i.e.*, allodynia for pressure ( $P = 0.04$ ), decreased range of motion ( $P = 0.05$ ), allodynia for movement ( $P = 0.03$ ), and bradykinesia sign ( $P = 0.03$ ).

### Side Effects

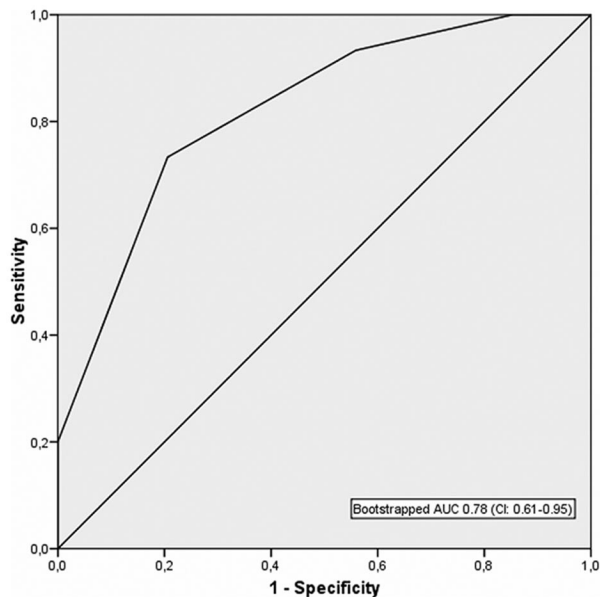
In 41 (84%) patients, transient side effects of the SB treatment were reported, and 8 patients had no side effects. In the patients treated with stellate ganglion block, 76% had difficulty in swallowing (dysphagia). In the patients treated with lumbar SB, 61% reported back pain that lasted for a maximum of 7 days (median, 2 days). The pain was reported to be

**Table 4.** Results of Chi-square and Univariate Regression Analysis in Symptoms and Signs for Unsuccessful Sympathetic Blockade Treatment

Classes of Symptoms	Symptom				Sign			
	N	P Value	OR	CI	N	P Value	OR	CI
Sensory								
Allodynia	17	0.03	5.13	1.0, 26.3	12	0.21		
Hyperesthesia	10	0.25	0.46	0.12, 1.69	10	0.48	0.59	0.14, 2.50
Hypoesthesia	20	0.04	2.92	0.96, 16.8	18	0.10	3.16	0.75, 13.26
Hyperalgesia	29	0.30	1.41	0.41, 4.82	27	0.86	1.11	0.33, 3.75
Hypoalgesia	14	0.63	0.72	0.19, 2.69	14	0.63	0.72	0.19, 2.69
Vasomotor								
Asymmetry in skin color	48	NE			22	0.65	1.33	0.39, 4.58
Asymmetry in temperature	46	0.92	1.14	0.10, 13.66	22	0.87	0.90	0.27, 3.05
Cold	26	0.97	0.98	0.29, 3.33	35	0.63	1.39	0.37, 5.18
Warm	16	0.47	0.63	0.18, 2.22	14	0.63	0.72	0.19, 2.69
Sudomotor								
Edema	44	0.64	1.59	0.24, 10.66	18	0.33	1.93	0.51, 7.30
Asymmetry in sweating	22	0.87	0.90	0.27, 3.05	5	0.15	0.25	0.04, 1.69
Mototrophic								
Decreased range of motion	39	0.15	2.9	0.69, 12.15	33	0.17	2.43	0.68, 8.64
Weakness	46	0.92	1.14	0.09, 13.66	31	0.34	1.83	0.53, 6.34
Dystonia	20	0.58	0.71	0.21, 2.42	3	NE		
Tremor/myoclonus	29	0.06	3.5	0.92, 13.2	3	NE		
Trophic disturbances	15	0.79	0.83	0.23, 3.07	9	0.54	1.69	0.31, 9.27
Bradykinesia	24	0.04	3.93	1.04, 14.9	23	0.06	3.48	0.92, 13.2
Subgroup of symptoms and signs for Budapest variables								
Z-scores								P Value
Sensory								0.12
Vasomotor								0.86
Sudomotor								0.98
Mototrophic								0.04

Dependent variable: unsuccessful sympathetic blockade.

CI = 95% confidence intervals; NE = not estimable due to cell with zero counts; OR = odds ratio.



**Fig. 3.** Performance of the predictive model with allodynia and hypoesthesia as negative predictive value. Receiver operating characteristic curve and bootstrapped mean area under the curve (AUC).

increased by 33–36% of the patients for 0–11 days; however, the numerical pain rating scale scores did not support this increase. This pain aggravation also occurred in two patients successfully treated with SB, but this episode lasted for a maximum of 2 days (table 5).

## Discussion

In our study, we found that 15 of 49 (31%) patients had good or moderate response to SB. Second, allodynia and hypoesthesia are predictors of a negative response to SB in CRPS-1. Third, the presence of cold-type or warm-type CRPS-1 in our study made no difference in the response to SB. Fourth, the patient subgroup with skin temperature increase of more than 1.5°C

after SB did not have more responders. Finally, a majority of patients (41 of 49; 84%) had (transient) side effects.

This prospective study on the initial outcome of SB contains the largest number of CRPS-1 patients ( $n = 49$ ) who have undergone SB. Other outcome studies on SB have included relatively small numbers, varying from 1 to 33 patients.<sup>9,10,22,30–32</sup> In addition, our study is the first that has reported systematically on the incidence of side effects after sympathetic blockade with local anesthetics.

Fifteen of 49 (31%) patients had good or moderate response to SB. This is equal to the results in other studies, although these studies usually included populations with both acute and chronic CRPS.<sup>30,33</sup> Our group consisted of patients with CRPS-1 with disease duration of less than 1 yr. The prognosis typically is better in early CRPS-1. Because we included only patients who had no pain relief after a standard conservative therapy protocol of at least 8 weeks, our patient group had therapy-resistant pain, with a poorer prognosis, qualifying them for SB.

In contrast to a previously published opinion,<sup>11</sup> in our study patients with cold-type CRPS-1 had more pain relief after SB than did patients with warm-type CRPS-1. The odds ratios show that the temperature difference or initial temperature was not a predictor of success; there was an equal chance of achieving pain relief or not after SB. In a previous study, the magnitude of temperature increase after SB predicted relief of pain and allodynia.<sup>34</sup> However, this observation by Tran *et al.* was made in a small subset of 11 patients, and more than one SB per patient was allowed to be performed, which may have introduced bias. In addition, in contrast to our study, skin temperature measurements were made only on the ipsilateral side, so correction for a possible skin temperature increase attributable to the environment of the examination room was not possible. In another study, skin temperature increase and asymmetries in skin temperature did not predict pain relief after SB.<sup>10</sup>

An interesting observation is the existence of responders in the group that had skin temperature increase of less than 1.5°C (6 of 16, 37%). There was no increase in responders in

**Table 5.** Side Effects in Days after Sympathetic Blockade

Side Effects	Stellatum Blockade ( $N = 21$ )		Lumbar Blockade ( $N = 28$ )		Total $N$ (%)
	$N$ (%)	Median (Min–Max) in Days	$N$ (%)	Median (Min–Max) in Days	
No side effects	2 (9.5)		6 (21.4)		8 (16)
Horner	11 (52.4)	0			
Blurred vision	4 (19.1)	0			
Increased pain	7 (33.3)	4 (1–7)	10 (35.7)	3 (0–11)	17 (34.7)
Headache	13 (61.9)	2 (1–6)	8 (28.6)	2 (0–3)	21 (42.9)
Nausea/vomiting	5 (23.8)	2 (2–5)	5 (17.9)	2 (1–3)	10 (20.4)
Dysphagia	16 (76.2)	3 (1–7)	1 (3.6)	1 (0–1)	17 (34.7)
Hoarseness	7 (33.3)	1.5 (1–6)	2 (7.1)	3 (2–4)	9 (18.4)
Hematoma	3 (14.3)	4 (4–6)	2 (7.1)	3 (2–4)	5 (10.2)
Back pain	5 (23.8)	3 (2–7)	17 (60.7)	2 (0–7)	22 (44.9)
Groin pain			5 (17.9)	2.5 (0–3)	6 (10.2)

Max = maximum; Min = minimum; 0 = day of intervention.

the group with a relative skin temperature increase of 1.5°C or more as opposed to the group that did not have such an increase. This indicates that the relative increase in skin temperature after the SB was not a predictive factor for its pain relieving effect. Possible explanations for the phenomenon of patients with response in the absence of an adequate skin temperature increase may include spillover of the local anesthetic to somatic nerves, systemic action of absorbed local anesthetic fluid, or placebo response.

Allodynia and hypoesthesia symptoms proved to be statistically significant predictors of a negative response to SB. In the subgroup of patients with CRPS-1 with more than 1.5°C skin temperature increase after SB, we found allodynia and hypoesthesia to be predictors for a negative pain relieving response. Allodynia is a well-known sign of central sensitization in the central nervous system at the level of the medullary cord or higher.<sup>35</sup> Hypoesthesia may be related to impairment of central processing of large-caliber peripheral A- $\beta$  fiber input. In an previous report, peripheral A- $\beta$  fibers were found to be intact in CRPS forearm skin in contrast to peripheral nociceptive small-diameter fibers (A- $\delta$  and C fibers), which were degenerated.<sup>36</sup> The central sensitization and altered sensory transmission may alter sensorimotor processing associated with central disinhibition, leading to signs and symptoms such as tremor, myoclonus, and bradykinesia.<sup>37,38</sup> With the presence of signs and symptoms of central dysfunction at the level of the spinal cord or higher, it is understandable why a peripheral intervention such as SB is not likely to benefit the patient.

In our study, not all SB were followed by a 1.5°C increase in relative temperature. Despite a radioscopically confirmed, correctly performed SB, 16 of 49 (37%) patients did not have this reaction. This might suggest that the technical procedure was suboptimal, causing misdistribution of the local anesthetic drug. However, the insufficient temperature increase after SB is a common occurrence in studies of SB.<sup>21,39</sup> In another study, the number of patients (10 of 33; 30%) who did not have the expected skin temperature increase after SB was similar to that of our study.<sup>22</sup> In addition, the number of responder patients in the current study corresponds to the number of responder patients in other studies.<sup>30,33</sup> Thus, we suggest that the technique used, as described in Materials and Methods, was optimally performed. This justifies the intention-to-treat analysis as performed in our study.

Although all patients met the IASP criteria, not all patients met the Budapest clinical criteria (90%) or the Budapest research criteria (76%), implying a possible lack of specificity in a small part of the patient sample. However, the Budapest criteria for CRPS were validated only recently (in 2010),<sup>19,20</sup> and at the time of our study in 2005 and until now, the IASP criteria are considered valid diagnostic criteria. Because our objective was to identify factors that could predict a positive response to SB, patient inclusion according to the IASP criteria seemed justified.

A potential limitation of this study involves the patient sample. The sample was based on available new patients with

CRPS-1. Thus, we chose conservative *P* values to build the model and performed a bootstrap procedure to check for overoptimism in the model performance. This procedure showed that the performance of the model remained good. It must be stressed that this study did not assess the long-term outcome of CRPS-1 after SB. Thus, we cannot make a statement on the long-term efficacy of SB in CRPS-1. We focused on the search for predictors of a positive response to SB to improve the selection of patients with CRPS-1 who are likely to benefit from this treatment.

When considering an invasive procedure such as SB, one should be aware of the possible side effects and complications of the procedure. We know the possibility of potentially life-threatening complications (1.7 in 1,000) that may arise from inadvertent subarachnoid injection or injection in the arteria vertebralis.<sup>12</sup> The existence of other less severe side effects did not receive much attention in the literature. Although our patients experienced no major complications, side effects seem to be considerable, as shown by our study. A majority of patients showed temporary side effects, such as headache, backache, nausea, blurred vision, groin pain, dysphagia, hoarseness, and hematoma at the puncture site. Temporary Horner syndrome often is considered a normal phenomenon after stellate ganglion block. However, the target when blocking this cervicothoracic sympathetic ganglion is its thoracic part because innervation of the arm is mediated *via* Th1 and Th2. As such, the accompanying Horner syndrome is an inconvenient, but unpreventable, aspect of the treatment when performed at the safer C6 or C7 level. Puncture at lower levels would increase the risk of pneumothorax. Seventeen of 49 (35%) patients had increased transient pain after SB, which returned to baseline 1 week after SB. Whether or not SB is an effective treatment for CRPS-1 cannot be answered from our results. Only good quality randomized controlled trials with appropriate sample sizes and robust outcome measures could prove if SB is indicated in CRPS-1. In clinical practice, indications for SB in CRPS-1 should be balanced carefully against possible complications or side effects. As for the effect of SB on pain in early CRPS-1 (less than 1 yr after the initiating event), allodynia and hypoesthesia predicted a negative response to SB. The procedure is as likely to cause a transient increase in pain as a decrease in pain. Patients should be informed accordingly.

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