Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: A double-blind randomized controlled study

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abstract
Pain relief in complex regional pain syndrome (CRPS) remains a major challenge, in part due to the lack of evidence-based treatment trials specific for this condition. We performed a long-term randomized, double-blinded active-control study to evaluate the efficacy of thoracic sympathetic block (TSB) for upper limb type I CRPS. The study objective was to evaluate the analgesic effect of TSB in CRPS. Patients with CRPS type I were treated with standardized pharmacological and physical therapy and were randomized to either TSB or control procedure as an add-on treatment. Clinical data, pain intensity, and interference (Brief Pain Inventory), pain dimensions (McGill Pain Questionnaire [MPQ]), neuropathic characteristics (Neuropathic Pain Symptom Inventory [NPSI]), mood, upper limb function (Disabilities of Arm, Shoulder and Hand), and quality of life were assessed before, and at 1 month and 12 months after the procedure. Thirty-six patients (19 female, 44.7 ± 11.1 years of age) underwent the procedure (17 in the TSB group). Average pain intensity at 1 month was not significantly different after TSB (3.5 ± 3.2) compared to control procedure (4.8 ± 2.7; \( P = 0.249 \)). At 12 months, however, the average pain item was significantly lower in the TSB group (3.47 ± 3.5) compared to the control group (5.86 ± 2.9; \( P = 0.046 \)). Scores from the MPQ, evoked-pain symptoms subscores (NPSI), and depression scores (Hospital Anxiety and Depression Scale) were significantly lower in the TSB group compared to the control group at 1 and at 12 months. Other measurements were not influenced by the treatment. Quality of life was only slightly improved by TSB. No major adverse events occurred. Larger, multicentric trials should be performed to confirm these original findings.

1. Introduction

Complex regional pain syndrome (CRPS) type I arises following trauma to a limb and is characterized by functional impairment in the affected body segment. It is associated with intense sensory, autonomic, motor, and trophic changes, which are disproportionate to the inciting event and cannot be accounted for by other causes of chronic pain [25]. Despite recent advances in the understanding of its pathophysiology, pain relief in CRPS remains a major challenge. This is partly due to the complexity of the mechanisms underlying the maintenance of pain and the functional impairment present in this syndrome, but it is also related to the lack of evidence-based treatment trials specific for this condition [22]. Most interventions used for CRPS relief are not supported by high-quality evidence-based data [39].

Sympathetic nerve blocks have been used for the treatment of CRPS since the beginning of the 20th century [6]. Despite the paucity of evidence-based information on its efficacy, it is commonly utilized in patients with CRPS, leading to variable analgesia when used in combination with physical therapy [4,17,50].

Different techniques of sympathetic blocks are frequently grouped together in efficacy analyses and CRPS reviews [49]. However, these procedures are not all similar, and their clinical efficacy may depend on variables such as the target anatomical structures,
the medication injected during the procedure, and the number of blocks performed [12,14]. For instance, the technique that is most commonly used to target sympathetic innervation of the upper limbs is the stellate ganglion block (SGB) [14,17,36]. Anatomical and clinical studies have suggested that this may not be the most effective technique for upper limb sympathetic block [6,26,27,38].

Second-order neuron cell bodies that supply the upper limbs are located in the intermediolateral horn of the thoracic spinal cord. Preganglionic fibers ascend cephalad and synapse on postganglionic fibers, primarily in the second (and to a lesser extent in the third) thoracic sympathetic ganglia, before ascending and passing through the stellate and the middle cervical ganglia en route to the upper limbs [44,46]. However, in 20% of the individuals, nerves from these 2 thoracic sympathetic ganglia project directly to the brachial plexus, bypassing the upper stellate and middle cervical ganglia [31,44,46]. Thus, different from SGB, which only influences nerve fibers that actually pass through this structure before reaching the upper limbs, thoracic sympathetic blocks (TSB) act directly on the main synapse site of most sympathetic fibers innervating this body segment [44,46]. Despite this potentially relevant anatomical information, TSB has rarely been evaluated in CRPS patients [1,57].

Given the lack of conclusive studies on the validity of the sympathetic block of the upper limb as a treatment for CRPS, as well as the reported limitations of the SGB technique and the lack of controlled long-term studies on sympathetic blocks in general for CRPS, we performed a 12-month randomized, double-blinded, active-control study to evaluate the efficacy of TSB for upper limb CRPS type I.

2. Methods

2.1. Clinical trial

The study was approved by our Institution’s Ethics Review Board (#0465/09) and is registered at www.clinicaltrials.org under (NCT01612364). Data were collected from October 2009 to October 2013.

2.2. Patients

Patients from our own institution and related outpatient clinics in our district area were screened for eligibility. All assessments and procedures were performed in our Institution’s Pain Center. The International Association for the Study of Pain 1994 diagnostic criteria for CRPS type I were used in the first months of the study during the screening phase and before any patient underwent the blocking procedure. After the publication of validation of the new criteria (Harden et al. 2010), an addendum was added to the project (approved by the Ethics Review Board) and since then, only the Budapest criteria were used for screening and inclusion in the protocol [24,51]. To be eligible, adult patients (18–70 years) needed to have CRPS I for at least 6 months and have failed to obtain pain relief (numeric rating scale [NRS] > 4) after conventional treatment. Patients needed to be on a stable dose of CRPS medications for at least 28 days prior to study entry. The exclusion criteria were pregnancy/lactation, substance abuse issues, history of serious brain trauma, epilepsy or stroke, presence of a serious systemic illness (eg, cancer), and serious or untreated psychiatric illness.

2.3. Treatments

2.3.1. Systematic standardized treatment

After study entry, all patients underwent a psychological assessment and were started on comprehensive standardized rehabilitation and pharmacological treatment (Fig. 1) for 4 weeks consisting of the following:

- a. A physical therapy program guided by a physiatrist and physical therapists. The standardized physical therapy program included a once-weekly session for 8 weeks (4 weeks before and 4 weeks after the intervention). A Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire was completed before and after (at 8 weeks) the standardized physical therapy sessions [41].
- b. Oral analgesic polytherapy was started: antidepressants (amitriptyline 25–75 mg/day or imipramine 25–75 mg/day), opioid analgesics (tramadol 100–400 mg/day; codeine 60–240 mg/day), non-steroidal anti-inflammatory analgesics (metamizole sodium 2–6 g/day or acetaminophen 1.5–3 g/day), and gabapentin (900–1800 mg/day). Patients remained on the same drug regimen throughout the duration of the study. Acute pain medications were allowed: morphine (10 mg 4 times a day [q.i.d.]), tramadol (50 mg q.i.d.), or codeine (30 mg q.i.d.). Patients who failed to comply with baseline medications were withdrawn from the study (Fig. 1).
- c. Psychological assessment: 2 interviews with a pain psychologist were performed to detect and evaluate major mood disorders and to assess patients’ coping strategies related to the presence of pain (Fig. 1).

Patients who were pain free after this standardized treatment phase of the study were excluded from the protocol. Patients who remained symptomatic (NRS > 4) were randomized into either TSB or control treatment and underwent the intervention (Fig. 1). From the 8th to the 52nd week of the study (ie, from 4 weeks after the blocking procedure until the 12-month follow-up visit), patients were seen in an outpatient setting. During this period, patients who were originally seen in our outpatient clinic and presented for follow-up consultations were asked to undergo a blinded supplementary clinical evaluation. For these patients, supplemental data from 2, 3, 6, and 9 months after the blocking procedure were obtained in addition to the baseline and 1- and 12-month assessments performed in all patients (Supplementary Table 1).

2.4. Clinical assessment

Blinded researchers who had no role in the blocking procedure or patient screening performed all clinical assessments. Assessments were performed at baseline, and at 1 and 12 months after the procedure (Fig. 1); they included the following:

- a. Pain location, intensity, and interference with daily activities were assessed using the short form of the Brief Pain Inventory (BPI) [18].
- b. The presence of a neuropathic component based on the Douleur Neuropathique 4 questionnaire (D4N) [9,48] and its symptom profile based on the Neuropathic Pain Symptoms Inventory (NPSI) [10,15] were assessed, as well as the different dimensions of chronic pain using the McGill Pain Questionnaire (MPQ) [35,42].
- c. Mood was assessed using the Hospital Anxiety and Depression Scale (HADS) [8] assessed at baseline and at the end of the study (12 months after the procedure).
- d. Quality of life was assessed by the World Health Organization Quality of Life questionnaire (WHO-QOL-bref) [20] administered at baseline and at the end of the study (12 months after the procedure) (Fig. 1).
erly placed and was not in the intravascular, intrapleural, or intrathoracic spaces. Then, 1 mL of iopamidol-75 mg/mL (Patheon Italia S.p.A., Ferentino, Italy) was injected at this site using radioscopy, but the solution was injected into the subcutaneous space. Fluoroscopy was used to document the location of the injection (Supplementary Fig. 1B). Fluoroscopic guidance was always used to assist in needle positioning and to document the final location of the needle. For patients in the control group, the same type of needle (22 Quincke) was used to puncture the skin before being positioned subcutaneously at the T2 level. In addition, the same 10 mL of anesthetic + corticosteroid solution (5 mL of 0.75% ropivacaine [AstraZeneca, London, UK] + 5 mL of 2% triamcinolone [Apsen; São Paulo, Brazil]) was injected into the T2 sympathetic thoracic ganglion, paralateral to the T2 vertebrae on the affected side. Fluoroscopy was used to document the location of the injection (Supplementary Fig. 1A). Fluoroscopic films documented the procedure. After blocking, the temperature in the limb was measured using a touch thermometer (TS-201, Techline, São Paulo, Brazil) over the volar aspect of the forearm at operating room temperature 21 ± 2 °C. A difference > 2 °C indicated that the TSB was successful [27].

2.5. Blocking procedure

Patients were randomly assigned to receive either TSB or control block. The randomization participants were asked to select a manila envelope from an urn containing 60 envelopes. Under sterile conditions, the patient was placed in the ventral decubitus position with their head covered with a blanket so that they were not able to observe the procedure. Both groups received the block in the same dorsal region on the same side as the affected limb. TSB was performed according to the technique described by Leriche and Fontaine in 1925 [33]. Before needle puncture, 5 mL of 1% lidocaine was used for skin and soft tissue anesthesia. A number 22-Quincke (B. Braun, Melsungen, Germany) needle for spinal anesthesia was positioned in the T2 plane under fluoroscopic guidance (Supplementary Fig. 1). The needle was inserted into the skin and advanced to the posterior third of the second thoracic vertebra. Then, 1 mL of iopamidol-755 mg/mL (Patheon Italia S.p.A., Ferentino, Italy) contrast was injected to ensure that the needle was properly placed and was not in the intravascular, intrapleural, or intramedullar spaces (Supplementary Fig. 1). Then, 10 mL of anesthetic + corticosteroid solution (5 mL of 0.75% ropivacaine [AstraZeneca, London, UK] + 5 mL of 2% triamcinolone [Apsen; São Paulo, Brazil]) was injected into the T2 sympathetic thoracic ganglion, paralateral to the T2 vertebrae on the affected side. Fluoroscopy was used to assist in needle positioning and to document the final location of the needle. For patients in the control group, the same type of needle (22 Quincke) was used to puncture the skin before being positioned subcutaneously at the T2 level. In addition, the same 10 mL of anesthetic + corticosteroid solution (5 mL of 0.75% ropivacaine + 5 mL of 2% triamcinolone) was injected at this site using radioscopy, but the solution was injected into the subcutaneous space. Fluoroscopy was used to document the location of the injection (Supplementary Fig. 1B). Fluoroscopic films documented the procedure. After blocking, the temperature in the limb was measured using a touch thermometer (TS-201, Techline, São Paulo, Brazil) over the volar aspect of the forearm at operating room temperature 21 ± 2 °C. A difference > 2 °C indicated that the TSB was successful [27].

2.6. Outcome measurements

Primary outcomes were the average pain score item from the BPI at 1 and 12 months after the blocking procedure. Secondary outcomes measures were the other pain intensity and interference scores from the BPI, NPSI, and MPQ at 1 and 12 months after the blocking procedure. Quality of life (WHOQOL-bref) and mood (HADS) were assessed before and 12 months after the block.

2.7. Side effects and blinding assessment

Patients were systematically assessed for adverse events related to the intervention right after the procedure and 1 month afterwards. Major side effects were defined as any event leading to hospitalization, death, or increase in pain of > 50% based on the NRS. Common minor side effects previously observed after sympathetic blocks performed in our institution and published in the literature were ranked and listed in a questionnaire and systematically assessed in all patients [1,40]. Blinding was assessed by asking patients a set of direct questions at the end of the study after their last assessment. These questions included the following: How much pain did you experience during the procedure? (NRS 0–10); Would you be able to tell which treatment you received? (yes/no); Which type of intervention do you think you received? (active/control); Would you be willing to undergo the procedure again if it was offered to you? (yes/no).

2.8. Sample size and data analysis

This study was powered to detect a 2-point reduction in NRS in the TSB compared to the control group. Based on the results of the sympathetic blocks performed at our institution in the 4 years preceding the study, we observed a 53% improvement (NRS) in patients treated with a thoracic sympathetic block, vs an 18% improvement in patients who received other peripheral procedures (eg, dry needling, nerve trunk block). We estimated that based on NRS reduction observed after TSB, it would be necessary to include 20 patients in each arm of the study, given a power of 0.80, a beta error < 20% and alpha < 5% (2-sided), and a 20% of estimation error. Then, 50 patients were expected to be included in the study based on a 20% dropout rate in the 12-month follow-up. Statistical analysis included all patients according to the intention-to-treat principle. Our main goal was to evaluate patients’ response to pain, for which we used the average pain intensity (BPI): α ≤ 5% risk of committing a type I error and a β ≤ 20% risk of committing a type II error. Data were expressed as the means ± SDs. The Kolmogorov-Smirnov test for normality was performed on the quantitative variables. Nonparametric data were compared with the Kruskal-Wallis, Mann-Whitney Test, and
Wilcoxon Signed Rank Test when indicated. Categorical data are presented as absolute frequencies (n) and relative frequencies (%). The associations between categorical variables according to the outcomes were analyzed with the $\chi^2$ test. When categories had <20 individuals, we adopted the Fisher’s exact test. We assumed, throughout the study, $\alpha \leq 5\%$ risk of committing type I, and $20\%$ $\beta$ risk of committing type II errors.

3. Results

Sixty-three patients were screened for eligibility. Fifty-one were included in the study and underwent the systematic, standardized treatment phase. During this initial phase, 14 patients were excluded before undergoing the blocking procedure: 5 had been screened for CRPS based on the previous diagnostic criteria, and 9 became pain-free after the standardized treatment phase. The remaining patients ($n = 37$) underwent the baseline evaluation and were randomized. After randomization but before the procedure, one patient from the TSB group was excluded due to the occurrence of unprovoked seizures. Thus, 36 patients underwent the blocking procedure (TSB; $n = 17$, control $n = 19$). After the 12-month follow-up, 15 patients were available for evaluation in the TSB group ($2$ lost) and 14 were available in the control group ($5$ lost) (Fig. 2).

3.1. Patient characteristics

Nineteen women (52.8%) participated in the study (8 [42.1%] in the TSB group and 11 [57.9%] in the control group). The mean age was $42.0 \pm 13.5$ years in the TSB and $44.4 \pm 8.9$ years in the control group. The mean disease duration was $22.7 \pm 26.3$ months in the TSB group and $21.0 \pm 21.6$ in the control group ($P > 0.4$). A history of previous general surgical interventions was significantly more common in the control group ($n = 14$) than in the TSB group ($n = 6$), $P = 0.021$. The left upper limb was more frequently affected in the control group ($n = 10$) than in the TSB group ($n = 1$; $P = 0.002$). Except for these differences, both treatment groups had similar baseline clinical, pain-related, and demographic characteristics ($P > 0.1$).

3.2. Block procedure and safety

The blockage procedure was performed in 36 patients. There were no major adverse events during the study in either group. Minor adverse events occurred in both groups (Supplementary Table 2). The total number of minor adverse events was similar between the groups (2.88 ± 2.3 vs 2.35 ± 2.4 in the TSB and control groups, respectively, $P = 0.531$). All patients in the TSB group had a > 2°C increase on the treated hand right after the procedure. Local

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**Fig. 2.** Study flowchart. TSB, thoracic sympathetic block.
temperature ranged from 27.1 ± 3.1°C before to 35.9 ± 0.8°C after the block. Seven (41.2%) patients in the TSB and none in the control group exhibited Claude Bernard-Horner’s sign after the blocking procedure.

The attendance to all scheduled physical therapy sessions appointments (total of 8 sessions) was 100% for 12 (70.6%) patients in the TSB and 14 (73.7%) patients in the control group. All of the remaining participants had ≥50% attendance to the sessions. All participants had 100% compliance to the physical therapy sessions performed before the blocking procedure (total of 4 sessions).

### 3.3. Primary and secondary outcomes

The mean of the BPI average pain intensity item at 1 month was not significantly different in the TSB (3.59 ± 3.2) compared to the control group (4.84 ± 2.7; *P* = 0.249). At 12 months, however, this score was significantly lower in the TSB group (3.47 ± 3.5) compared to the control group (5.86 ± 2.9; *P* = 0.046) (Fig. 3). Some secondary outcome measures improved after TSB. Compared to baseline values, the current pain intensity score (BPI) at 1 month decreased from 5.59 ± 2.9 to 3.53 ± 3.7 (*P* = 0.035) in the TSB group but did not significantly change in the control group (6.16 ± 3.0 to 5.84 ± 2.9) (Table 2). The MPQ total score was significantly lower in the TSB (36.56 ± 16.2) compared to the control group (42.33 ± 8.5; *P* = 0.024) at 1 month. At the 12-month assessment, the TSB group continued to report significantly lower scores on the MPQ (27.20 ± 22.2) compared to the control group (45.43 ± 23.6; *P* = 0.042; Table 2). The subscores of evoked pain in the NPSI (question 8, 9, and 10) in the TSB group (5.59 ± 1.7) were significantly lower at 1 month (3.43 ± 1.8; *P* = 0.035) and 12 months (3.02 ± 1.9; *P* = 0.02) compared to the control group (Table 2).

More patients in the control group took tramadol as a rescue medication than in the TSB group (*P* = 0.039), 1 month after the nerve block (Table 2). There were no significant differences between the groups in the number of patients taking other rescue drugs, including morphine, at 1 month or 12 months after the blocking procedure (2 patients in the control group and one in the TSB group).

The quality of life scores (WHOQOL-bref) were similar between groups at baseline and did not differ 12 months after the procedure, except on 4 subitems (of 24) related to self-satisfaction, sexual life, acceptance of body appearance, and perceived need to take medications, all of which were significantly improved by TSB. The baseline anxiety and depression (HADS) scores were similar between the groups at baseline. Although the anxiety scores did not differ between the groups at the 12-month assessment,
the depression scores were significantly lower in the TSB group compared to the control group at 12 months (Table 2). Scores from the DN4 and DASH did not differ between the groups.

### 3.4. Interim analyses

Twenty-six patients (72.2%) were available for interim pain analysis at 2, 3, 6, and 9 months. These patients were already followed by our institution's outpatient clinic and were available for supplementary assessment during follow-up. Because the trial only included 3 assessments as obligatory (baseline, 1 month, and 12 months) and covered travel expenses, these interim assessments were performed exclusively in patients attending our center on an outpatient basis. Data from these assessments suggest a better outcome in the TSB group than in the control group and are shown in the supplementary materials (Supplementary Table 1). A supplementary analysis was performed comparing the scores and clinical characteristics from patients who were available for interim assessment compared to those who were not. The analyses showed that both groups of patients had similar pain and demographic characteristics.

### 3.5. Blinding

A trained researcher assessed blinding with no other role in the research at the end of the study. The intensity of pain during the procedure did not differ between the groups; in addition, the number of patients who reported that they could guess which treatment group they were in and the type of treatment they received also did not differ between the groups ($P > 0.1$). Similarly, the number of patients who would be willing to undergo a new procedure did not differ between the groups ($P > 0.1$).

### 4. Discussion

Compared to the control group, patients undergoing TSB reported significantly lower scores on the MPQ, decreased evoked pain scores, lower current pain intensity (BPI), and lesser analgesic use of rescue tramadol at 1 month after the procedure. At the 12-month assessment, most of these improvements persisted and were accompanied by further improvements in the average pain scores, depressive symptoms, and some aspects of quality of life.

This is the first randomized, double-blinded, controlled study of TSB in CRPS and is one of the largest using sympathetic blockade in general. To date, only 2 uncontrolled studies have assessed the effects of TSB in this patient group. They found an average of 50% pain intensity reduction lasting for at least 1 week after a single TSB procedure in 85 CRPS patients [1,57]. These studies assessed pain intensity based on the visual analogue scale and Likert scale, with no specific measurements of neuropathic pain components, mood, or quality of life [1,57]. Eight prospective randomized studies assessed the analgesic effects of anesthetic block of the SGB for upper limb CRPS. These studies have marked methodological heterogeneity. For instance, only one clearly described the randomization process [52] and only 2 were double-blinded [3,43]. In 5 studies, the blinding procedure was unclear [7,37,45,52,56], and one was not blinded at all [47]. The number of patients included in these trials ranged from 4 to 82 [43,47]. The timing of assessment also was quite variable, ranging from right after the blocking procedure [43] to 3 months post treatment [47]. Some studies (n = 6) used control blocks with active drugs such as guanethidine [7], lidocaine with clonidine [37], phenolamine [45,56], or continuous infracavicular brachial plexus block [52]. In one study, physical therapy was added to the baseline treatment [47]. Two placebo-controlled studies were negative [3,43]. The
remaining active-control studies reported negative (n = 5) [7,37,45,52,56] or minimal responses (n = 1) after SGB [47].

Some have suggested that the stellate ganglion may not be the most suitable target for upper limb sympathetic block in CRPS patients [6,14,17,27]. This suggestion is mainly due to the fact that SGB may miss the sympathetic nerve fibers traveling to the upper limb in a significant proportion of individuals [31]. Thus, by blocking T2 and T3 ganglia rather than the stellate ganglion, all of the sympathetic fibers are affected by the block. In fact, Hogan et al. [27] showed that in 100 consecutive technically well-performed SGB procedures monitored by pupillary and hand temperature changes, the clinical signs of upper limb sympathetic blockade were detected only after 27 of the procedures [27]. Kuntz [31] has demonstrated that in 20% of individuals, the ganglionic sympathetic fibers projected to the upper limb directly, thus bypassing the stellate ganglion after synapsing in the upper thoracic ganglia [17,44,46]. This is important given the major difference between TSB and SGB. In TSB, the blocking agent is injected at the location of the cell bodies of the third-order sympathetic neurons. It has been demonstrated that neuronal cell bodies have more receptors to steroids and are more amenable to chemical modulation than peripheral axons [32,53]. Hence, one important methodological aspect of the current study is that we directly injected corticosteroids into the thoracic sympathetic ganglion. Autoimmune attack against peripheral nerves might trigger leukocyte extravasation, autoantibody exudation, neuroinflammation, and neuroimmune activation in associated dorsal root ganglia, sympathetic ganglion, and the spinal cord, and this has been suggested as a possible underlying mechanism of the development of CRPS [5,13,23,30,34,54]. There are data supporting pain improvement in CRPS patients after the use of systemic steroids [11,19,28]. Because steroids injected into sympathetic ganglia and the subcutaneous space will also act systemically, one cannot rule out that part of the analgesic effect observed was due to the use of this medication (and local anesthetic) in both groups [11,19,28,53]. Triamcinolone long-acting repository formulations are absorbed slowly from the injection site and provide anti-inflammatory effects for 1–4 weeks. The hypothalamic-pituitary-adrenal axis may be inhibited for up to 6 weeks after intramuscular or spinal injection [4,21]. However, it is highly unlikely that the effect of a single acute infusion of steroids lasted for all of the 12-month follow-up period. We hypothesize that the early (1–2 month) effect of the blocking procedure positively influenced other aspects of pain and its treatment, such as the efficacy of physical therapy [2], reduced use of medication and positive effects on mood, that as a whole, provided long-term positive effects. In fact, our results suggest that the positive effect of the treatment built up during the early study phase and persisted for 12 months.

This is also an important issue when considering the active-control group used in the present study. If, on one hand, this “fully treated” control group increases the number of patients necessary to prove an active intervention as actually effective, on the other hand it expands the external validity of these findings because the protocol approaches what actually happens in clinical practice. Long follow-ups are frequently associated with an increase in dropouts and blinding issues [29]. We had a lower-than 20% dropout rate, which was similar to other long-term studies [16]. We also performed a systematic blinded interim assessment in the patients in our outpatient clinic at 2, 3, 6, and 9 months (Supplementary Table 1). Despite the low number of patients available for this assessment, these patients did not significantly differ in terms of clinical pain and sociodemographic characteristics from those who did not present to our center during this period. These assessments suggest that while the 1-month evaluation had some positive results favoring TSB over the control group, these changes are clearer in the second month after treatment. Blinding is equally a central subject in long-duration clinical trials. In addition to diligently preventing patients from observing the site of injections during the procedure by placing them in a ventral decubitus position and performing all assessments and evaluations in a double-blinded fashion, we assessed the quality of blinding by using a standardized questionnaire. Patients from both groups answered the questions similarly. In addition to all these measures, one cannot be completely sure that the presence of Claude Bernard-Horner’s sign or blurred vision after the procedure would not bias blinding. However, because all the other minor side effects were similar between the groups and because patients were sympathetic block naïve, we believe that these aspects did not play a major role in biasing the results. Another important issue is the safety of the procedure. Based on the present results, there were no major adverse events related to the blocking procedure and most minor side effects were similarly distributed between both groups. Therefore, we believe that TSB is a safe procedure. Larger controlled trials are needed to confirm this initial impression. In a larger open study including results from 322 TSB procedures guided by computed tomography scans, adverse events occurred in 7.1% of the procedures and included 3 cases of pneumothorax and one spinal cord puncture [1]. In a study on 557 neurolytic TSB with phenol or alcohol and fluoroscopy guidance [40], complications occurred in 7.5% of the procedures and included neuritis (n = 23), Horner’s syndrome (n = 14), and pneumothorax (n = 3) [40].

A clear limitation of the study is its relatively small sample size. We calculated the number of patients based on our clinical experience with TSB, but this estimation method is clearly associated with limitations. In addition, the dropout rates expected in a long-term trial led to a relatively small overall percentage of patients who completed the study (81.6%). While this is one of the largest published trials based in this area that used a controlled, double-blinded methodology, we believe that a study with a larger number of patients would more strongly support the external validity of our finding. At the end of the study, recruitment was much lower than expected and we could not include the expected 20 patients per arm described in the original plan. In addition, randomization would be more accurate if performed in blocks, which was not the case and could be the reason why some variables were not evenly distributed in both groups, such as handedness and the number of previous surgical interventions.

In conclusion, our data showed that a single TSB is a safe procedure and has both short- (1-month) and long- (12-month) term positive impact on upper limb CRPS type I as an add-on treatment to a standardized rehabilitation and pharmacological treatment program. While the impact of the procedure on quality of life is slightly significant, pain reduction, decrease in evoked pain, and amelioration of depressive symptoms, were significantly superior to the control treatment.

Conflict of interest statement

There are no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2014.08.015.