EVIDENCE-BASED MEDICINE

Evidence-Based Interventional Pain Medicine According to Clinical Diagnoses

16. Complex Regional Pain Syndrome

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■ Abstract: Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy is a pain syndrome with an unclear pathophysiology and unpredictable clinical course. The disease is often therapy resistant, the natural course not always favorable. The diagnosis of CRPS is based on signs and symptoms derived from medical history and physical examination. Pharmacological pain management and physical rehabilitation of limb function are the main pillars of therapy and should be started as early as possible. If, however, there is no improvement of limb function and persistent severe pain, interventional pain management techniques may be considered.

Intravenous regional blocks with guanethidine did not prove superior to placebo but frequent side effects occurred.

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Therefore this technique receives a negative recommendation (2 A–). Sympathetic block is the interventional treatment of first choice and has a 2 B+ rating. Ganglion stellatum (stellate ganglion) block with repeated local anesthetic injections or by radiofrequency denervation after positive diagnostic block is documented in prospective and retrospective trials in patients suffering from upper limb CRPS. Lumbar sympathetic blocks can be performed with repeated local anesthetic injections. For a more prolonged lumbar sympathetic block radiofrequency treatment is preferred over phenol neurolysis because effects are comparable whereas the risk for side effects is lower (2 B+). For patients suffering from CRPS refractory to conventional treatment and sympathetic blocks, plexus brachialis block or continuous epidural infusion analgesia coupled with exercise therapy may be tried (2 C+). Spinal cord stimulation is recommended if other treatments fail to improve pain and dysfunction (2 B+). Alternatively peripheral nerve stimulation can be considered, preferentially in study conditions (2 C+).

Key Words: complex regional pain syndrome, reflex sympathetic dystrophy, evidence based medicine, nerve block, sympathetic block, spinal cord stimulation

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INTRODUCTION

This article on Complex Regional Pain Syndrome (CRPS) is part of the series "Evidence-Based Interventional Pain Medicine according to Clinical Diagnoses." Recommendations formulated are based on "Grading strength of recommendations and quality of evidence in clinical guidelines" described by Guyatt et al.,¹ and adapted by van Kleef et al.² in the editorial accompanying the first article of this series.² (Table 1) In the description of the interventional therapy, we focused primarily on therapies used in anesthesiological practice. The latest literature update for this article was performed in December 2009.

CRPS is a syndrome occurring as a complication of surgery or trauma, most often in 1 extremity; however. CRPS in multiple extremities has been described. Spontaneous development can also occur.³ The most recent definition from the International Association for the Study of Pain (IASP) is that CRPS is a collection of locally appearing painful conditions following a trauma, which chiefly occur distally and exceed in intensity and duration the expected clinical course of the original trauma, often resulting in considerably restricted motor function. CRPS is characterized by a variable progression over time.

The clinical picture was first described more than 100 years ago by Sudeck and in the 1860s by Mitchell. A review of the literature reveals 72 different names for this syndrome, like Sudeck's atrophy, algodystrophy, posttraumatic dystrophy, and the most frequently used

term, reflex sympathetic dystrophy. Since a consensus meeting of the IASP in Orlando in 1993, "Complex Regional Pain Syndrome" has been the term agreed upon. A distinction is made between Type 1 (without) and Type 2 (with demonstrable nerve damage).⁴ More recently, a third type has been added, namely CRPS Not Otherwise Specified (NOS), involving a syndrome that only partially complies with the diagnostic criteria, but where no other diagnosis can be made. Bruehl et al.⁵ defined a number of subtypes, namely: a relatively limited syndrome with predominating vasomotor symptoms, a relatively limited syndrome with predominating neuropathic pain/sensory disturbances and a florid CRPS comparable to the classic description of reflex sympathetic dystrophy with the highest levels of motor and trophic signs. The estimated incidence varies from 5.46 to 26.2 per 100,000 person years. CRPS in adults occurs slightly more often in the upper extremities. A fracture is the most common initial event when it occurs in the upper extremity. Women are affected 3.4 to 4 times more often than men. The mean age at diagnosis does not differ between men and women and varies between 47 and 52 years.^{6,7}

PATHOPHYSIOLOGY

In the literature, there is ongoing debate on the pathophysiology of CRPS.

Current understandings involve peripheral, afferent, efferent and central mechanisms.

| Table 1. Summary of Evidence Scores and Implications for Recommendation | Tab | le | 1. | Sum | mary | of | Evide | ence | Scores | and | Impl | icat | ions | for | Recommend | lat | ion |
|---|-----|----|----|-----|------|----|-------|------|--------|-----|------|------|------|-----|-----------|-----|-----|
|---|-----|----|----|-----|------|----|-------|------|--------|-----|------|------|------|-----|-----------|-----|-----|

| Score | Description | Implication |
|--------------|---|-------------------------|
| 1 A+ 1 B+ | Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens One RCT or more RCTs with methodologic weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens | Positive recommendation |
| 2 B+ | One or more RCTs with methodologic weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens | J |
| 2 B± | Multiple RCTs, with methodologic weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens. | Considered, preferably |
| 2 C+ | Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens | study-related |
| 0 | There is no literature or there are case reports available, but these are insufficient to suggest effectiveness and/or safety. These treatments should only be applied in relation to studies. | Only study-related |
| 2 C– | Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit | |
| 2 B- | One or more RCTs with methodologic weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit | Negative recommendation |
| 2 A- | RCT of a good quality which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefit | J |

RCT, randomized controlled trial.

Peripheral mechanisms include hypoxia caused by vasoconstriction induced by endothelial dysfunction, leading to a decreased level of nitric oxide (NO) and increased level of endothelin-1 (ET-1) in the affected extremity. Sterile inflammation has been demonstrated by increased levels of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha).⁸ Neurogenic inflammation is caused by excretion of neuropeptides from nociceptive C-fibers, which was demonstrated by elevated levels of substance P, bradykinin, and calcitonin gene-related peptide (CGRP).⁹ Denervation hypersensitivity can be caused by peripheral degeneration of small fiber neurons in the skin of affected limbs, leading to inappropriate firing.¹⁰ Nociceptive afferent input may be caused by an increase in the number of alpha 1 receptors in the affected extremity, increased peripheral alpha adrenergic receptor hypersensitivity, and chemical coupling between sympathetic and nociceptive neurons in the skin of CRPS affected limbs.¹¹ Possible efferent mechanisms are sympathetic dysfunction leading to variable vasoconstriction, hypoxia, and sweating abnormalities. Dysfunctional efferent motor pathways may lead to involuntary movements, dystonia, and decreased range of motion. Central mechanisms, such as (supra)spinal sensitization through N-methyl-D-aspartate (NMDA) and neurokinin-1 (NK-1) receptor interaction, have also been described, as well as (secondary) psychological factors like pain-related fear and movement anxiety.12

I. DIAGNOSIS

I.A HISTORY

CRPS is usually preceded by trauma or surgery, the affected area usually extends beyond the original injury. The disease arises mostly glove-like in an arm or socklike in a leg. The symptoms consist of a combination of continuous pain, sensory dysfunction, vasomotor and sudomotor dysfunction, and motor and trophic signs. Case reports of CRPS-like symptoms without pain are mentioned, yet these are rare.

I.B PHYSICAL EXAMINATION

Sensory dysfunction of the skin may include hyperalgesia and mechanical allodynia, but also hypoalgesia and mechanical hypoesthesia. Asymmetry of skin temperature and changes in skin color occur, as well as edema and hyper- or hypohidrosis. Signs of motor dysfunction include a reduction in the "range of motion" of affected joints and/or weakness, tremor, involuntary movements, bradykinesia, and dystonia. Abnormal skin hair growth and changes in nail growth may be observed. Symptoms may vary over time, and pain and other symptoms are often exacerbated with exertion of the affected extremity.⁴

I.C ADDITIONAL TESTS

There is no specific diagnostic test available, but various additional tests can be important in excluding other diagnoses. Laboratory tests such as full blood count, erythrocyte sedimentation rate, and C-reactive protein are normal in CRPS, but may help to exclude infection or rheumatologic disease. Duplex scanning and ultrasound may exclude peripheral vascular disease. Nerve conduction studies are helpful in excluding peripheral neuropathic disease or confirming nerve involvement in CRPS-2. Plain radiographs of the skeleton and contrastenhanced magnetic resonance imaging (MRI) may demonstrate osteoporosis in the affected limb, but are of no diagnostic value.¹³ Three-phase bone scanning may demonstrate increased uptake of technetium Tc 99m biphosphonates due to increased bone metabolism.¹⁴ Skin temperature measurements by infrared thermometry may reveal long-term changes in skin temperature and skin temperature dynamics between the affected and non-affected side.¹⁵ Other tests may only be of value to quantify or substantiate the clinical symptoms and are predominantly of use in scientific research. These include: quantitative sensory testing; resting sweat output; provocative sweat output test by the quantitative sudomotor axon reflex test; sympathetic skin response; volumetry in edema of the extremities; visual analogue scales for pain; impairment level sumscore; skills questionnaires; walking, rising and sitting down skills questionnaires, and upper limb activity monitoring.¹⁶

I.D DIFFERENTIAL DIAGNOSIS

Diagnosis is based upon criteria obtained from medical history and physical examination. The most commonly used criteria are the original IASP-criteria and the modified diagnostic criteria according to Harden and Bruehl.¹⁷⁻¹⁹ The criteria as described by Veldman are often used in the Netherlands.³ All criteria have essentially been determined empirically and overlap partially, whereby the IASP criteria are the most sensitive, and the modified criteria according to Harden and Bruehl the most specific (Tables 2 to 4).^{18,19}

Table 2. IASP Criteria (Merskey, 1994)

- 1. Develops after tissue damage (CRPS type-1) or nerve damage (CRPS type-2)
- 2. Continuous pain, allodynia or hyperalgesia disproportional to the inciting event.
- 3. Evidence at some time of edema, abnormal skin blood flow and sudomotor abnormalities in the region of pain.
- 4. Other causes of pain or dysfunction are excluded.

Criteria 2,3, and 4 must be fulfilled

Table 3. Modified Diagnostic Criteria (Harden, 2007)

- 1. Continuous pain, disproportionate to the inciting event.
- 2. Patients should have at least 1 symptom in each of the following
- categories and 1 sign in 2 or more categories. Categories:
 - 1. Sensory (allodynia, hyperalgesia, hypoesthesia)
 - 2. Vasomotor (temperature or skin color abnormalities)
 - 3. Sudomotor (edema or sweating abnormalities)
 - 4. Motor/trophic (muscle weakness, tremor, hair, nail, skin abnormalities)

Table 4. Dutch criteria (Veldman 1993)

- A. 4 or 5 of the following symptoms:
- 1. Inexplicable diffuse pain
- 2. Difference in skin color between affected and contralateral extremity
- 3. Diffuse edema
- 4. Difference in skin temperature between affected and contralateral extremity
- 5. Limited "active range of motion"
- B. The occurrence or increase of above-mentioned symptoms with use of the involved extremity.
- C. Above-mentioned symptoms are present in an area that is greater than the area of original trauma or surgery and distal to this area.

CRPS requires an extensive differential diagnosis, because many of the symptoms can also be caused by other diseases. Distinction should be made with vascular and myofascial pain syndromes, inflammation, vascular diseases, and psychological problems. (Table 5)

II. TREATMENT OPTIONS

II.A CONSERVATIVE MANAGEMENT

The primary treatment of CRPS consists of early active mobilization physical therapy combined with pharmacological pain treatment. Physical therapy proved superior to occupational therapy and superior to a control group in a randomized controlled trial (RCT) of 135 CRPS-1 patients.²⁰ More recently, good results with a high level of evidence have been described with graded motor imagery therapy with imagined hand movements and mirror therapy for upper extremity CRPS.^{21–23} The use of

Table 5. Differential Diagnosis of Complex RegionalPain Syndrome

- Neuropathic pain syndromes
- Peripheral (poly)neuropathy
- Nerve entrapment
- Radiculopathy
- Postherpetic neuralgia
- Deafferentation pain after CVA
- Plexopathy
- Motor neuron disease
- Vascular diseases
- Thrombosis
- Acrocyanosis
- Atherosclerosis
- Raynaud's disease
- Erythromelalgia

- Inflammation • Erysipelas
- Inflammation NOS
- Bursitis
- Seronegative arthritis
 - Rheumatologic diseases
 - Mvofascial pain
 - Overuse
 - Disuse
 - Tennis elbow
 - Repetitive strain injury
 - Fibromyalgia

Psychiatric problems

- Somatoform pain disorders
- Münchhausen syndrome

pharmacological agents is guided by the involved mechanism (symptom oriented treatment, see algorithm in (Figure 1). Psychological support may be initiated if there is no improvement with the above mentioned regime.

Anti-inflammatory Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of CRPS were only studied in a small trial comparing scintigraphic outcome of calcitonin with NSAIDs. NSAIDs were inferior to calcitonin.²⁴

A number of RCTs studied the effect of oxygen radical scavengers. Topical application of dimethyl sulfoxide 50% (DMSO-50%) has been found superior to placebo and oral N-acetylcysteine was generally equally effective as DMSO in the treatment of CRPS-1.^{25,26}

Intravenous mannitol, however—another free radical scavenger—has proven to be ineffective.²⁷ Biphosphonates, which reduce the increased bone turnover, such as oral alendronate or intravenous pamidronate, were studied in 2 RCTs showing effect in favor of the biphosphonates.^{28,29} Calcitonin, a polypeptide hormone with a similar mode of action as the biphosphonates, can be administered subcutaneously or by intranasal spray. The different studies on these preparations for the management of CRPS show mixed results. A critical review concluded that in well-designed trials, the effectiveness cannot be demonstrated.³⁰

In a placebo-controlled RCT with 23 CRPS patients, the use of prednisone maximum 10 mg thrice daily for 3 weeks and then taper the dose during the next weeks until a maximum treatment period of 12 weeks, led to 75% improvement in all 13 treated patients as compared to only 2 out of 10 patients who received placebo.³¹



Another RCT compared the use of 40 mg prednisolone per day with piroxicam in CRPS following stroke and found significant improvement after 1 month of prednisolone treatment.³² However, since the use of corticosteroids may lead to potential serious complications, longterm use of corticosteroids is not recommended.

Analgesic Therapies

There are no studies on the analgesic action of acetaminophen (paracetamol) in CRPS. As such, the usefulness

Figure 1. Clinical practice algorithm for the treatment of CRPS.

of acetaminophen and NSAIDs is questionable. Slow release morphine (90 mg/d) was not effective in a double-blind placebo-controlled trial, so opioids are not likely to be of any benefit. The pain in CRPS is of neuropathic nature. First-line therapy of neuropathic pain consists of tricyclic antidepressants (TCA) like amitriptyline, the most frequently investigated drug for neuropathic pain. It improves pain and sleep impairment and can be given in CRPS although there are no trials that evaluate TCAs in CRPS.³³ Carbamazepine in a dose of 600 mg/d significantly reduced pain in a placebocontrolled RCT.³⁴ Gabapentin has a mild effect on pain in a subpopulation of CRPS patients and is therefore worth trying.³⁵ The NMDA blocker, ketamine, administered intravenously in subanesthetic dosages of maximal 20 to 25 mg/h/70 kg, has been shown to be effective in relieving CRPS-associated pain in 1 retrospective case series report and 2 randomized doubleblind placebo-controlled trials.³⁶⁻³⁸

Vasodilatory Therapy

Patients with hyperactive vasomotor symptoms leading to (intermittent) cold extremity CRPS may respond to alpha 1 adrenergic blockers like phenoxybenzamine and terazosin, or calcium channel blockers like nifedipine.^{39,40}

Spasmolytic Therapy

Oral spasmolytic therapy with oral benzodiazepines or oral baclofen may be used in CRPS related dystonia, tremor or myoclonus.¹⁶

In conclusion: Physical therapy with active mobilization and graded motor imagery treatment, together with a symptom-oriented pharmacological treatment, is the best initial approach of CRPS.

II.B INTERVENTIONAL MANAGEMENT

If conventional therapy fails to give adequate relief of symptoms (eg, pain score more than 4), interventional pain management techniques may be considered. These techniques are: intravenous regional blocks, sympathetic blocks of the ganglion stellatum for CRPS in the arm, and of the lumbar truncus sympathicus for CRPS in the leg. Peripheral and spinal cord stimulation and epidural or intrathecal drug administration may also be considered. Somatic and central neuraxial blocks for the management of CRPS have also been described.

Intravenous Regional Blocks

Intravenous regional blocks (IVRBs) with guanethidine for the treatment of CRPS-1 were first described by Hannington–Kiff.⁴¹ The technique consists of the intravenous administration of 10 mg to 20 mg of guanethidine in a heparinized, isotonic saline solution of 25 mL, after elevating the arm for 1 minute and inflating a tourniquet at 50 mm Hg above the patient's systolic blood pressure. The tourniquet is maintained for 15 minutes to 30 minutes, after which it is let down slowly. This technique causes displacement of noradrenalin (NA) from presynaptic vesicles and prevents the re-uptake of NA leading to an increase in skin blood flow for several days.

Intravenous Regional Blocks with Guanethidine. The effect of IVRB with guanethidine for CRPS was studied in several case series,^{42–44} prospective trials⁴⁵ and 3 RCTs.^{46–48} The outcome of case series is variable.

One study of 17 patients treated with a series of IVRB guanethidine and lidocaine resulted in successful outcome in all patients. The high success rate in this series in attributed to the fact that 25 blocks were given over a period of 11 weeks compared to the usual 1 block to 6 blocks.⁴³ This high frequency of IVRB is not common practice and cannot be supported.

In a prospective case-controlled study of 26 patients with CRPS of the hand significantly better pain reduction and improvement of function was observed after treatment with DMSO-50% ointment 4 times daily during 3 weeks when compared to treatment with IVRB guanethidine twice a week during 3 weeks.⁴⁵ In a double-blind crossover study with saline, high-dose guanethidine, and low-dose guanethidine, no significant difference between groups was found. All groups reported less than 30% pain reduction; there was no evidence of a dose-response for guanethidine. The trial was stopped prematurely after serious adverse events in 2 patients with the high dose of guanethidine.⁴⁶ A double-blind controlled multicenter RCT comparing IVRB with guanethidine or placebo in a group of 60 CRPS patients found no differences in long-term outcome.⁴⁷ In another RCT, in a group of 57 CRPS patients, comparing IVRB with guanethidine to saline, again, no significant long-term differences were found.⁴⁸

Intravenous regional blocks with other medications. IVRB with lidocaine and methylprednisolone was not effective when compared to saline in a RCT in 22 CRPS-1 patients.⁴⁹ In a retrospective case series of 61 patients treated with IVRB containing lidocaine and ketorolac, 26% of patients had complete resolution of pain, 43% had partial response, and 31% had no response to this therapy.⁵⁰ In 1 double-blind placebo-controlled study, the use of intravenous regional ket-anserin, a potent vasodilator, had a pain relieving effect.⁵¹

In conclusion, there is evidence that IVRB with guanethidine is not effective for the management of CRPS. The use of ketanserin was only studied in an earlier small trial.

Sympathetic Blocks: Ganglion Stellatum (Stellate Ganglion) and Lumbar Block

The sympathetic nervous system has been implicated in numerous pain syndromes ranging from neuropathic pain to vascular pain to visceral pain. A role for sympathetic block (SB) is presumed. Recently, this was extensively reviewed by Day.⁵² He concluded that despite frequent use of minimally invasive sympathetic blocks and neurolysis, their efficacy for providing analgesia has been sparsely reported in the literature. Focusing on sympathetic block for CRPS, we could identify 13 articles: 2 on SB (Ganglion stellatum, stellate ganglion block [SGB] and lumbar sympathetic block [LSB]), 6 on SGB, and 5 on LSB.

Ganglion Stellatum (Stellate Ganglion) block. Ganglion stellatum (stellate ganglion) block (SGB) is commonly performed for CRPS of the upper extremity. This cervicothoracic ganglion sends sympathetic afferents to the truncus cervicalis of the plexus brachialis, and is located anterolaterally to the head of the first rib, lateral to the musculus longus colli, and posteromedial to the arteria vertebralis⁵³ (Figure 2).

Linson et al.⁵⁴ described the use of SGB for patients with CRPS in the upper arm. Twenty-eight patients were all treated with indwelling-catheter injections of bupivacaine 0.5%, 4 times a day during a mean of 7 days (range 1 day to 14 days). Short-term outcomes were good: 90% of patients improved during treatment. In the long-term, at 6 months to 6 years, 2 patients were lost to follow-up. Of the remaining 26 patients, 19 felt that their pain had remained improved. Seven patients however, judged the pain improvement in the long term as minimal. Another study also found prolonged SGB with bupivacaine useful if intermittent SGBs plus conservative treatment with analgesics, tranquilizers and physical therapy failed. After an average of 3 years follow-up, there was 25% relapse rate and 75% marked to complete improvement in a group of 26 posttraumatic CRPS patients.55 The combination therapy of daily SGB with up to 10 to 15 injections, together with oral amitriptyline up to 100 mg per day, was found to give significant improvements in both VAS pain ratings and grip force strength.56 In another study, SGB performed within 16 weeks after onset of symptoms gave significantly better pain relief than if performed later than 16 weeks after symptom onset. Moreover, it was found that a decrease in skin perfusion of the CRPS extremity as compared to the normal side, adversely affected the efficacy of the SGB.57

In a small case series of 6 patients, the effect of opioid infiltration for CRPS-1 was examined; the data showed no efficacy of morphine when injected around the ganglion stellatum.⁵⁸

Radiofrequency (RF) denervation of the ganglion stellatum was found comparably effective to other methods of SGB blockade with 40.7% of patients having more than 50% pain relief, in a selected group of patients who responded positively to a diagnostic block with 4 mL to 6 mL lidocaine 1%.⁵⁹

LSB. LSB is frequently performed at the L2 to L4 lumbar levels for complex regional pain syndrome of the lower extremity. Pre- and post ganglionic fibers form a synapse in the sympathetic ganglia. These ganglia are located at the anterolateral side of the lumbar vertebrae (Figure 3). Unlike the SGBs, imageguided techniques are mandatory. Under fluoroscopic guidance, the technique has been demonstrated to be easy to perform.⁶⁰ Computerized tomography (CT),⁶¹ MRI,62 and ultrasound based techniques have also been described and their reliability demonstrated.63 However, since CT and MRI are time-consuming and less suitable for daily practice, fluoroscopy remains the method of choice. Ultrasound-based techniques, however, may become more important in the near future.

LSBs can be performed by repeated injections of local anesthetic. In order to achieve longer-lasting results, neurolysis with, for example, phenol, has been used. Radiofrequency treatment of the lumbar sympathetic chain is a third method for performing LSB.

In 29 patients with CRPS of the lower limb following total knee replacement, LSB was performed with intermittent injections of 20 mL bupivacaine 0.375%. Complete pain relief was found in 13 (45%) patients, partial pain relief in 12 (41%) patients and no pain relief in 3 (10%) patients. One patient dropped out due to technical failure.⁶⁴ Iohexol, a regularly used watersoluble contrast dye, was found not to alter the effect of LSB and even improved pain relief. In a subset of 11 patients, who agreed to report some aspects of pain in more detail, it was noted that the increase in skin temperature correlated significantly with the relief of allodynia.⁶⁵

RF LSB at the L2–L4 sympathetic ganglia was documented in a case series of 20 patients with CRPS; 5 (25%) became pain free and 9 (45%) had temporary pain relief.⁶⁶ RF LSB was compared with phenol neurolysis. It was found that phenol retained sympatholytic



Figure 2. Anatomic illustration of the ganglion stellatum; Illustration: Rogier Trompert Medical Art. http://www.medical-art.nl



Figure 3. Anatomic illustration of the lumbar truncus sympathicus; Illustration: Rogier Trompert Medical Art. http://www.medicalart.nl

effects in 89% of patients after 8 weeks, as compared to only 12% in the RF group.⁶⁷ In a RCT performed in 20 CRPS-1 patients, it was found that RF treatment at 80°C for 90 seconds at the L2–L4 sympathetic ganglia was as effective as phenol neurolysis at the same ganglia (3 mL phenol 7% at each lumbar level). All patients had statistically significant reduction from baseline of various pain scores at 4 months follow-up; however, phenol caused neuropathic pain symptoms in 1 patient (10%).⁶⁸

Sympathetic Blocks. In a double-blind, placebocontrolled crossover study, it was found that the duration of pain relief by SB with local anesthetics was reliably longer (90 hours) as compared to saline (20 hours).⁶⁹ Sympathetic blocks were examined (SGB and LSB) with weekly injections of 14 mL to 16 mL bupivacaine 0.25%, or continuous bupivacaine 0.25% infusions of 5 mL per hour for 5 days (if pain relief was limited to the duration of the local anesthetic). Significant long-term improvement of pain (47% reduction in VAS pain score) and functionality was found in all patients at a mean follow-up of 9.4 months. A 50% or greater relief from pain after diagnostic block was highly correlated with improvement at long-term follow-up. Mechanical and thermal allodynia predicted a positive response to initial sympathetic block. Anxiety negatively influenced pain relief and functional outcome.70

A recent trial in 9 patients with CRPS-1 of more than 6 months duration compared the analgesic action of LSB with bupivacaine to LSB with bupivacaine mixed with botulinum toxin A (BTA); it was found that BTA significantly increased the analgesic action of the LSB. Analgesia duration was prolonged from fewer than 10 days (95% CI: 0 to 12) to 71 days (95% CI: 12 to 253). The mechanism of action being explained by the BTA preventing the release of acetylcholine from the preganglionic sympathetic nerves and thus inducing long-lasting but not permanent sympathetic block.⁷¹

In conclusion: SGB by means of intermittent injections of local anesthetic for the management of CRPS of the upper limb was documented in retrospective and prospective studies. RF SGB was evaluated in a retrospective study. LSB with local anesthetic was demonstrated to be superior to placebo injection. RF LSB yields comparable results to phenol neurolysis. The latter may produce a longer effect but the risk for deafferentation pain is higher; therefore, RF treatment is preferred.

Neurostimulation

Transcutaneous Electrical Stimulation. Transcutaneous electrical nerve stimulation (TENS) may give pain relief in a subgroup of patients with CRPS.⁷² Although there is no conclusive evidence for the use and effectiveness of TENS, this therapy is noninvasive with only minimal adverse events, the most common being a contact allergy for the skin electrodes.⁷³ This makes TENS suitable as a preliminary or adjunctive therapy.⁷⁴

Spinal Cord Stimulation. For patients with chronic CRPS who do not respond to conservative medical and rehabilitation therapy or sympathetic blocks, Spinal Cord Stimulation (SCS) may be considered. The shortterm effect of this therapy in patients with CRPS has been demonstrated in a randomized study.75 In this study, 54 patients with CRPS were included and randomized 2:1 to receive SCS and physical therapy or a standard regimen of physical therapy alone. Thirty-six patients were assigned to and treated with a test SCS. Twenty-four of those reported a reduction in pain and in these patients a definitive system was implanted. Eighteen patients only received physical therapy. Six months posttreatment, the intention to treat (ITT) analysis showed a clear reduction in pain intensity in the group with stimulated patients despite the fact that only 24 of the 36 patients were actually treated with SCS. The positive effects on pain and global perceived effect remained in an ITT analysis 2 years after implantation.⁷⁶ Pain reduction was identical in patients treated with a cervical lead compared to a lumbar lead.⁷⁷ Five years after the start of treatment the differences were smaller, but the patients who were treated with SCS were still doing better than the patients who had a negative test SCS or those who were in the control group. At the end of the follow-up period, despite the diminishing effect, 95% of the patients treated with the SCS indicated that they would have been willing to undergo the treatment again to achieve the same result.⁷⁸ A recent review on the clinical and cost-effectiveness of SCS in the management of chronic neuropathic or ischemic pain suggests that this treatment is effective in reducing the chronic neuropathic pain of CRPS type 1.⁷⁹

Peripheral Nerve Stimulation. In a prospective case series, peripheral nerve stimulation (PNS) with surgically placed plate type electrodes connected with an implantable pulse generator reduced allodynic and spontaneous pain in 19 (63%) out of 30 implanted

patients with CRPS and symptoms in the distribution of 1 major peripheral nerve.⁸⁰ In a retrospective study with 52 patients (48 CRPS-2 patients and 4 phantom limb patients), 47 patients were implanted after a positive trial stimulation. Of these patients, 43 (91%) had lasting excellent to good success with marked pain reduction and reduction of pain related disability.⁸¹ In another retrospective study 41 PNS devices were implanted in 38 patients with pain in a peripheral nerve distribution. Over 60% of patients had significant improvement of their pain of more than 50% following implantation of the peripheral nerve stimulator.⁸² The technique can only be applied if the pain is in the distribution of a peripheral nerve and is thus less suitable for most CRPS-1 patients.

Somatic and Central Neuraxial Blocks

Plexus Brachialis Block. Somatic nerve block of the plexus brachialis also blocks the efferent sympathetic nerves around it. Theoretically somatic blockade increases the ability to tolerate physical therapy, especially if the shoulder is also affected. In a retrospective case series in 25 patients, of which 17 CRPS patients, improvement in pain and range of motion was found after interscalene block with 30 mL to 40 mL bupivacaine 0.125% injected every other day up to a total of 10 injections. This approach was suggested if sympathetic blockade failed.⁸³

In a small case series of 6 CRPS patients treated with continuous or daily axillary injections with bupivacaine together with physical and occupational therapy, 3 out of 6 patients responded well to this therapy; another patient also responded well initially, but the catheter had to be removed due to infection at the insertion site. The 2 poor responders were chronic CRPS patients.⁸⁴

Epidural Administration of Drugs. The epidural administration of opioids and other drugs is increasingly being offered for non-malignant pain. Epidural bupivacaine in high anesthetic doses for 2 days to 3 days followed by epidural infusion of opioids for up to 7 days together with continuous passive motion allowed for recovery of the knee function in patients with CRPS of the knee.⁸⁵ Epidural clonidine has been demonstrated to give short-term pain relief in chronic CRPS and to be possibly effective in the long term with small VAS reductions from 7.0 ± 0.4 to 5.1 ± 0.6 (P < 0.05).⁸⁶

Unilateral cervical epidural analgesia with low dose bupivacaine and clonidine by continuous infusion for CRPS may be an interesting approach. The low bupivacaine dose gives only minimal limb muscle weakness and allows for active rehabilitation therapy.⁸⁷ In a retrospective study, 37 CRPS-1 patients were treated with this unilateral epidural catheter technique with continuous bupivacaine and fentanyl infusions. Of these patients almost 90% improved significantly when treated within 1 year after onset of symptoms. If treatment was initiated more than 1 year after onset and if more than 1 limb was involved, the success rate decreased dramatically.⁸⁸

Intrathecal Administration of Drugs. The intrathecal administration of drugs has been utilized increasingly in the last 30 years. Intrathecal administration of morphine with a totally implantable drug delivery system gave > 50% pain relief in a case series of 5 patients with chronic CRPS.⁸⁹ Intrathecal treatment of CRPS pain with bupivacaine in high anesthetic doses up to 90 mg per day was studied in a small series of 3 patients. The infusion improved pain but did not prevent the syndrome from becoming chronic and was therefore not recommended.⁹⁰

Intrathecal baclofen improves dystonia, pain, disability, and quality of life in patients with CRPS-1 associated dystonia but is associated with a high complication rate as described below.⁹¹

Intrathecal ziconotide (a nonopioid analgesic) may be a promising drug for the treatment of refractory CRPS pain but requires more research.⁹²

II.C COMPLICATIONS OF INTERVENTIONAL MANAGEMENT

Complications of the Intravenous regional Blocks

The IVRB technique is a relatively safe procedure to perform but with frequent minor side effects like dizziness (41% of patients) after release of the tourniquet.⁵⁰ Serious orthostatic hypotension may occur.⁴⁶

Complications of the Ganglion Stellatum (Stellate Ganglion) Block

The incidence of severe complications is 1.7 in 1,000 patients. Potentially life-threatening complications usually arise from inadvertent subarachnoid injection or injection in the arteria vertebralis. This makes ECG monitoring and placement of an intravenous line prior to performing the procedure mandatory.⁹³ Actually the autonomic innervation of the arm occurs via Th1. However puncture at this level gives a small chance of injecting into the thoracic pleural cavity. To prevent this

it is possible to first inject towards C7 and then adjust the needle in the direction of Th1. One potential side effect is the occurrence of Horner's syndrome caused by the local anesthetic spreading to the cervical truncus sympathicus. Hoarseness can also occur via spread to the nervus laryngeus recurrens.

Complications of the Lumbar Sympathetic Block

Blocking the sympathetic nervous system causes vasodilatation in the extremity which may lead to (orthostatic) hypotension. Therefore patients should receive intravenous fluid infusion prior to treatment. During recovery blood pressure should be measured intermittently over a period of 45 minutes. After the recovery period sufficient fluid intake during the first 24 hours is advised. Patients can sometimes develop a warm and edematous leg that can possibly be interpreted as overshoot. These symptoms usually disappear spontaneously after about 6 weeks. Another possible complication is damage to the nervus ilioinguinalis or more frequently (5% to 10%) the nervus genitofemoralis. This can give a neuropathic deafferentation pain. An alternative approach, the transdiscal technique, has been demonstrated to lower the risk of nervus genitofemoralis neuritis.94 Similarly, this risk is reduced if RF denervation of the lumbar truncus sympathicus is used instead of injecting a neurolytic agent.⁶⁷ With bilateral chemical LSB men can become impotent.

Complications of Spinal Cord Stimulation

Possible complications that require reoperation include electrode dislocation or pain from the implanted pulse generator pocket.⁷⁶ Life-threatening complications like meningitis are rare but other adverse events like infection, dural puncture, pain in the region of a stimulator component, equipment failure, revision procedures other than battery change and removal operations occur in 34% of the patients.⁹⁵

Complications of Peripheral Nerve Stimulation

Possible complications requiring reoperation are related to the surgical technique or PNS equipment design and include migration of the electrode in 33%, infection in 15% and the need for placement in an alternative location in 11% of patients.⁹⁶

Complications of Plexus Brachialis Block

Plexus brachialis block is a relatively safe procedure with the most common complication being infection of the catheter skin insertion site.

Table 6. Summary of Evidence for Interventional Pain Management of CRPS

| Technique | Score | | |
|--|-------|--|--|
| Intravenous regional block guanethidine | 2 A- | | |
| Ganglion stellatum (stellate ganglion) block | 2 B+ | | |
| Lumbar sympathetic block | 2 B+ | | |
| Plexus brachialis block | 2 C+ | | |
| Epidural infusion analgesia | 2 C+ | | |
| Spinal cord stimulation | 2 B+ | | |
| Peripheral nerve stimulation | 2 C+ | | |

Complications of Epidural and Intrathecal Drug Administration

Frequent complications of epidural drug administration include infections and catheter or pump failure.⁹⁷ Adverse effects of intrathecal drug administration include infections, catheter and pump system failures, post dural puncture headache, and the formation of intrathecal granulomas, carrying the potential to produce spinal cord compression.

II.D EVIDENCE FOR INTERVENTIONAL MANAGEMENT

A summary of the available evidence is given in Table 6.

III. RECOMMENDATIONS

Based upon the available evidence with regard to effect and complications, we recommend the following interventional techniques for the treatment of CRPS.

For patients with CRPS with severe pain, allodynia, or with a clear skin temperature difference as compared to the nonaffected extremity that do not respond to medication and physical therapy, a diagnostic block of the ganglion stellatum or the lumbar sympathetic nervous system can be performed. If this block provides at least 50% pain reduction, this procedure can be repeated a few times with local anesthetic. Radiofrequency therapy of the ganglion stellatum or the lumbar sympathetic ganglia is a suitable alternative. In the case of persistent symptoms, SCS can be recommended after multidisciplinary evaluation. Somatic plexus brachialis block, epidural analgesia and PNS can be considered, preferentially within the context of a clinical study.

III.A CLINICAL PRACTICE ALGORITHM

The practice algorithm is illustrated in Figure 1.



Figure 4. Ganglion stellatum (stellate ganglion) diagnostic block: AP view of the needle position with contrast solution.



Figure 5. Ganglion stellatum (stellate ganglion) block: oblique view.

III.B TECHNIQUE(S)

Ganglion Stellatum (Stellate Ganglion) Block

Injections have traditionally been guided by palpable anatomical landmarks.⁹⁸ Supportive technology such as fluoroscopy,⁹⁹ computed tomography¹⁰⁰ and ultrasound¹⁰¹ have been demonstrated to make the procedure technically more reliable. SGB's may be performed by injection of local anesthetics or by RF denervation.

The patient is placed in a supine position with the head slightly hyperextended. The level of C6-C7 is determined by fluoroscopy with the C-arm in anteroposterior position. The C-arm is adjusted until the vertebral end plates are aligned. After local disinfection, the skin is anesthetized using 1% lidocaine and a needle is inserted at the junction of the processus transversus and the corresponding C6 or C7 corpus vertebralis. After contact with the bone, oblique projection is used to check if the needle is anterior to the foramen intervertebrale. If the needle is past this level no contact has been made with the base of the processus transversus and the needle needs to be repositioned. Once the needle is in the correct position a small amount (0.5 mL to 1 mL) of contrast dye is injected in order to prevent intravascular injection. The contrast dye must spread craniocaudally. (Figures 4 and 5)

For a test block, the injection is given using a 60 mm, 20 gauge radiocontrast needle. After C-arm fluoroscopy confirmation of the correct position 5 mL 1% lidocaine or 0.25% bupivacaine is injected depending on the spread of the contrast dye.

For a definitive block using RF, a 60 mm, 20 gauge RF needle is combined with a thermocouple probe for thermometry and thermal lesioning. After confirmation of the correct needle position with fluoroscopy, electrical stimulation is performed at 50 Hz (sensory stimulation) and 2 Hz (motor stimulation) to 1 mA, to ensure that there is no contact with a segmental nerve root (the patient should not feel anything apart from a faint feeling in the shoulder and/or arm). Then 0.7 mL 1% lidocaine in injected, after which a thermal lesion is carried out for 1 minute at 80°C. This procedure can be repeated if necessary.

Lumbar Sympathetic Block

The patient is placed in the prone position on the treatment table, a cushion can be placed under the abdomen in order to reduce the lumbar lordosis. The C-arm fluoroscope is used to identify the L2–L4 levels. The C-arm is adjusted in the cranio-caudal direction until the vertebral end plates are aligned. Then the C-arm, is turned laterally until the distal end of the processus transversus projects inline with the lateral edge of the corresponding



Figure 6. Lumbar sympathetic diagnostic block injection point: oblique projection.

L2-L4 corpora vertebrae. After local disinfection, the skin is anesthetized using 1% lidocaine and a needle is inserted using a tunnel view until the front of the vertebra has been reached (Figures 6 and 7). The lateral projection is used to assure that the needle does not pass the anterior border of the corpus vertebrae. Also an AP projection is used to assure that the needle point projects over the facet joint of the spinal column. The truncus sympathicus can be reached by a single needle approach at the L3 corpus vertebrae¹⁰² or by a multiple needle approach at the L2-L4 corpora vertebrae. If there is a good contrast outline of the dye when starting with the single needle approach at L3 there is no need for the multiple needle approach. In either case, a small amount (0.5 mL to 1 mL) of contrast dye should be injected (injection of too much contrast dye makes repositioning of the needle more difficult). In the AP projection, the contrast dye should be visible as a cloud in front of the corpus vertebrae, but not laterally. In the case of a streaky lateral spread the needle could be in the musculus psoas compartment and the needle needs to be inserted more deeply. Using lateral projection, a string will be seen running along the anterolateral aspect of the corpus vertebrae (Figure 8).

A 20 gauge, 150 mm needle at the level of L3 is used for a test block. After confirmation of the correct needle positioning by radiocontrast dye, 5 mL to 10 mL of 1% lidocaine or 0.25% bupivacaine is injected.



Figure 7. Lumbar sympathetic chain diagnostic block injection point: oblique projection with needle using a tunnel view (co-axial).



Figure 8. Lumbar sympathetic chain diagnostic block injection point: lateral projection with needle using a tunnel view.

For a definitive block using RF a 20 gauge, 150 mm long RF needle with a 10mm non-insulated tip is used combined with a thermocouple probe for thermometry and thermal lesioning. Consideration can be given to

only blocking at 2 levels, I.3 and I.4. After confirmation of the correct position with the fluoroscope, electrical stimulation is carried out, using consecutively 50 Hz (sensory stimulation) and 2 Hz (motor stimulation) to 1 mA, to ensure that there is no contact with a segmental nerve root (patient should not feel anything apart from a faint feeling in the abdomen). At each level 0.7 mL 1% lidocaine is injected after which a thermal lesion is carried out for 1 minute at 80°C. This procedure can be repeated if necessary.

Spinal Cord Stimulation

All patients in the discussed studies received trial SCS with a temporary electrode after the prophylactic administration of 1,500 mg of cefuroxime (a cephalosporin) intravenously. With the patient in prone position, under direct fluoroscopy a Tuohy needle was introduced in the epidural space. The electrode was advanced until the tip was at C4 in the case of upper extremity CRPS and at T12 in the case of lower extremity CRPS. The electrode was positioned so that there was adequate stimulation as reported by the patient as paresthesias covering the area of pain. The needle was then withdrawn and the electrode connected to an external stimulator. The trial SCS was carried out at home for at least 1 week. Meanwhile, patients were encouraged to perform their normal daily activities. A permanent implant was performed if there was a 50% pain reduction score or if there was a score of at least 6 (meaning much improvement) on a 7 point scale for global perceived effect of treatment.

The permanent implantation technique used consisted of the introduction of an epidural stimulation electrode via a 5-cm midline incision with the patient in prone position after prophylactic administration of 1,500 mg of cefuroxime intravenously. The electrode was fixed with special clips. After placing the patient in a lateral position the electrode was connected with an internal pulse generator in the left lower anterior abdominal wall by a tunneled extension lead. The patient remained in the hospital for 24 hours after implantation and was given 2 additional doses of 750 mg cefuroxime. Stimulation parameters used consisted of high frequency stimulation (rate 85 Hz) with a pulse width of 210 ms. The pulse intensity was controlled by means of a patient programmer that allowed the patient to adjust the amplitude of stimulation from 0 V to 10 V.

IV. SUMMARY

There is no gold standard for diagnosis of CRPS. Clinical history and physical examination form the cornerstones of the diagnostic process.

When conservative treatment with physical and medical treatment fails, multidisciplinary evaluation should follow. If there is no improvement in pain and dysfunction, sympathetic blockade should be performed. If this block is effective, it may be followed by repeated injections or RF treatment. If symptoms persist, a continuous epidural infusion, intermittent or continuous plexus brachialis block in combination with exercise therapy may be useful. If symptoms persist SCS after a successful trial stimulation period may yield positive results.

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