Current management of reflex sympathetic dystrophy syndrome (complex regional pain syndrome type I)

Jean-Marie Berthelot

Service de rhumatologie, Hôtel-Dieu, CHU de Nantes, 1, place Alexis, Nantes cedex 01, France

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Abstract

Although no major advances have occurred in the curative treatment of reflex sympathetic dystrophy syndrome (RSDS), new pathogenic insights may soon lead to innovative approaches, which may also prove effective in alleviating some forms of neuropathic pain. Preventing nerve compression and ischemia-reperfusion injury constitute valuable measures for preventing RSDS. Vitamin C administration can also prevent RSDS, together with clonidine in high-risk patients. Short-term glucocorticoid therapy has been found effective in preventing RSDS after stroke but has not been evaluated in other situations. Beneficial effects of bisphosphonates have been documented in several placebo-controlled trials. Placebo-controlled trials of ketamine and spinal cord stimulation are in order to confirm or refute the promising results obtained in open-label studies. Mirror visual feedback was introduced recently for the rehabilitation of patients with RSDS but needs to be evaluated in randomized controlled trials.

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1. Introduction

Reviews of the recent literature on treatments for reflex sympathetic dystrophy syndrome (RSDS) face three obstacles. First, most studies included not only patients with RSDS, but also patients with other forms of complex regional pain syndrome Type I (CRPS-I). Whereas bone and joint abnormalities are among the characteristic features of RSDS, they are lacking in several other disorders classified as CRPS-I [1–3]. Second, no universally accepted tools for measuring outcomes in patients with RSDS are available. However, severity scores have been developed recently [4], including a 0-10 score for the upper limbs [5] and a 5-50 score for the lower limbs [6]. Third, placebo responses in patients with RSDS are both common and marked. Therefore, caution is in order when interpreting the results of studies that did not use a randomized controlled design. For this reason, only randomized controlled trials are discussed in this review.

2. Does sympathetic block help?

Although the pathophysiology of RSDS remains controversial, there is strong agreement that the symptoms stem from a variable combination of peripheral nerve sensitization [7–10] and abnormal sensory input integration by the cerebral cortex [11–13]. The sympathetic system is no longer believed to play a central role, although it may contribute to worsen the symptoms initially [14,15]. In addition, the abnormalities found at the warm stage suggest a decreased sympathetic response [2,10], and venous blood noradrenalin levels are far lower on the affected side than on the healthy side [16–18]. Furthermore, the microcirculation disturbances and diffuse increase in radionuclide uptake seen in RSDS resemble the abnormalities induced by sympathectomy. Sympathetic denervation induces hypersensitivity of noradrenoceptors to circulating monoamines [2,10,16]. Pain and depression and/or chronic overactivity of the sympathetic system [16] may lead to increased monoamine release by the adrenal medulla, so that episodes of vasodilation (related to predominant sympathetic denervation) alternate with episodes of arterial spasm (in response to monoamine release by the adrenal medulla). Sympathetic responsiveness returns to
normal after about 3 months [18], more rapidly than receptor sensitivity to monoamines, marking the passage of the warm to the cold phase. Sympathetic block at the limbs further increases the sympathetic denervation that characterizes the warm phase of RSDS. At the warm phase, sympathectomy merely alleviates the pain exacerbations induced by systemic adrenergic responses [19]. Sympathectomy may therefore be appropriate only when performed at the cold phase. Many studies have challenged the long-term superiority of sympathetic blockade over placebo treatment [14,20,21]. In randomized controlled trials, intravenous phentolamine, phenylepinephrine, reserpine, droperidol, and ketanserin [15,22] were not more effective than a placebo. Furthermore, symptom exacerbation has been reported after sympathetic blockade [22]. For instance, in a prospective randomized placebo-controlled trial of 57 patients, guanethidine blockade was associated with more pain and with more vasomotor instability after 6 months [23].

The only drug that seems effective, at least when used preventively, is clonidine. In a randomized double-blind study comparing intravenous clonidine to a placebo in 84 patients who underwent surgery on a limb previously affected with RSDS, recurrences were seen in only 4 of the 42 clonidine-treated patients compared to 31 of the 42 placebo-treated patients [24]. Intravenous administration is easier than epidural administration, which was more effective than a placebo in a small cross-over study of 26 patients [25]. Although these results are promising, other studies failed to produce convincing evidence that clonidine relieved pain in patients with RSDS [22,26].

3. Look for regional nerve compression

Nerve ending irritation may initiate or perpetuate RSDS. Patients who experience RSDS after hand surgery should be evaluated for irritation of the median or ulnar nerve at the wrist, which may be related to a tight cast or splint. Whether surgery to release the nerve is warranted remains to be determined. In a recent study of eight patients, the pain score fell from 75 to 18 after nerve release surgery [27]). However, this was an open-label study in which most of the patients had CRPS Type II (formerly called causalgia). The report does not provide details about the presence of subchondral bone lesions typical for RSDS [27].

4. Combat venous stasis (which leads to free radical release) and give early vitamin C therapy (which neutralizes free radicals)

One factor that may lead to nerve sensitization and thereby to RSDS is sluggish blood flow after a period of ischemia (for instance related to a cast,) even in individuals with no history of trauma [28]. In the rat model of RSDS developed by Coderre et al. [29], a tourniquet is placed on a hindlimb of an anesthetized rat, left for 3 hours, and removed to allow reperfusion before the end of anesthesia. Reperfusion is associated with arteriovenous shunting, transient acidosis, and free radical generation [29]. Similarly, in Secretan’s syndrome induced by repetitive contusions or intentional constriction of a limb, the clinical manifestations resemble those of RSDS, and RSDS is often preceded by a period of immobility or by other factors associated with sluggish blood flow.

The RSDS model developed by Coderre et al. [29] and other studies showing that antioxidants such as vitamin C can alleviate neuropathic pain support the findings reported by Zollinger et al. [30]. In their double-blind placebo-controlled trial in 123 patients with wrist fractures, treatment with 500 mg of ascorbic acid per day for 50 days significantly reduced the risk of RSDS developing within the next year (from 22% to 7%) [30]. Subsequent open-label studies further support the beneficial effects of prophylactic vitamin C therapy. Other agents that protect against free radicals have been found effective, such as topical 50% dimethyl sulfoxide, although the only randomized controlled trial included only 32 patients and showed very modest improvements [22].

5. Target the increased subchondral bone turnover and resulting acidosis

After a number of encouraging open-label studies [31–33], at least four randomized controlled trials were conducted to evaluate the efficacy of bisphosphonate treatment [31]. Two of them evaluated pamidronate using fairly satisfactory study designs. The other two were high-quality studies of clodronate [34] and alendronate [35], respectively. Evidence of efficacy was obtained in all four studies. Varenna et al. [34] compared clodronate (300 mg intravenously per day for 10 days) to a placebo. On day 40, the 15 clodronate-treated patients exhibited significantly greater improvements than the 17 placebo-treated patients [34]. To investigate alendronate, Manicourt et al. [35] used the drug (40 mg/day for 8 weeks) in 20 patients and a placebo in 20 other patients. After 8 weeks, alendronate therapy was associated with marked improvements in spontaneous pain, tolerance to pressure, and range of motion. These improvements were detectable after 4 weeks and still present after 12 weeks. The most likely mechanism involves a decrease in bone acidity related to the decrease in bone turnover induced by bisphosphonate administration. The higher pH is associated with decreased sensitivity of peripheral nerves (as seen also with osteoprotegerin treatment in an animal model of bone cancer). This hypothesis is consistent with the efficacy of intranasal calcitonin in a double-blind placebo-controlled trial [36], although calcitonin was not effective in an earlier placebo-controlled trial [37]. However, spinal cord and/or cerebral neuromodulation by bisphosphonates cannot be ruled out. Calcitonin may also exert neuromodulating effects, as suggested by a randomized cross-over study in which calcitonin was more effective than a placebo in alleviating phantom limb pain [38]. New-generation bisphosphonates act by inhibiting the enzyme farnesyl diphosphate synthase, thereby modulating the expression of GTPases such as Ras, Rac, Rho, and Cdc42 [39], which contribute to signal transmission in the spinal cord and may therefore be involved in the genesis of neuropathic pain or...
even of pain due to RSDS. Thus, the analgesic effects of new-generation bisphosphonates may be partly ascribable to slower transmission of signals, particularly those involved in postsynaptic plasticity.

6. Topical anesthetics: their role is minimal

Intravenous lidocaine was superior over a placebo in a randomized double-blind placebo-controlled cross-over study in 16 patients with allodynia, [40]. However, alleviation of spontaneous pain was achieved only with the highest dosage (3g/ml) and for a brief period [40]. In another randomized controlled trial, intravenous regional anesthesia (bier block) with 40mg methylprednisolone and 10ml of 2% lidocaine was not better than the placebo in alleviating symptoms of CRPS Type I [41].

7. Glucocorticoid therapy may help when used very early, whereas the role for cytokine inhibitors remains unclear

Nonsteroidal antiinflammatory drugs were not effective [22]. Glucocorticoid therapy provided sustained improvements compared to a placebo in patients with RSDS associated with stroke [42]. The benefits from glucocorticoid therapy seem greatest during the first 3 months, and a satisfactory treatment schedule may be 30 mg/day for 212 weeks followed by rapid tapering to nothing [22,43]. Mediators of inflammation related to proinflammatory neuropptide release by nerve endings in 20 patients with RSDS were assayed in blister fluid [44]. Blisters were produced using a suction method on the affected and unaffected sides, and microdialysis was used for the assays. The affected side had higher concentrations of IL-6 (53.5pg/ml vs. 6.2pg/ml), TNF-α (31pg/ml vs. 8mg/ml), and tryptase (37ng/ml vs. 12.5ng/ml) [44]. These data may warrant randomized trials of early administration of agents that inhibit IL-6, TNF-α, and tryptase.

8. Analgesics (including opioids) and anticonvulsants have limited effects

Although several controlled trials suggested that opioids might be effective, the only randomized placebo-controlled trial showed no significant differences after 8 days of treatment [45]. Furthermore, long-term opioid therapy may contribute to perpetuate allodynia [22]. Studies in animals, as well as experience reported by several authors, indicate that dextromethorphan may potentiate the effects of opioids [22]. However, this possibility has not been confirmed in recent randomized controlled trials.

Gabapentin has been described as beneficial in patients with diabetic neuropathy or postzoster neuralgia. No evidence of efficacy was obtained in the only randomized controlled trial of gabapentin for RSDS [46]. This was a cross-over study in 58 patients with CRPS-I who took the placebo and gabapentin for 3 weeks, in random order, separated by a 2-week washout period. The gabapentin dosage was increased gradually from 600 to 2400 mg/day [46]. The results of this trial contradict those of 13 open-label studies suggesting a modest beneficial effect of gabapentin in patients with RSDS. However, Gilron et al. [47] reported that single-drug therapy with gabapentin was only slightly better than a placebo in alleviating neuropathic pain (pain score reduction, 57 to 42 with gabapentin and 57 to 45 with the placebo). No randomized controlled trials are available for phenytoin or lamotrigine. Carbamazepine 600mg/day for 8 days was somewhat effective in a randomized controlled trial [22] but should be reserved for carefully selected patients, given the risk of serious adverse effects.

Antidepressants have been found helpful in patients with neuropathic pain [22]. No randomized controlled trials of antidepressants are available for RSDS. Tricyclic agents (imipramine, amitriptyline) inhibit the reuptake of both noradrenalin and serotonin and may be preferable to antidepressants that act on a single neurotransmitter [22].

9. Spinal cord treatments deserve to be evaluated in double-blind studies

Treatments that target the dorsal horns of the spinal cord include ketamine and spinal cord stimulation. Ketamine is an anesthetic that inhibits the NMDA receptor. A systematic review included 37 double-blind placebo-controlled studies of low-dose ketamine used to treat opioid-resistant pain [48,49]. The results suggested a probable modest effect in about half the studies. Higher doses may provide greater efficacy but often cause side effects such as lightheadedness and hallucinations [22,49] or severe schizophrenia-like behavioral disorders. A single study of intravenous ketamine used to treat RSDS/CRPS-I is available [50]. This retrospective uncontrolled study in 33 patients showed complete pain relief in 76% of patients, with no rebound pain over the next 3 months in 54% of cases; only 6% of patients reported no pain relief [50]. In the 12 patients who experienced relapses, complete pain relief of at least 1 year’s duration was obtained after a second ketamine infusion [50]. Despite the risk of side effects, randomized controlled trials of ketamine are warranted in patients with the rheumatological form of CRPS-I (i.e. RSDS strictly speaking, with bone and joint involvement).

Spinal cord stimulation has been extensively investigated, although only 7 of 583 articles retrieved by a systematic review were of adequate methodological quality [51]. The only randomized controlled trial compared physical therapy alone to physical therapy plus spinal cord stimulation in patients with RSDS [53]. Half the patients randomly assigned to the spinal cord stimulation group reported at least 50% pain relief after 6 months [52]. However, the study was not blinded, and the results deteriorated somewhat by 1 year [53]. In addition, no functional improvements occurred [53]. Finally, spinal cord stimulation carries risks: in a metaanalysis by Turner et al. [51], 34% of patients experienced adverse events and 23% required repeat surgery.
10. New avenues for rehabilitation therapy: using mirrors

Symptoms common to CRPS-I and to phantom limb pain (pain, numbness, paresthesia, sensation of coolness or warmth, and heaviness in the limb) were produced in 27 of 41 subjects by using mirrors to create a mismatch between motor intention and sensory feedback [54]. The similarities with phantom limb pain constitute a further argument against amputation in patients with RSDS. Functional imaging studies suggesting disruption of cortical connections in patients with RSDS [22, 55] have prompted studies of mirror visual feedback, in which the patient simultaneously performs the same exercises with both limbs while watching the unaffected limb and its mirror image, the affected limb being hidden. This method had been used successfully in patients with phantom limb pain [55] or stroke. Early attempts to use mirror visual feedback in patients with RSDS produced disappointing results related both to a high rate of neglect-like symptoms (reported by 84% of patients, with 54% needing to direct their mental attention to move the limbs [56]) and to pain upon imagined movements [57]. The technique was therefore modified to include hand laterality recognition exercises followed by imagined movements and finally by mirror movements [55,57]. In a randomized controlled trial, the score on the 0 to 100 neuropathic pain scale fell by 25 points with this sequential program, compared to conventional management [58]. However, the improvements fell short of a full recovery, and the hand laterality recognition exercises, which were based on photographs of right and left hands and feet in a variety of positions, required a high level of patient compliance and had to be performed during at least 20% of the day.

11. Dystonia

Rheumatologists have limited knowledge of tonic dystonia, as this feature is uncommon in patients with RSDS strictly speaking [59]. Neurologists and pain specialists, in contrast, are familiar with tonic dystonia associated with other forms of neuropsychic pain. Dystonia usually causes flexion at the upper limbs and extension at the lower limbs and may develop within a few hours or days after the injury. The dystonia may spread to other limbs or to the spine. Improvements are obtained in 50% of patients with intrathecal baclofen [60], a GABA-derived agent used to treat spasticity and capable of preventing the release of excitatory amino acids such as glutamate and aspartate. Baclofen may be less effective at the feet than at the hands.

12. Conclusion

Although no major advances have been achieved in the curative treatment of RSDS, new pathogenic insights may soon lead to innovative treatment approaches, which may also prove effective in the treatment of neuropsychic pain. Careful attention should be directed to preventive measures, which include preventing nerve compression and ischemia-reperfusion events, as well as administering vitamin C or, in some cases, clonidine. Short-term glucocorticoid therapy has been found effective in preventing RSDS associated with stroke but has not been studied in other situations. Randomized double-blind placebo-controlled trials have shown that bisphosphonate therapy is beneficial, and studies are ongoing to evaluate the contribution of new-generation bisphosphonates in the treatment of RSDS.

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