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Pharmacological and Non-pharmacological Treatment for Complex Regional Pain Syndrome (CRPS): A Review

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ABSTRACT

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD) or causalgia, is a chronic debilitating neurological disorder characterized by limb pain, that can be developed after a minor trauma, fractures or lesions of the peripheral or central nervous system. The prevalence of CRPS is relatively low; and the symptoms of this dynamic disease are distinct among different patients. No specific diagnostic test is available and hence diagnosis is mainly relied on clinical examination and supportive laboratory findings. Also, since the symptoms are individual-specific, there exist no single drug which is effective globally among the patient community. An early recognition, prompt initiation and a multidisciplinary approach including pharmacological, rehabilitation and psychological therapies seems to be effective in treating CRPS, to obtain an optimum outcome. This review encompasses recent advances in the treatment strategies – medical and non-medical – employed in the management of CRPS.

Key words: causalgia, complex regional pain syndrome, CRPS, reflex sympathetic dystrophy, Sudeck's atrophy, pain

1. INTRODUCTION

Complex regional pain syndrome (CRPS) remains endlessly fascinating to all persons interested in pain management. No other chronic pain syndrome is as shrouded in confusion and controversy-to the detriment of efforts to rigorously define an evidence-based treatment strategy. CRPS is a chronic neurological disorder characterized by clinical features such as disabling (spontaneous) pain, swelling (edema), vasomotor instability, sudomotor abnormality, and impairment of motor function.[1-5] The disorder usually develops after minor trauma or surgery. In fact there is confusion regarding the terminology itself. Historically, CRPS has been described by a number of terms that include causalgia, Sudeck's atrophy, reflex sympathetic dystrophy (RSD), algodystrophy, post-traumatic dystrophy, algoneurodystrophy, reflex neurovascular dystrophy, fracture disease and shoulder-hand syndrome. In order to bring some uniformity to this problem, International Association for the Study of Pain (IASP) in 1993 introduced the term CRPS to describe a wide variety of post-traumatic neuropathic pain conditions of the limbs.[6] The use of the term CRPS has also been questioned and perhaps another more appropriate term will be developed in the future. In the meantime, CRPS is the term used routinely by pain specialists and neurologists and the use of traditional terminology like RSD and causalgia is dwindling. CRPS is most often associated with surgery of the distal upper extremity to complicate recovery, delay return to work, diminish health-related quality of life, and increase the likelihood of poor outcomes and/or litigation.[7] This article presents a brief historical overview followed by a review of the medical and non- medical management of CRPS.

2. HISTORICAL BACKGROUND

The history of CRPS is controversial and its denomination changed significantly over time. The earliest documentation on CRPS could probably be the report by Ambroise Paré, father of modern surgery.[8] He reported a severe, persistent pain and contractures experienced by French King Charles IX of Valois after a limb phlebotomy. The first written description of CRPS was a clinical case report by Denmark, a British surgeon who linked the persistent burning pain to the involvement of the radial nerve in a gun-shot injury of the upper arm.[9]

Few decades later Silas Weir Mitchell, the father of American neurology, gave the first detailed description of several clinical cases of gun-shot wounds and the exaggerated experience of pain, related to the peripheral nerve injuries in veterans of American Civil War.[10] The clinical condition was coined a name causalgia, in a later work by Mitchell, in 1872.[11] Causalgia is characterized by exquisite burning pain that begins in the distribution of an injured peripheral nerve and then spreads beyond it; mostly associated with an injury to a major nerve trunk. Another noted step in the history of this disease was made by Paul Sudeck; when he presented a paper in the 29th Congress of the German Society of Surgery.[12] He described the clinical and radiological features of post-traumatic reflex atrophy of bone (later came to be known as Sudeck atrophy), on patients who had undergone X-ray examinations. Rene Lichie 1916 laid another milestone in the history of the disease by linking the sympathetic nervous system to causalgia, and reported a pain relief in a patient after extensive periarterial nerve stripping. He coined the term "sympathetic neuritis" to show the fundamental role, in his opinion, of the sympathetic nervous system in the pathogenesis of neuropathic pain.[13] In 1946, James A. Evans, an American physician introduced a term Reflex Sympathetic Dystrophy (RSD) for this abnormality of the sympathetic nervous system; and suggested that sympathetic nerve blocks might help to relieve the pain.[14] In 1980s reports came up by referring the RSD as Sympathetically Mediated Pain (SMP) or Sympathetically Independent Pain (SIP).The use of differing terms with imprecise classifications and unclear pathogenesis thus resulted in misdiagnosis and mistreatments of patients with the pathology. In 1993, the International Association for the Study of Pain (IASP) formed a task force aiming at reviewing the nomenclature related to the disease, standardising and developing the diagnostic criteria. Later, in at a consensus workshop held in Orlando, Florida in 1993, the term Reflex Sympathetic Dystrophy was abandoned, and the strictly descriptive term CRPS (complex regional pain syndrome) was introduced, and the diagnostic criteria for CRPS was proposed. CPRS was sub-divided into CRPS type-I, which follows an injury such as a fracture or sprain but without a definable nerve damage (90% of the clinical presentations of CRPS are Type-I); and CRPS type-II, to refer the cases with nerve injury in the limb.[15,16] In a nut-shell, type-I refer to RSD or Sudeck's syndrome and type-II refers to causalgia.

The aim of treatment of CRPS is pain control followed by recovery of limb function. Although a number of treatment options have been reported in the literature, these are empirical at best and no reliable protocol is available for use in all patients. Medications used specifically include NSAIDs (Non-steroidal anti-inflammatory drugs),opioids, corticosteroids, bisphosphonates, topical capsaicin, tricyclic's, antiepileptic's and free radical scavengers. Treatments aimed at pain reduction and rehabilitation of limb function form the mainstay of therapy. Comorbidities such as anxiety, depression, and loss of body image should be treated concurrently. Besides pain therapy, non-medications (physiotherapy and occupational therapy) aim at improving and restoring function of limb which plays an important role in the treatment.

3. MEDICAL OPTIONS

The following sections detail the typical medical options employed in the treatment of CRPS:

3.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

The first painkillers often used to treat CRPS are over-the-counter painkillers called non-steroidal anti-inflammatory drugs (NSAIDs), such as paracetamol, ibuprofen, aspirin and naproxen. These medications can help reduce the pain caused by the injury that triggered CRPS. They can also treat CRPS-associated pains, such as muscle pain in the shoulder when the CRPS is in the hand. However, NSAIDs are unlikely to directly reduce CRPS pain. The anti-inflammatory properties of NSAIDs may have an effect on the inflammatory mediators of CRPS, especially in the acute phase. Prolonged use of NSAIDs in children should be accompanied by gastric protection. If OTC drugs are not helpful, stronger pain relievers are recommended.

3.2 Opioids

Opioid medications may be an option. Taken in appropriate doses, they may provide acceptable control of pain. Opioids are only moderately successful in the treatment of neuropathic pain.[17] Their use is indicated when pain is not controlled with other oral or topical medications. Morphine, Hydrocodone or oxycodone is commonly used to treat RSD / CRPS is debated and there are potential hazards. Dosage will need to be individually titrated according to response, and adjuvant drug therapies must be employed. Therefore, in order to ensure appropriate informed consent, it is recommended that the patient sign a doctor-patient "contract."

3.3 Corticosteroids

The anti-inflammatory effects of corticosteroids have led to their use in the acute phase of CRPS in adults. Steroid medications, such as prednisone, may reduce inflammation and improve mobility in the affected limb.[18,19] Steroids have multiple effects: they inhibit the production of inflammatory mediators, reduce the transcription rate in dorsal root ganglia cells (thereby reducing the neuropeptide content of sensory neurons), and facilitate degradation of neuropeptides. As a result, development of

neurogenic inflammation and neuropathic pain may be prevented. Typical dosage is 30 mg daily for 3 weeks, with a gradual taper over a month.[20,21] In general, long-term use of corticosteroids beyond 3 months is not recommended.

3.4 Bisphosphonates

Bisphosphonates are agents that affect the bone turnover. Oral alendronate, risedronate, intravenous pamidronate, intravenous clodronate have been shown to significantly improve symptoms of CRPS in randomized clinical trials.[22,23] Side effects such as fever and asymptomatic hypocalcaemia were observed frequently but disappeared quickly. By reducing local acceleration of bone remodelling bisphosphonates may alleviate pain by effects on nociceptive primary afferents in bone.[24] Calcitonin, a polypeptide hormone produced by the thyroid, also has antinociceptive effects independent of its effects on bone, and it has been found effective for several other types of acute and chronic pain conditions. It is usually nasally administered and is without significant adverse effects in normocalcemic individuals.[25] Calcitonin at a dose of 100 IU thrice daily for 3 weeks has shown improved pain intensity, whereas 200 IU calcitonin twice daily for 4 weeks reported no improvement.[26, 27]

3.5 Topical treatments

Topical medications remain local to reach dermal nerve endings, blood vessels and other cells in the skin. Topical medications are appealing by virtue of their lack of systemic effects, rashes and allergies are their major adverse effect and they are currently popular with patients. Topical options for CRPS include the 5% lidocaine-impregnated patch, the eutectic mixture of local anaesthetics (EMLA) cream, capsaicin and dimethylsulfoxide (DMSO)[28].Capsaicin the vanilloid compound in chilli peppers, is a highly selective agonist for the transient receptor potential channel, vanilloid-receptor type 1 (TRPV1) that is expressed on central and peripheral terminals of nociceptive primary sensory neurons. Capsaicin has been tried in a concentration of 5-10% as a topical application. However, CRPS patients are often unable to tolerate application of topical capsaicin due to the associated burning sensation and hyperalgesia reported in about 10% of cases.[29]

3.6 Antidepressants

Tricyclic antidepressants (TCAs) are the most commonly used drugs in neuropathic pain. Their beneficial effect has been demonstrated, particularly in diabetic neuropathy and postherpetic neuralgia, but not specifically in CRPS.[30] The analgesic effect of TCAs is based on serotonin and noradrenaline reuptake inhibition centrally and blockade of N-methyl-D-aspartate receptors on spinal cord dorsal horn neurons. In addition, they cause blockade of sodium channels of injured axons.[31] Amitriptyline remains the most commonly used drug in this class. Dosage starts at 10 mg nocte, gradually titrated up to 75 mg nocte as necessary. In addition to their analgesic effect, TCAs improve depressive symptoms and sleep impairment by their mildly sedative effect. The newer serotonin-specific reuptake inhibitors are less effective compared to amitriptyline in the treatment of pain in CRPS.[30]

3.7 Antiepileptics

Gabapentin is an anticonvulsant with analgesic properties, and its effectiveness in the treatment of painful diabetic neuropathy and postherpetic neuralgia has been established however, its efficacy as an analgesic in CRPS has not been proven.[32, 33] Only one randomized, double-blind, placebo controlled crossover trial of gabapentin therapy for CRPS has been reported.[34] Fifty eight patients with type I CRPS were randomly given gabapentin or placebo capsule at the start for 3-week treatment periods, separated by a 2 –week "washout," and then followed by a further 3-weeks of crossover treatment. Patients reported significant pain relief in favour of gabapentin in the first treatment period, but the therapeutic effect was less in the second. Combining results from first and second periods demonstrated no significant beneficial effect. The beneficial effect seen in the first period was at least partially related to a placebo effect. In a further randomized, double-blind study involving 307 patients with various neuropathic pain syndromes, gabapentin-treated patients experienced a significantly greater reduction in pain score than patients who received placebo.[35] Overall, there was no good evidence for it use in CRPS, but it may benefit some patients and is therefore worth trying if first line medical agents have failed. The pain relieving mechanism of gabapentin has not been determined. Dosage starts at 300 mg nocte, gradually increased to 1,200 mg t.d.s. as necessary. There were no convincing reports for other antiepileptic drugs such as pregabalin, phenytoin, and carbamazepine.[36]

3.8 Free radical scavengers

Free radical scavengers such as dimethylsulfoxide (DMSO) and N-acetyl cysteine (NAC) demonstrated that both drugs were effective in CRPS. The postulated mechanism is decreasing the excessive production of toxic oxygen free radicals an hence the inflammatory response.[37] DMSO seems to be more effective in 'warm' CRPS (characterised by increased temperature in the affected extremity, along with oedema, redness and other signs of inflammation) and NAC in 'cold' CRPS (characterised by reduced temperature and tissue atrophy); the efficacy of both drugs tend to decrease over disease duration.[37]

3.9 Regional anaesthesia techniques

These are useful in patients with moderate to severe pain that do not respond to physiotherapy and pharmacologic therapy. The two major types of regional anaesthesia technique available are a sympathetic nerve block and a combined somatic/ sympathetic nerve block. Sympathetic blocks aim to alleviate the sympathetically mediated pain and can be used in combination with botulinum toxin to prolong the duration of analgesia. Sympathetic nerve blocks are chosen when the patient has marked improvement after a diagnostic sympathetic block. A somatic plus sympathetic block is used in patients who do not respond to the diagnostic sympathetic block.[38]

3.10 Sympathetic blockade

Local anaesthetic with or without steroid sympathetic blockade has been used to treat CRPS. Sympathetic blockade may be more effective if applied early in CRPS before central pain pathways set in. A sympathetic block of the upper extremity is called a stellate ganglia block (SGB). The SGB is performed by inserting a small needle alongside the windpipe (trachea). A sympathetic block of the lower extremity is called a lumbar sympathetic block (LSB). For patient comfort and safety, LSBs should be performed with the aid of a fluoroscope (X-rays). Long-term sympathetic blockade can be achieved with sympathectomy, which can be carried out surgically or by chemical and radiofrequency ablative techniques.[38-40]

3.11 Sympathectomy (chemical/surgical/radiofrequency)

Sympathectomy is a destructive procedure that interrupts the sympathetic nervous system. Chemical sympathectomies use alcohol or phenol injections to destroy sympathetic nervous tissue (the so-called "sympathetic chain" of nerve ganglia.[39] Surgical ablation can be performed by open removal or electrocoagulation (destruction of tissue with high-frequency electrical current) of the sympathetic chain, or by minimally invasive procedures using thermal or laser interruption. Nerve regeneration commonly occurs following both surgical and chemical ablation, but may take longer with surgical ablation. Radiofrequency sympatholysis has not been shown to offer any advantage over phenol techniques.[41] If there is a significant decrease in pain following the sympathetic block, the patient is said to have sympathetically maintained pain (SMP). If there is not a significant decrease in pain, the patient has sympathetically independent pain (SIP).Only patients with SMP should be considered for a sympathectomy.[42-44] Sympathectomy is a relatively invasive procedure with potential complications and should be pursued by the patient only if they are certain about the temporary therapeutic benefits that they received from a series of SGBs or LSBs.

Recently, laparoscopic sympathectomy has been developed for sympathectomy of the upper extremity.[45] This technique requires the placement of three small holes temporarily in the side of the chest wall while the patient is under general anaesthesia. For the lower extremity, the patient has the choice of dissolving (destroying) the sympathetic nerves with phenol injected through a needle while the patient is awake (percutaneous phenol sympathetic neurolysis) or a surgical sympathectomy under general anaesthesia. Other techniques for sympathectomy have also been used. The patient must be informed of the pros and cons of each approach.

Post-sympathectomy pain (neuralgia) is a potential complication of all types of sympathectomy.[46,47] This pain is typically proximal to the original pain (e.g. proximal means that the pain may appear for the first time in the groin or buttock region for sympathectomy of the lower extremity and pain in the chest wall region for sympathectomy of the upper extremity). Patients may think that their RSD/CRPS have spread to a new region after sympathectomy because the pain feels similar to their original RSD/CRPS pain. The post-sympathectomy pain usually resolves on its own or with 1-3 sympathetic blocks. Thus for some patients, sympathectomy may be a two-step procedure; destruction of sympathetic nerves followed by a sympathetic block. The selection criteria for sympathectomy are critical in achieving long-term success.[46,47]

3.12 Somatic blockade

Somatic conduction block of the brachial or lumbar plexus can be performed in patients with on-going disabling pain in whom sympathetic ganglion blockade is unsuccessful.[48] The aim of somatic block is to provide sufficient control without motor blockade so that the patient can participate in physiotherapy.

3.13 Neuromodulation

It involves the modulation of central pain pathways by delivery of an electrical current or chemical application to the central neural axis. Neuromodulation techniques include spinal cord peripheral nerve stimulation, acupuncture, transcutaneous electrical nerve stimulation (TENS) and intrathecal injection of baclofen, clonidine or opioids.[49-51] These techniques are invasive and should be reserved for patients in whom other measures have failed.[28]

3.14 Spinal cord stimulation (SCS)

In spinal cord stimulation, a fine wire is implanted in the epidural space close to the nerves in your back. This is connected to an external hand-held control unit that allows you to control the stimulation. This is usually done for a trial period and if it helps then a battery unit can be implanted in your tummy or buttock. The wire and the battery can be removed later on if you no longer need

SCS. Hence SCS, uses low intensity, electrical impulses to trigger selected nerve fibres along the spinal cord (dorsal columns), which are believed to stop pain messages from being transferred to the brain. SCS replaces the area of intense pain with a more pleasant tingling sensation called paraesthesia.[52-55] The tingling sensation will remain relatively constant and should not hurt. Moreover, SCS is expensive and has a25-75% complication rate (infection, electrode fracture and migration, equipment failure.[56] This treatment is only available in specialist centres for people who haven't benefited from other treatments.

4 NON-MEDICAL OPTIONS

The non-medical options are described here:

4.1 Psychotherapy

Psychiatric illness or personality disorder does not cause RSD/CRPS but it is likely that personality contributes to the disease.[57, 58] Psychology is a critical mainstay of treatment in CRPS, and in some patients may be essential to recovery. This technique should be selected depending upon the individual situations. CRPS is not 'all in the mind' but long-term severe pain is likely to affect mood and can sometimes lead to depression. The treatment modalities include stress management, relaxation techniques as well as biofeedback and cognitive behavioural therapies (CBT).CBT works in synergistic fashion along with physical rehabilitation medical management of CRPS.[59]

4.2 Rehabilitation therapy

Physical and occupational therapy are the key components of rehabilitation process and is recommended as the first line treatment when started in the early stages. The aim of physiotherapy is focused on maintaining activity of the affected limbs despite pain; reduce edema, and prevent the development of contractures. As a result of the gruelling physical therapy and prolonged period of pain, CRPS patients can develop kinesophobia; and the objective of the therapy is primarily to overcome the fear of pain and enable the patient to gain the best functional use of the affected limb. This program is tailored specifically to suit each individual and can involve multiple modalities which include elevation, massage, temperature-contrast (alternating hot and cold) baths, pain-relief therapies such as transcutaneous electrical nerve stimulation (TENS), H-wave therapy, a gentle range of motion isometric strengthening exercises and stress-loading program of the affected limb (traction and compression exercises) along with provision of adequate analgesia.

The following physiotherapeutic treatments with behavioural therapy components are suitable.

4.3 Mirror therapy

This therapeutic process relies on employing imagined limb postures and movements and is most effective in patients with acute CPRS where by the mirror image of the pain-free, healthy extremity seen in the place of the affected part, an illusion is created such that the injured limb is moving without pain and other symptoms of CRPS.[60] McCabe reported on using mirror therapy alone in treating CRPS and found that treatment was effective in patients with early CRPS (under 8 weeks) and intermediate (less than 1 year).[61]

4.4 Graded motor imagery (GMI)

This rehabilitation technique consists of three sequential phases each of approximately 2 weeks duration. The first phase is termed as laterality recognition task (identification of the left/right extremities); the second step is explicit motor imagery (or imagined limb movements); and as the final phase mirror therapy is conducted. Even though the technique is typically delivered sequentially, the approach is flexible and patient-centred.[62]

4.5 Pain-exposure physical therapy (PEPT)/graded exposure in vivo program (GEXP)

PEPT is a progressive-loading physical exercise program and management of pain-avoidance behaviour. In PEPT, patients are directly exposed to painful stimuli and are stressed to regain their normal daily activities as soon as possible, without the use of medication, and are instructed to ignore their pain. The tailored progressive-loading exercises focus on specific daily activities, using muscle strength training and joint mobility exercises, both passive and active. The key to success of PEPT relies on the internal motivation and adherence of the patient, to the therapy.[63] Graded exposure *in vivo* program (GEXP) developed for patients with chronic pain who report substantial and irrational pain-related fear, and fear of movement. GEXP is aimed primarily to reduce the fear, and the fear of movement/re-injury. By the gradual and repeated encounters with the feared activities and; following a highly structured, protocolized and individually-tailored format the goal of the program is to restore a normal pattern of daily function or even including the complete return to work.[63,64]

4.6 Occupational therapy

Occupational therapy encourages use of the affected limb in activities of daily living. The use of specialized garments or wrappings may reduce edema and sensory overload of the affected limb. Occupational therapy typically involves phases such as desensitisation, relaxation and/or stress management procedures and body perception awareness. Desensitisation is a technique that aims to normalize the touch sensation in the affected limb. It

involves touching the skin frequently with different textured fabrics and other substances (for example, wool, silk, cotton wool), gradually working towards the painful areas. It is important to focus fully on the sensation of touching the normal limb and to remember that feeling when you touch the affected limb. Getting as relaxed as possible before starting can help the patient to manage these touches. As you practise you can start to progress from gentle movement like stroking to firmer stroking, tapping or circular movements.[64]

5 CONCLUSION

This review has examined multiple treatment options for CRPS/RSD. Although no drug is approved by the U.S Food and Drug Administration specifically for CRPS, and no single drug treatment that works for everyone with CRPS, a wide range of treatment options can be used to manage the symptoms of the disease. A multimodal pharmacologic regimen that combines several different classes of medication may be superior, when used early in the course of the disease. The selection of the drug is determined by the severity of pain. However, pain medications can be useful to reduce pain to a level that allows commencing of rehabilitation therapies. The treatment will try lower-strength painkillers first, and will only use stronger painkillers if necessary. As CRPS is a chronic disease, successful treatment would ideally require a multidisciplinary approach consisting of pharmacotherapy, physiotherapy, psychological counselling and occupational therapy. An early recognition and a multidisciplinary approach to the pain-management are essential in achieving an optimal outcome. Nevertheless, a disturbing reality by resorting to medical treatments is the number and severity of side effects that accompany many treatment options.

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