COMPLEX REGIONAL PAIN SYNDROME: A REVIEW OF CURRENT TREATMENTS

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Abstract

Complex Regional Pain Syndrome (CRPS) is a syndrome that develops infrequently in patients that experience a minor or severe trauma to a bodily extremity. CRPS has two subtypes; Type-I and II, both are clinically characterized by hyperalgesia. During its acute stage, CRPS hyperalgesia is clinically characterized by edema in the subcutaneous tissues of the epidermis, allodynia, and localized bone resorption. In the later chronic stage, hyperalgesia is aroused by the disregulation of blood flow to the extremity and permanent dystonic and trophic changes to the skin. Because the epidemiology and central causation of CRPS remains unknown until today, health professionals are challenged to diagnose and treat its unique and changing presentations as they appear. This approach, has led to a plethora of tests and treatments that address the syndrome as it presents its clinical features. This paper is an in-depth review of available treatment modalities and surmise the efficacy of the treatments based the quality of the available research. By reviewing the effectiveness of some of the currently available treatment modalities we may gain some understanding of this enigmatic syndrome.

Introduction and History

CRPS type-I has previously been known as Sudeck's Atrophy and Reflex Sympathetic Dystrophy. Sundeck's Atrophy was the syndrome's original name. It was named after Paul Sudeck who proposed in 1902 that this syndrome was an exaggerated response to nerve damage, or soft tissue injury, (Janig, 2003). In the 1950's, John Bonica, the founder of the International Association for the Study of Pain, proposed the name Reflex Sympathetic Dystrophy; "sympathetic" dystrophy because it aptly described the pathology of the syndrome that was discovered to be maintained by the Sympathetic Nervous System. This SNS trend was discovered after patients treated with a temporary blockade of the sympathetic nervous system experienced relief from the syndrome's symptoms, (Bonica, 1990).

CRPS Type-II was previously known as Causalgia, a derivative of the Greek terms, "Caus", and "Algia", which mean, heat and pain, respectively. The name, Causalgia, was coined by Dr. Silas Weir Mitchell, a nerve pain pioneer during the American Civil War. He noted in his observations the exaggerated nature of the presentation of pain in relation to the injury, a problem that was frequently found in veterans of the Civil War who were exposed to low velocity, high mass missiles used by the confederates, which overtime caused an extreme inflammatory response, followed by trophic changes at the site of injury. He also recorded, that the ensuing level of pain following injury was dependent on the extent of peripheral nerve damage, (Lau and Chung, 2004).

It became evident in the 1990's that the dissonance created by the syndromes varying names was affecting the ability of doctors to accurately diagnose this syndrome. With this in mind a consensus workshop was held in Orlando, Florida in 1993 to develop singular terminology for the syndromes multiple etiologies and manifestations. The term Complex Regional Pain Syndrome Type-I and II was determined to be a more accurate and descriptive of the syndrome. At the same conference consensus diagnostic criteria were also laid out for two CRPS types, (Stanton-Hicks, et al., 1995).

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The defined IASP diagnostic criterion for CRPS type-I is: The presence of an initiating noxious event or a cause of immobilization. Continuing pain, allodynia or hyperalgesia that is disproportionate to the inciting event. Evidence, at some time, of edema, changes in skin blood flow, or abnormal sudomotor activity in the area of pain. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction.

The defined International Association for the Study of Pain diagnostic criterion for CRPS type-II is: The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve. Evidence, at some time, of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction, (1995).

A majority of CRPS patients can identify an initial noxious event that preceded the clinical features of CRPS. In the case of CRPS type-I, which presents without a nerve lesion, the initial event is usually a minor trauma, such as an ankle sprain. In the case of CRPS type-II, which presents with a nerve lesion, a severe trauma is the usual culprit. Both CRPS Type-I and II usually present in a unilateral fashion with only one limb being affected. Both CRPS Type-I and II are marked by the dysfunction of the sympathetic nervous system (SNS), which leads to many forms of pain. About 81% of patients complain of spontaneous burning and stinging pain. Discoloration and vasomotor changes occur in 86.9% and 78.7% of patients, respectively. Allodynia, found in 69% of patients, is an abnormal sensitivity to normal mechanical or temprature stimuli. The sensitivity is so great with regards to mechanical and temperature stimuli, that clothing resting on a limb, or a breeze passing over the limb, instigates hyperalgesia. Additionally, CRPS type-II patients have symptoms that are common to neuropathy, i.e. electrical sensations, shooting pain, (Birklein, 2005).

CRPS type-I and II are marked by three distinct stages. The “Acute Stage”, during which patients are found to be undergoing an extreme inflammatory response and which is characterized by reddening and edema at the distal end of the affected limb. During the second “Chronic Stage” the affected limb begins turning bluish and cold and is said to be undergoing sudomotor dysfunction. During the final “Trophic Stage”, permanent changes to the underlying tissues occur leading to extreme weakness and fixed dystonia in the affected limb, (Johan, et al,. 2011).

Incidence rates of CRPS are unclear; two population-based studies arrived at very different data sets. A Netherlands based study found 26.2 cases per 100,000 person-years, and a USA based study found 5.5 cases per 100,000 person-years. Based on these varying data sets it can be surmised that there may be between 20,000-80,000 new cases per year in the USA. CRPS, once considered a rare syndrome, has lately become a more prevalent diagnosis, (Johan, et. al,. 2011). Some medical professionals believe its discovery by personal injury lawyers has greatly increased the reported incidents of CRPS, (Harden, 2011).

1. CRPS Susceptibility via Genetic, Physiological, Psychological Predispositions and Onset Prevention

A predisposition to Complex Regional Pain Syndrome (CRPS) would go far in helping to explain why only some patients with CRPS inducing injuries go on to develop the full-blown syndrome and why others do not.

A. Genetic Predisposition

Two studies have been done focusing on genetics being a predisposition variable in the onset of Complex Regional Pain Syndrome. A study by Dutch researchers found evidence that CRPS, "runs in the family". In this study, families with multiple familial CRPS occurrences were recruited through the Dutch Association of CRPS Patients and through referral by clinicians. The number of affected members per family and the phenotypic expression and inheritance were assessed. Demographic and clinical characteristics of Familial CRPS (fCRPS) patients were compared with those of sporadic CRPS (sCRPS) patients from a Dutch population-based study. Thirty-one CRPS families with two or more affected relatives were identified, including two families with five, four with four, eight with three and 17 with two affected relatives. In comparison with sCRPS patients, fCRPS patients had a younger age at onset and more often had multiple affected extremities and dystonia. The study concluded that CRPS could occur in a familial form, but no with clear inheritance pattern, even in the absence of a trauma, for siblings of young on-set patients. The sibling recurrence risk ratio provides the ratio of risk of disease for a person given that a sibling is affected, compared with the risk to develop the disease in the general population. The study outcome found the sibling with a familial occurrence of CRPS under the age of 50 had recurrence risk ratio of 3.4 to 5.6, values higher than 1 are indicative of familial aggregation, (de Rooij et al, 2008).

Another CRPS genetic study, used gene technology to type the Class-1 and Class-2 Major histocompatibility complexes of CRPS patients. The study found that it's fifty-two CRPS patients CRPS were found to have a higher frequency of the HLA-DQ1 antigen then the general population (M.A. Kemler et al, 1999).

Taken as whole, these results indicate that there may be a genetic component to CRPS, and that young patients with a history of familial CRPS (fCRPS) should be aware that they carry a greater risk of developing this CRPS even in the absence of a severe trauma.

B. Physiological Predisposition

Early studies have found that the immobilization that follows an injury, especially in the case of fractures, due to casting, leads to physiological susceptibility and can cause the onset of CRPS (Johan et al, 2011). Supporting this theory, a recent study found that mechanosensitivity and thermosensitivity, characteristic features of CRPS, can be artificially induced, in healthy individuals, by immobilizing an extremity for four weeks, (Terkelsen et al, 2008).

C. Psychological Predisposition

In the past, there was a school of thought that promoted the concept of a "Sudeck personality" that predisposes one to CRPS. This "personality" construct was premised on the idea that individuals

with a specific psychiatric pathology are prone to develop CRPS. This psychiatric perspective of CRPS has persisted even in the absence of evidence to support such a conclusion (Feliu and Edwards, 2009). In fact, a recent multi-center cohort study of 600 bone fracture patients, clearly disputes the psychiatric perspective (Johan et al, 2011). In the study, 600 patients were made to undergo the "Symptom Checklist-90", which is an instrument that helps evaluate a broad range of psychological problems and symptoms of psychopathology. The checklist results found that none of the psychological factors included in the list predicted the onset of CRPS (Beerthuzin et al, 2011). This isn't to say that physio-phsyco co-morbidity does not exist in patients with CRPS. It has been definitively proven that CRPS patients have higher incidences of depression and anxiety then the general populace, (Bruhel, 1992). Whether patients with CRPS have a higher rate of depression and anxiety then patients with other chronic pain syndromes is as of yet undetermined, (ibid).

Regardless of if depression is a factor in the onset of CRPS, treatment for depression with tricyclic anti-depressants has tri-fold benefits for CRPS patients. A majority of CRPS patients are depressed because of the pain and immobility that CRPS causes. Tricyclic anti-depressants relieve the depression. Pain is reduced due to the inhibitory affects that anti-depressant agents have on the re-uptake of norepinephrine and sertonin, known analgesics. Patients with CRPS are known to suffer from insomnia due the incessant pain they experience. Some anti-depressant medications have sedation type affects that bring a welcome respite from the incessant pain, (Rho et al, 2002)

D. CRPS Onset Prevention - Vitamin C

An interesting, randomized, double blind trial, studied 123 patients with casted wrist fractures to see if vitamin C could help prevent the onset of CRPS. The experimental group was treated with 500 mg of Vitamin-C per day for 50 days; the control group was treated with a placebo. Seven percent of patients in the group taking vitamin C developed CRPS-I, against 22% of patients in the control group, (Paul Zollinger et al, 1999).

There are many pharmacotherapy and interventional therapeutic techniques that are available in the treatment of CRPS. A line can be drawn between those with a discernible mechanism and those without. In addition, some treatments are directed at a specific presentation of the syndrome, while others are non-specific to the chronology and treat the general pain that is present in CRPS.

I. Pharmacotherapy & Interventional Therapeutic Techniques that are Stage Specific with Known Mechanisms.

Acute Stage – Inflammation, Testing, Pain, and Treatment

The origin of the inflammation during the acute stage of CRPS has pharmacotherapy implications, but its presence alone plays an important role in the diagnosis of CRPS, (Getson, 2006). Infrared Thermography is used to test for inflammation. The test is conducted on several symmetrical points on the affected and contra-lateral extremity, a temperature difference of 0.1 Celsius between contra-lateral limbs is considered telling and unusual, (Rho et al, 2002). Magnetic Resonance Imaging (MRI) machines are also used in diagnosing the inflammatory component of CRPS because of their

ability to show activity deep in the muscle and connective tissue. The unusual MRI abnormalities found in the acute phase of CRPS are consistent with muscular edema, interstitial edema, and vascular hyper-permeability. Such MRI findings usually suggest the presence of hemodynamic abnormalities caused by sympathetic changes which may lead to ischemia of affected muscles. Chronic phase abnormalities indicated the presence of muscle atrophy and fibrosis or fatty infiltration of the affected muscle (Nishida, et al,. 2009).

Three types of inflammation are possibly at play during the acute stage of CRPS, each with its own mechanism and treatment options:

- **A.** The Classic Inflammatory Response
- **B.** Neurogenic Inflammation
- **C.** Autoimmune Inflammation

A1) Classic Inflammatory Response - Mechanism

Cornelius Celsus, a Roman encyclopediast, was the first to observe and transcribe the "Classic Inflammatory Response" as the presence of calor, dolor, tumor and rubor, which translate to warmth, pain, swelling, redness (Celsus, 47 BC). In the case of CRPS patients, an acute Classic Inflammatory Response is undoubtedly present. Today, the cause of Celsus's observations are known to be the result of localized macromolecule extravasation, tissue acidosis, and reduced oxygen extraction, which leads to severe pain via the formation of free oxygen radicals that damage and thicken the basement membrane, (Goris, 1991).

A2) Classic Inflammatory Response - Treatment

The theorized role that free oxygen radicals play in the pain and inflammation associated with CRPS has been shown to be efficacious by the successful use of treatment modalities that scavenge and remove free oxygen radicals. In a comprehensive randomized double blind study two free radical scavenger medications were used. Topical 50% Dimethylsulfoxide (DMSO) was applied five times a day, or N-Acetylcysteine (NAC) tablets were ingested three times a day. Both treatments were found to be equally effective in providing temporary relief from CRPS's inflammatory response, (Perez et al, 2002).

B1) Neurogenic Inflammation - Mechanism

A second possible culprit in CRPS's inflammatory response may be caused by abnormal cytokine activity at the trauma site, which leads to "Neurogenic Inflammation". Cytokines are heavily involved in the cascading reaction that activates the natural nociceptor response by the retrograde depolarization of small-diameter primary afferent nerves. This leads to the release of numerous neuropeptides, including, Substance P, Calcitonin Gene Related Peptide (CGRP), and Somatostatin, (Birklein F. , 2001). These neuropeptides in turn evoke a vasodilation and a protein extravasation response in the epidermis, leading to the signature reddening, warming, and edema, of CRPS, (Weber et al, 2000).

B2) Neurogenic Inflammation - Treatment

Some neuropathic pain treatments that are used in treating other neuropathic pain conditions can be used in treating CRPS "Neurogenic Inflammation". Capsaicin, a topical analgesic provides some inflammation relief for CRPS patients.

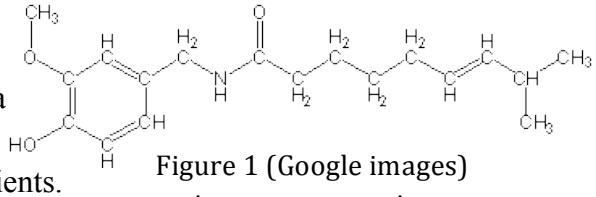

Figure 1 (Google images)

found primarily in the fruit of the Capsicum genus, is the primary capsaicinoid in the chili pepper fruit and is the cause of its pungent and spicy flavor. Structurally (Figure 1), Capsaicin or 8-methyl-N-vanillyl-6-noneamidemide is almost always found in the trans isomer form. Cis form, would place the CH(CH3)2 and the longer chain on the other side of the double bond causing them to repel each other slightly; leading to severe steric hindrance which does not exist in the trans isomer, (Reyes-Escogido et al, 2011).

Capsaicin works by binding to Transient Receptor Potential Vanilloid 1 (TRPV1), a non-selective, ligand-operated cationic channel, located primarily in the small fibers of nociceptive neurons. Bonding of Capsaicin to the TRPV1 receptor increases intra-cellular calcium and triggers the release of the neuropeptides: Substance P and calcium gene-related peptide (CGRP), which produces inflammation and a localized heat sensation by activating TRPV1's heat-sensitive subunit. The initial release of Substance-P and CGRP is quickly followed by the inhibition of the re-uptake of Substance P from the terminals afferent nerves, which produces an analgesic affect due to the desensitization of the sensory neurons caused by Substance P depletion. CRPS patients with Allodynia, are hypersensitive to touch, and may not be able tolerate this topically applied treatment, (Reyes-Escogito et al, 2011).

A CRPS double-blind study that investigated the use of Capsaicin in treating CRPS found it to be an effective pain reliever; all of the study's 10 patients reported an average 4 point drop on the Verbal Analog Scale (VAS) which measures pain, (Wendye, Robbins et al, 1998). A mitigating variable may have been the use of commercially unavailable concentrations of capsaicin, average Capsaicin concentrations in over the counter creams are 2%, this study used much higher concentrations of 5%, 7.5% and 10 percent. Because such high concentrations were administered the study's patients were treated with epidural anesthesia prior to its application to avoid the intense burning sensation that it provoked. It is very possible that the administration of the epidural anesthesia may have invalidated the study's outcome by playing a role in modulating the neurologic and sensory response to the treatment.

C1) Autoimmune Response - Mechanism

A third, recently researched possibility, posits that CRPS inflammation is an "Autoimmune Response". A study published in the journal of Clinical and Experimental Immunology found that an elevated monocyte count was not present in CRPS patients, a raised monocyte count being the usual marker of an autoimmune response. Still present, was an elevated count of the pro-inflammatory monocyte subgroup, CD14+CD16+. This result, coupled with research showing that patients with high CD14+CD16+ have low plasma concentrations of interleukin-10, a dominant player in the suppression of pro-inflammatory cytokines, lends credence to an autoimmune theory of CRPS inflammation (Ritz et

al, 2011). A small trial at University College London gave further support to an autoimmune inflammation theory. Participants in the trial were prescribed Intravenous Immunoglobulin (IVIG) antibodies, an autoimmune treatment modality, to treat CRPS inflammation. The study found that patients experienced 50% more pain relief with Intravenous Immunoglobulin over placebo, (Andreas Goebel et al, 2010). Limitations of the trial were its small size and that the effective dosage was not ascertained.

C2) Autoimmune Response - Treatment

Ketamine, a veterinary and human anesthetic has been found to be efficacious in treating the CRPS "Autoimmune Response" inflammation. Recent research found that ketamine suppresses lipopolysaccharide-induced tumor necrosis factor-A, interleukin (IL)-6, and IL-8 production, and recombinant human tumor necrosis factor-induced IL-6 and IL-8 production in human whole blood, all of which play a role in the proliferation of pro-inflammatory cytokines, (Kawasaki et al, 1999). In a recent case study in Germany, a single CRPS patient was treated with Ketamine after other CRPS treatment modalities failed to relieve the symptoms. Under standard ICU conditions the patient was given bolus injections of Ketamine while sedated with Midazolam. Upon waking the patient was relieved of all CRPS pain. After discharge from the hospital, the patient's chief complaint was regarding the psycomimetic side effects of Ketamine. Steady treatment with Midazolam helped negate this side effect, which abated after a month. In a subsequent German study, a larger grouping of patients was used. The study concluded that Ketamine is only effective during the acute stage of CRPS, when pain and swelling is localized to the distal end of a limb. It was ineffective in treating chronic CRPS patients whose symptoms were refractory and spreading, (Kiefer et al, 2007). A recent double-blind study arrived at similar findings with Ketamine delivering significant pain relief when administered on an outpatient basis and in low doses, (Schwartzman et al, 2009). The aforementioned study did not find any evidence that Ketamine was ineffective based on the duration of the syndrome; the case study outcome can therefore be called into question.

Corticosteroids – A non-mechanism specific inflammation treatment

Corticosteroids, known commonly as steroids are part of a number of options that health professionals have when treating inflammation. Steroids are one of the most oft prescribed anti-inflammatory drugs and are an accepted treatment for the acute inflammatory stage of CRPS. The predominant effect of corticosteroids is to switch off multiple inflammatory genes that encode for, cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins that are activated during a chronic inflammatory process, (Fischera et al, 2010).

A recent study evaluated the use Prednisolone, a steroidal anti-inflammatory, versus Piroxicam, a non-steroidal anti-inflammatory. The study found Piroxicam to be an effective inhibitor of arachidonic acid metabolism, an inflammation enhancing intermediate. It was also found to inhibit the production of the pain neurotransmitters, substance P and Calcitonin Gene Related Peptide, which play a part in the production of inflammation enhancing leukotrienes. The study concluded that Piroxicam seems to have

definitive chemical benefits, but little if any benefit in actually reducing sensory and motor pain, which continued unabated, (Kalita et al, 2005).

These findings suggest a dominant neural mechanism in the pathophysiology in CRPS. Confounding this possibility was the study's discovery that Prednisolone, the steroidal anti-inflammatory, was very effective in relieving actual pain in 83% of patients, (ibid). A drawback to this study was the failure to address this discrepancy. Some of the recorded side effects of long-term steroid use are hematologic, hepatic, musculoskeletal, neurologic and psychiatric damage and in some cases a severe weakening of the heart, (Parker and Thompson, 2010).

IV. Acute Stage - CRPS Bone Resorption, Testing, Pain and Treatment

Bone Resorption Testing

Bone resorption in CRPS can be diagnosed by simple radiography and Three Phase Bone Scintigraphy tests. Both tests register the presence of bone resorption and osteoporosis. A normal bone scan finding, without radiographic osteoporosis, precludes a diagnosis of adult CRPS. Some disagreement has been registered as to how early-on radiography can be used. A study by P.H.J.M Veldman (1993) I in the Netherlands, found spotty osteoporotic changes 4-8 weeks after a CRPS diagnosis. Other research has pointed to there being spotty changes earlier at the two-week marker, (Rho and Brewer, 2002).

Three Phase Bone Scintigraphy coupled with the tracer, Technetium Tc-99 Bisphosphonates, is highly sensitive test that can detect osseous changes earlier then radiography. A positive result will register a marked increase in tracer uptake during bone scintigraphy's, blood pool, blood, and mineralization phases. Increased tracer uptake is an indication of increased bone metabolism and breakdown. Some variability in the results of Bone Scintigraphy has been found based on the duration of CRPS , (Rho and Brewer, 2002).

Bone Resorption Pain

Immunohistochemical studies of the bone have shown there to be an extensive network of peptidergic and sympathetic sensory fibers that are present throughout the bone marrow and periosteum, Included in this network are two acid sensors, Acid-Sensing Ion Channels (ASICs) and Transient Receptor Potential Vanilloid Subtype 1 (TRPV1). In CRPS patients these pain-inducing receptors are activated by the presence of an acidic microenvironment in the bone. CRPS's acidic bone environment is generated by osteoclasts, a membrane bound proton pump that releases protons (acid) through Vacuolar H+-ATPase. Osteoclasts are the primary culprit in bone resorption, (Yanow et al, 2008).

Also active and present during CRPS bone inflammation are: mast cells, macrophages, endothelial cells, osteocytes, osteoblasts, and bone marrow stromal cells, which are involved in the production and storage of Nerve Growth Factor (NGF) protein. When present, NGF initiates the transcription for genes that encode the TRPV1 pain receptor, causing a further increase in the already painful CRPS nociceptive response. Cytokines and Prostaglandins are also found in the CRPS bone micro-environment and act synergistically to activate the network of nociceptors innervating the bone and bone marrow (Leon and Buriani, 1994).

Bone Resorption Treatment

An accepted treatment for CRPS bone related pain are, nitrogen and non-nitrogen bisphosphonates, which have anti-nociceptive properties that ameliorate bone pain; bisphosphonates work on osteoclasts and inhibit their activity leading to a decrease in the proton concentration and Nerve Growth Factor expression in the bone micro-environment. The non-nitrogen bisphosphonates, Clodronate ® and Etidronate ®, work by causing the buildup of metabolites in the cell which inhibit osteoclasts from functioning, causing cell death. Nitrogen-containing bisphosphonates, such as Alendronate®, Risedronate® and Zoledronate® interfere with the mevalonate biosynthetic pathway and protein lipidation, and in the signaling functions of key regulatory proteins, also leading to cell death. Bisphosphonates are a well-vetted and efficacious treatment, which has been well documented in four studies, (Manicourt et al, 2004; Robinson and Sandom, 2004; Varenna and Zucchi, 2000; Admai and Fossaluzza, 1997).

The randomized, double-blind study done by Varenna and Zucchi on the use of Clodronate®, found that 72% of patients showed significant pain relief 40 days into the trial. The numbers continued to improve with the passage of time, 75% at 90 days and 93.2% at 180 days, all experienced significant pain relief. Taken as a whole, these studies point to bisphosphonates being very useful in the treatment of CRPS bone related pain. The aforementioned studies did not find that bisphosphonates relieved any of CRPS other symptoms and the pain associated with them. Since their use is limited to bone pain, bisphosphonates need to be incorporated into a complete pharmacotherapy solution in order for CRPS patients to gain effective relief from the syndrome.

V. Non-Stage Specific Pharmacotherapy & Interventional Therapeutic, with known mechanisms.

Neurogenic Pain relief via Regional Sympathetic Blockade

Intravenous regional anesthesia was first proposed by Dr. August Bier in 1908 and till today is known as the “Bier Block”. Technically the treatment is simple. A tourniquet is applied to the ailing extremity creating a complete venous blockade followed by the injection of an analgesic. This treatment modality has since been used in the treatment of many localized pain diseases. In 1974 John Hannington-Kiff proposed a CRPS treatment with a derivative of the Bier Block, called Intravenous Regional Sympathetic Blockade (IRSB), (Hanington-kiff, 1974). The favored analgesic for this procedure was Guanethidine, because it is sympatholytic that selectively prevents peripheral sympathetic nerve transmission with the following mechanism: at first, when injected, Guanethidine causes the release of norepinephrine from the synaptic cleft, followed by the movement of Guanethidine into the synaptic cleft via uptake 1; it is then transferred into the presynaptic norepinephrine vesicle via norepinephrine transporter, also known as NET. Because norepinephrine is prevented from returning to the vesicle there is an initial spike in the sympathetic tone of the limb. Once the released norepinephrine

is metabolized, the Guanethidine populating the norepinephrine vesicle prevents the further production and release of norepinephrine, leading to a state of analgesia, , (Tollison and Satterthwaite, 2002).

The few double-blind studies that have reviewed the use of Guanethidine have shown it to be ineffective against a saline placebo in both short and long-term observations, (Kingery, 1997). A number of other sympatholytics such as Reserpine®, and Clonidine® have been found to be ineffective in relieving CRPS pain, aside from Bretylium®, which showed positive effects when used in the IRSB treatment, (ibid).

Local Anesthetic Sympathetic Blockade (LASB) is another Bier Block type treatment modality that is precluded from needing a tourniquet because the anesthetic solution is injected directly into the spine's sympathetic structures. In this procedure, one of two spinal structures are targeted, either the stellate ganglion, or the lumber sympathetic chain. The injection takes place under fluoroscopic or computed tomographic guidance to avoid damaging the spinal column. Once injected, the anesthetic solution induces a complete signal blockade. All sympathetic signals to and from the affected limb are effectively muted by the anesthetized spinal structure.

In the past, the "gold standard" for the treatment of CRPS was the local anesthetic sympathetic blockade (LASB). The LASB treatment played a unique role in diagnosing and treating CRPS. It was unique in this dual application. The 1993 Orlando Conference changed this role when CRPS's diagnostic criterion was modified to exclude an analgesic response to a sympathetic nerve block. Thereafter, LASB was no longer considered an essential piece of confirmatory diagnostic information because the syndrome's classification was broadened to include patients without Sympathetically Maintained Pain (SMP). Accordingly, a response to a sympathetic block is not required to diagnose CRPS because the syndrome's criterion now includes patients without sympathetic dysfunction. Identifying patients who have Sympathetically Maintained Pain is still very important because of the short term relief gained from a sympathetic blockade; this effective short term relief has made the LASB the go to adjunctive therapy for patients undergoing physiotherapy, (Sharma and Williams, 2006).

But this positive view of LASB has been tempered by a comprehensive review on behalf of the Chocrane Collaboration where little evidence was found to support the positive view of LASB . The Chocrane Collaborations criteria for inclusion were that the trials be randomized and double blind. Excluded from the review were studies evaluating somatic nerve blocks and studies evaluating the effects of orally, intravenously and epidurally administered anesthetic or sympatholytic drugs. Two unpublished studies cited in this review, fit this criterion. One, a double-blind study by Dr. Donald D. Price, found that six out of seven patients experienced at least 50% short-term pain relief when treated with the anesthetic Lidocaine® over normal saline. The duration of relief was 3 days for local Lidocaine® versus 19.9 hours for the saline placebo. A second study by R.J. Verdugo found that 12 of 16 patients had at least 50% short-term pain relief while receiving Bupivacaine® versus the saline placebo. The combined Relative Risk Ratio of these two trials was 1.17. A Relative Risk Ratio of 1.17 is slightly greater then a Risk Ratio of 1, which implies little significant difference was found between experimental and control groups in the study. These findings clearly show that LASB treatment needs further research to reclaim its status as a "gold standard" in treating CRPS. The studies long-term outcomes were precluded from being combined in a Risk Ratio because the both studies gauged

different outcomes. Dr. Price recorded the *duration* of pain relief, while Dr. Verdugo evaluated *number of subjects* who had at least 50% of pain relief (Cepeda et al, 2010).

Neurogenic Pain Treatment: Surgical and Chemical Sympathetic Denervation

CRPS patients with Sympathetically Maintained Pain (SMP) suffer from a dysfunctioning Sympathetic Nervous System. Permanently denervating the system inhibits signaling and can be achieved via a surgical or chemical sympathectomy.

Surgical denervation

Surgical denervation is accomplished via Open Lumbar or endosopic sympathectomy surgery, (Bandyk et al, 2002). In these procedures the sympathetic ganglion are destroyed via its open removal or by electro-coagulation. A well recognized side effect to a surgical sympathectomy is hyperhidrosis, this side effect was recognized as early as 1933, when a Dr. J. Paterson Ross lectured at the Royal College of Surgeons in London and recounted that, "some of our patients have stated emphatically that the secretion of sweat has been considerably more profuse in areas not affected by the operation . . . the remark has been so frequently made that the possibility of compensatory hypersecretion cannot be excluded", (Ross, 1933)**.** Current research wholly concurs with his observation. In one study, patients experiencing palmer hyperhidrosis that underwent a sympathectomy almost all experienced some form of compensatory sweating, usually in the trunk area, (Gossot et al, 2003; Ojimba & Cameron, 2004). Another study of 73 patients found that 8 out of the 83 surgical sympothectamy procedures done in the study, 10 of the studies 73 patients needed the procedure to be repeated, resulted in Hyperhidrosis, (Bandyk et al, 2002).

Chemical Sympathectomy

Chemical Sympathectomy is achieved by injecting 50% to 100% ethanol or 7% to 10% Phenol into sympathetic ganglia, (Dunn, 2000). Phenol, a strong anti-septic solution causes protein coagulation and necrosis when directly applied to nerves (Copping et al, 1969). Ethanolcauses alcohol neurolysis, which involves the extraction of phospholipids and cerebrosides from the neural membranes and by precipitation of mucoproteins. Both are effective in causing nerve / ganglion death which delivers anesthesia by the inhibition of nociceptive signaling. The only available double blind of chemical sympathectomy contrasted the use of chemical sympathectomy to radio frequency sympathectomy. Both treatments were found to equally effective in delivering 50% pain relief in a grouping of 20 patients, (Straube et al, 2010).

VI. Pharamcotherapy & Interventional Therapeutic Techniques with Unknown Mechanisms

Bone Resorption Treatment - Calcitonin

In 1961, Dr. D.H. Copp discovered a calcium-regulating neuropeptide hormone. At the time of his discovery he was studying the control of calcium secretion by parathyroid hormone (PTH) when he found that a neuropeptide was released in the presence of hypercalcemia that lowered plasma calcium by

inhibiting osteolysis. The newly discovered neuropeptide was named calcitonin (Copp, 1994). Subsequently, experiments were performed to see if in vivo use of calcitonin would be useful in the treatment of osteoporosis / bone resorption, (Özoran and Seçkin, 2005), studies have concluded that Calcitonin is an effective in the treatment of osteoporosis, (Karsdal et al, 2010).The use of intramuscular or subcutaneously injected calcitonin is not without side effects. Its most common side effects being gastrointestinal: anorexia, nausea, vomiting, a metallic taste and diarrhea are the prevalent presentations of its gastrointestinal effects. Vascular phenomena, such as flushing or shivering, are also observed in some patients. Generally these side effects are dose related and inconvenient rather than serious, but they can occur in up to 80% of patients on high doses, (Siminoski et al, 1996).

In addition to inhibiting osteoporotic type bone resorption, calcitonin was found have analgesic effects on bone related pain, making it a perfect candidate for the treatment of CRPS patients suffering from bone resorption and bone pain, (Blau, 2003). A study of CRPS patients by Fushun Sahin and Figen Yilmaz assessed the efficacy of salmon calcitonin in a randomized, single-blind study. The control group received Paracetamol®, an over the counter analgesic 1500 m/day, while the other experimental group received salmon calcitonin 200 IU/day, for 2 months. Both the control and experimental groups showed remarkable recovery on either paracetamol or calcitonin when given the treatment in conjunction with physical therapy, but little marked difference was found between the two groups. The study concluded that physical therapy combined with a simple analgesic is an efficient means of therapy and that calcitonin makes little or no contribution in the treatment of patients with acute CRPS, (Sahin et al, 2006).

Another study utilized nasal calcitonin given the disadvantage in the administration of regular calcitonin, i.e. it must be administered parenterally. This prospective randomized double-blind study; using sensitive methods of measuring the response to treatment, did not demonstrable any effect on the clinical or skeletal progression of CRPS bone resorption,. The authors hypothesized, “not finding a difference between the treated and placebo wing is that the bioavailability of the nasal formulation was too low. Although there was a small decrease in serum calcium during the treatment period, the response was not associated with changes in the indices of bone turnover. In particular, the fasting urine excretion of calcium did not change. This suggests that the decrease in serum calcium was due to a decrease in renal tubular reabsorption of calcium, a known action of calcitonin”, (Bickerstaff and Kanis, 1992)

A blinded meta-analysis of 21 CRPS treatment clinical trials concluded that using Calcitonin in the treatment of CRPS has a positive effect on pain on average and encouraged its use, (Perez et al, 2001). Perez based his assertion on a study that found calcitonin to have the conclusively beneficial effect of significantly less pain, (Gobelet et al, 1992). Calcitonin’s mechanism and effectiveness as a treatment option, remains as of yet undetermined. The antinociceptive properties of calcitonin have been attributed to serotoninergic and cathecholaminergic mechanisms, Ca 2 fluxes, protein phosphorylation, endorphin production, cyclooxygenase inhibition and histamine inference. None of these mechanisms have been conclusively proven.

Gabapentin

Gabapentin was marketed for the first time in Febuary 1994 as an anti-convulsant drug. Today it is widely viewed as an affective adjunctive therapy for seizures. Structurally, it is an analogue of y-aminobutyric acid (GABA). It's synthesis as a GABA mimetic drug was so that it could cross the blood-brain barrier. Pharmacologicaly it is different from other substances that interact with GABA synapses for the reason that it binds only in the outer layers of the neocortex and hippocampus and does not bind with GABA receptors at all.

The first gabapentin study on RSD patients had a remarkably successful outcome with all six patients, with one fully recovering from RSD. The authors hypothesized that a gabapentin induced an increase in 5HT, (which are serotonin receptors) and serotonergic-like activity at a novel receptor site in the CNS, and also via serotoninergic fibers in the raphe magnus which descend into the posterior portion of the lateral funiculus of the spinal cord.

These descending fibers they posited blocked the transmission of nociceptive information through the dorsal horn and root ganglion by reciprocally blocking pain-inducing catecholamines, resulting in a gradual reduction of the nor-adrenergic induced hyperalgesia, , (Mellick and Mellick, 1995). A problem with their hypothesis is that it was vicariously deduced from the increased presence of serotonin in patients treated with gabapentin. Therefore few definitive conclusions can be drawn from it. Even so, the efficacy of the use gabapentin to treat CRPS "pain" is well founded. A double-blind and randomized placebo-controlled 8-week study of 304 CRPS patients found that measured pain scores decreased by 21% in patients receiving gabapentin and by 14% in placebo treated patients, (Serpell, 2002).

Spinal Cord Stimulation

Spinal cord stimulation is a relatively new therapeutic modality to gain acceptance in the treatment of CRPS. In 1965, Melzack and Wall published a revolutionary paper that theorized that a "gate" existed in the dorsal horn of the spinal cord which controlled the transmission of neural activity that signaled pain. This "gate" was said to be open when there was an excess of small over large afferent fiber activity in the peripheral nervous system, and the gate was closed when there was an excess of large-diameter afferent fiber activity. On the basis of this theory, scientists have tried to selectively activate large diameter afferent fibers through electrical stimulation, thereby closing the "gate" and reducing or eliminating painful inputs to the spinal cord and brain, (Melzack and Wall, 1965). Utilizing this theory, medical professionals have been able to induce this effect using a spinal cord stimulator which is surgically placed along the spine. It is theorized that its analgesic effect may come from neuromodulation that restores normal gamma-aminobutyric acid (GABA) levels in the dorsal horn and affects the release of adenosine, which is an anti-inflammatory, thereby reducing neuropathic pain (Oakley and Prager, 2002).

A systematic review of the literature on spinal cord stimulation reported a meaningful 2-point mean reduction in the Visual Analogue Pain Scale ratings in patients with CRPS type-I, (Taylor et al, 2006). This was based on results derived from a randomized controlled study (Kemler et al, 2000), and 25 other case series. The controlled study wasn't blinded for the obvious reason that it is not advisable to

try to mimic parasthesia-type effects on the spinal cord of patients in the placebo group. The controlled study showed -2.7 drop on the Visual Analogue Pain Scale scale in the spinal cord stimulated group at 12 months, while the control group had a +0.4 increase on the Visual Analogue Pain Scale pain scale. The systematic review data showed that almost two-thirds of CRPS type-I and type-II patients, reported at least 50% improvement in their pain scores over a median follow-up period of 33 months. It can be concluded that spinal cord stimulation is an efficacious treatment for CRPS patients with sympathetically maintained pain.

In addition to the study's pain analysis, Taylor also reviewed treatment cost to ascertain long term cost of spinal cord stimulation vis-à-vis physical therapy. He found that the control group which received physical therapy cost $6000 over 12 months. The spinal cord stimulation treatment group had a significantly higher balance of $10,200. But in an interesting turn around, the cost numbers reversed over time and the spinal cord stimulation treatment produced a lifetime cost saving of approximately $60,000.

Opioids

Opioids are one of the oldest classes of pain relievers, (Ballantyne and Mao, 2003). Victorian women were said to use a morphine containing tincture called, laudanum, which is a 40% ethanol solution of dissolved opium and herbs. This was done to treat the travails and boredom of Victorian life, accomplishing what is known in the vernacular as getting high, (Berridge and Edwards, 1987). Opioids are still used in the treatment of chronic nociceptive and neuropathic pain, (Harke et al, 2001). Research has shown that opioids are ineffective in delivering analgesia in low dosage; concurrent research has found that the use of opioids in large dosage can itself cause hyperalgesia, a key symptom of CRPS. Other known opioid side effects are hypogonadism, long-term cognitive impairment, personality changes, tolerance, long-term toxicity and drug dependence (Harden, 2007). The use of opioids in treating neuropathic pain has been frowned upon for some time, not because of its cornucopia of side effects, but also because research found it be an ineffective treatment modality. A study found infusions of morphine to be completely ineffective in relieving neuropathic pain, (Arnér and Meyerson, 1989).

Current research is slowly shifting this negative opioid perspective. A randomized control study used Methadone to treat 20 patients and found statistically significant pain relief P 0.013-0.020 on the Visual Analogue Pain Scale scale, (Morley et al, 2003). Dose titration must be done cautiously, since large differences in Methadone dose tolerance have been found**,** (Cruciani, 2007). In too large dosage Methadone causes drug toxicity and affects the heart by causing an elongated QTc interval, (Kornick et al, 2003). Still, its prolonged half-life, potency, and low cost make it a preferable candidate amongst other opioids. Tramadol, another opioid, has also been vindicated as an effective reliever of allodynia and other pain in recent randomized double-blind study, (Sindrup et al , 1999). Intrathecal analgesia can be achieved with an injection of Baclofen for patients that cannot tolerate orally administered opioids because of their side effects, (Cohen 2007)**.**

Physical Therapy

Physical Therapy is broadly mentioned in the literature as an important aspect in recovering from CRPS, (Harden R. 2011; Kemler et al, 2000; Rho et al, 2002). Unfortunately there is little hard evidence to support this treatment modality. An oft mentioned proof of Physical Therapy's effectiveness, is randomized double-blind study of patients with CRPS Type-I of less than one year of duration, which indicated that physical therapy was superior to occupational therapy, and that both physical therapy and occupational therapy were more effective then social work therapy, (Oerlemans et al, 2000). Unfortunately, the study's outcome was tempered by the fact no significant differences were found in the long-term for active range of motion of the shoulder, elbow, and forearm utilizing the three treatment modalities. The immediate improvement seen in patients that were treated with physical therapy weren't any different then the control group a year after inclusion in the study.

Conclusion

If left untreated, CRPS can result in permanent deformities and chronic pain requiring a range of long-term pharmacologic and non-pharmacologic treatments. If CRPS is caught early, sympathetic nerve blocks may be used to stop or cure the progression of the disease. Other therapies used to treat patients with CRPS such as, spinal cord stimulation, opioids, anti-inflammatory medications can all play a role in modulating and sometimes curing CRPS pain. The absence of well-defined criteria for the diagnosis of this syndrome has resulted in a lack of Randomized Controlled Trials for the treatment of CRPS. Some of the medications that have been tested to treat the CRPS population include certain antidepressants, anticonvulsants, anesthetics, anti-inflammatories, opioids, calcitonin, bisphosphonates, and neuropathic coanalgesics. There are no medications that are FDA approved for the treatment of CRPS.

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