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# Complex Regional Pain Syndrome


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## INTRODUCTION

The International association for the study of pain (IASP) defines Complex regional pain syndrome (CRPS) as follows: *It is a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at the same point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, allodynia or hyperalgesia*.[1]

Complex regional pain syndrome is a condition that results in significant impairment of activities of daily living and ability to function thus has serious consequences regarding quality of life. In a recent review it was noted that incidence to be 26.2 per 100 000.[2] It is more likely to affect women compared to men at a ratio of 4:1, more commonly affects the upper limbs and typically affects individuals between the ages of 50 to 70 years.[3]

### History

- Ambroise Pare (16$^{th}$ century) – The first known documentation of features suggestive of or related to CRPS was by this individual while he treated the French King Charles IX of Valois, after a limb phlebotomy. He is also considered the father of modern surgery.[4]

- Silas Weir Mitchel (1872) - An American Physician during World War 1 published a book called "*Injuries of nerves and their consequences*". A condition called causalgia was described by him, this condition was characterized as a chronic burning pain that was located distal to the injury site with associated skin changes.[4]

- Paul Sudeck (1900) - A German Surgeon described x ray changes, namely bone resorption. He noted that features were associated with acute inflammation following fractures, ligament injury and nerve injury.[4]

- Rene Leriche (1917) - A French Surgeon was the first to perform a periarterial sympathectomy in a patient that suffered from chronic hand pain. The patient reported complete resolution of the pain. Leriche went on to describe the importance of the parasympathetic system in the pathogenesis of neuropathic pain. Reflex sympathetic dystrophy (RDS) was the term subsequently coined by James A Evans (American physician).[4]

- John J Bonica (1953) – An American aneasthesiologist and founder of the IASP, He proposed that RDS be changed to CRPS and that CRPS is characterised by 3 distinct stages.[4]

- IASP (Orlando Conference) (1994) – The Orlando Criteria is developed for the diagnosis of CRPS.

- IASP (Hungary Conference) (2012) - Revised Budapest Criteria are adopted.

**Clinical presentation and Diagnostic Criteria**

CRPS has been divided into subtypes:

CRPS Type 1 (Reflex sympathetic dystrophy)
Onset is typically determined by noxious events e.g. Minor trauma, surgery.
There is no detectable nerve injury.
Patients typically present with the following features.[5]

- Sensory symptoms
  Hyperalgesia- enhanced intensity of pain sensation.
  Allodynia- Pain resulting from a stimulus that would not normally cause pain.
  Sensory abnormalities- Occur distal to inciting lesion and are not restricted to a particular nerve distribution.

- Motor Symptoms
  Muscular weakness of affected limb.
  Physiological Tremor (increased).
  Loss of range of motion.

- Trophic changes
  Abnormal hair growth and nail growth.
  Osteoporosis.

- Autonomic abnormalities.
  Hypo/hyperhidrosis.
  Limb Swelling.
  Skin blood flow changes.

CRPS Type 2 (Causalgia)
It typically develops following demonstrated injury to the affected nerve.
The Symptomology is similar to CRPS 1.[5]

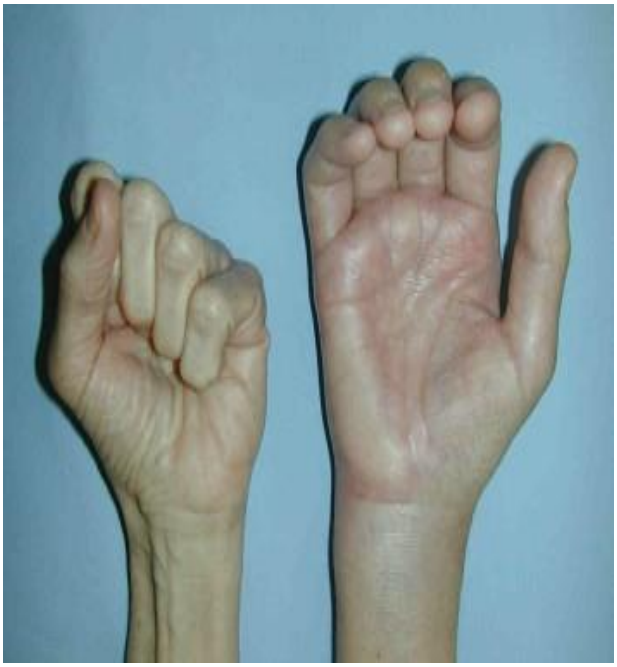
CRPS-Not otherwise specified.
The type does not fully meet the criteria for CRPS.

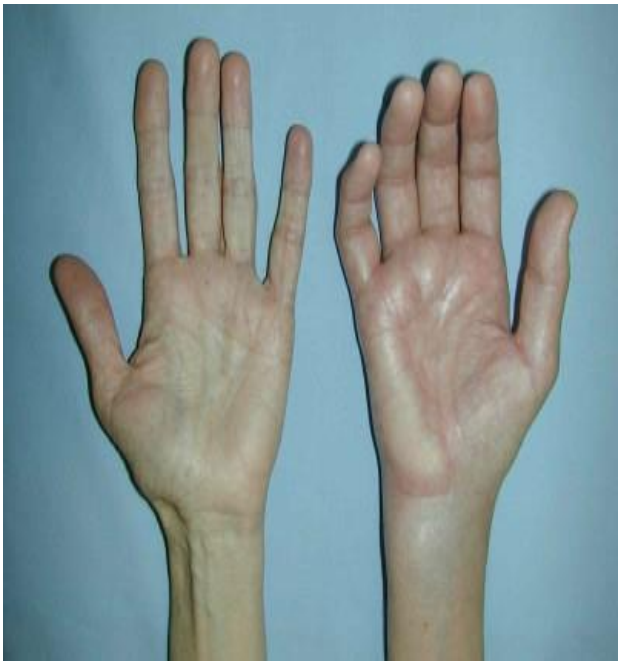
**CRPS has further been described to occur in 3 stages:**

1. Acute Phase 0-3 months
   Patients present with pain not that is not limited to a particular nerve distribution.
   Warm and oedematous limb.
   Reduced range of motor activity of affected limb.[4, 6]

2. Dystrophic phase 3-6 months
   Soft tissue changes predominate- Reduced hair growth, discoloration, etc.[4, 6]

3. Atrophic phase
   Pain severity is reduced but is still persistent
   Skin changes are present-thin, waxy, ulcerated, etc.
   Osteoporotic changes on X-ray. [4, 6]





CRPS is informally also distinguished as warm CRPS (acute setting) or cold CRPS (chronic setting). It has been noted that transition from warm CRPS to cold CRPS tends to occur 12 months after the injury.[3]

Risk factors that have been shown to lead to an increase in development of CRPS include:[2, 7]

1. Surgery
   It has been shown that CRPS is more likely to develop after operative orthopaedic procedures have been performed, upper limbs tend to be more affected than lower limbs. The following injuries/procedure in descending order likely to lead to CRPS are: Dupuytren"s contracture surgery, distal radial surgery, shoulder surgery and carpal tunnel surgery. Most of the cases tend to resolve after 3-6 months, likely explaining varying incidence reports.

2. Menopause
3. Asthma
4. Angiotensin converting enzyme inhibitor
5. Osteoporosis
6. Migraine

The initial 1994 guidelines IASP (Orlando guidelines) grouped distinct signs and symptoms e.g. Vasomotor and sudomotor signs and did not require both signs and symptoms for the diagnosis of CRPS. Although having a sensitivity 0.97 the criteria had a specificity of 0.41 leading to an overdiagnosis of CRPS. [3, 8]
The current revised 2012 Budapest criteria recognised 4 distinct subgroups of signs and symptoms, that is: Sensory, Vasomotor, sudomotor/oedema and trophic/motor. It also required that both signs and symptoms for the 4 subgroups be sought in order to diagnose CRPS. Although this resulted in the reduction of the sensitivity 0.85 it also lead to an increase in the specificity 0.69.[3, 8]

Clinical Diagnostic Criteria for CRPS (Budapest criteria)

1) Continuing pain, which is disproportionate to any inciting event.

2) Must report at least one symptom in three of the four following categories:
- Sensory: hyperalgesia and/or allodynia.
- Vasomotor: Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
- Sudomotor/Oedema: Oedema and/or sweating changes and/or sweating asymmetry.
- Motor/Trophic: Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

3) Must display at least one sign at time of evaluation in two or more of the following categories:
- Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
- Vasomotor: Evidence of temperature asymmetry and/or skin colour changes and/or asymmetry.
- Sudomotor/Oedema: Evidence of oedema and/or sweating changes and/or sweating asymmetry.
- Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

4) There is no other diagnosis that better explains the signs and symptoms.

## PATHOPHYSIOLOGY

The pathophysiology of CRPS is poorly understood, it thought that multiple factors contribute to the process and development of CRPS. Multiple factors that have been shown to contribute to the development of CRPS include: Central and peripheral sensitisation, Inflammatory factors, Dysfunctional sympathetic nervous system, Genetic factors and Psychological factors.

### 1. Central and peripheral sensitization

Acute noxious stimuli results in the direct activation of nociceptors and also the release of inflammatory mediators. These inflammatory mediators e.g. ATP, PE2 also interact with their receptors activating the nociceptors resulting in activation of the C-fibres and A-Delta fibres. The two important peripheral neurotransmitters, are Substance P and Calcitonin gene-related peptide (CGRP) are released as a result of the process described above. The sympathetic nervous system is also activated, resulting in the release epinephrine and norepinephrine which further augments nociceptor activation.

The C-fibres and A-Delta fibres synapse at the rexed laminae (second order neurons) within the spinal cord. The important second order neuron groups that have been described include those that are involved in proprioception, nociception and wide dynamic range (WDR) neurones.

Within the spinal cord glutamate a neurotransmitter binds to mainly AMPA (Alpha-amino-3-hydoxy-5-methyl-4-isoxazoleproprionic acid) one of the 3 receptors, it also binds to the NMDA (N-methyl-D-aspartate) and G protein coupled metabotropic receptor. The second order neurones ascend and synapse with both the thalamus and cerebral cortex. At both the thalamus and cerebral cortex the pain is interpreted resulting in a response. In addition the periaqueductal grey matter (PAG), rostroventromedial medulla and reticular formation are activated as well (descending inhibitory pathway). This leads to the attenuation of nociceptive transmission.[9]

Peripheral sensitization occurs as a result of a prolonged inflammatory process leading to a number of changes one being the increased production of substance P and CGRP. This reduces the pain threshold for both mechanical and chemical stimuli.[3, 9]

During central sensitization the normally dormant NMDA receptors are activated as a results of continuous nociceptive stimulation. Dormant wide dynamic (WDR) second order neurones are subsequently activated. This process is described as the wind-up phenomenon. There is also activation of the glial cells which contribute to increased neuronal activity and receptor up-regulation.[3, 9]

The changes described above lead to the features of allodynia and hyperalgesia that are seen in patient that suffer from CRPS.[3]

**2. Sympathetic Nervous system**

It was initially postulated that vasomotor and trophic changes that CRPS patients presented with were as a result of excessive sympathetic outflow. Subsequent studies have demonstrated patients with reduced sympathetic nervous system activity are at an increased risk of developing CRPS. In the acute setting, the reduced sympathetic nervous system function causes vasodilation which results in a warm and swollen limb.
Progression of CRPS leads to up-regulation of the catecholamine receptors to compensate for the reduced sympathetic outflow. This predisposes patients to excessive vasoconstriction, with a presentation of a cool and sweaty limb. [3, 5] [10]

Studies have demonstrated increased activity of afferent nociceptors with sympathetic activity. This has led to the description of the phenomenon termed sympatho-afferent coupling, whereby sympathetic activity is coupled to afferent nociceptors. There is development of catecholamine receptors on afferent nociceptive fibres. With the release of catecholamines there is stimulation of these nociceptive fibres resulting in augmented pain (Sympathetically mediated pain).[3, 5]

**3. Central Nervous System**

Somatosensory cortical representation of affected limbs in patients with CRPS has been noted to have shrunken, this has been demonstrated by imaging studies. It has also further been demonstrated that the descending inhibitory pathway function is reduced in patients with CRPS.[3, 10]

**4. Inflammatory and immune related factors**

Some of the features that occur in the acute phase of CRPS that is warm, swollen and oedematous limb may be explained by the involvement of the inflammatory system. Both cell mediated inflammation and neurogenic inflammation have been implicated in this process. In cell mediated inflammation there is release of systemic cytokines (interleukins and Tumour necrosis alpha) resulting in localised vasodilation, extravasation of fluid and hyperhidrosis.[3, 5, 10]
Oxidative stress has been theorized as another pathway leading to inflammation and that this may predispose to the development of CRPS. This is as a result ischaemic reperfusion injury.

Substance P, bradykinin and CGRP are important neuropeptides that are implicated in the development of neurogenic inflammation. Studies have shown that these neuropeptides are elevated in patients that present with CRPS. It has further been shown that Substance P and tumour necrosis alpha also activate osteoclasts that leads to bone resorption.[3, 5, 10]

### 5. Psychological factors

Patients suffering from CRPS symptoms tend to be anxious and are often depressed. This led to the theory that CRPS was a result of psychogenic disorder. Subsequent studies have gone to show that psychological symptoms are more as a result of as opposed to the cause of CRPS.[3, 10]. Patients that are depressed and anxious have been shown to have greater intensity CRPS symptoms (Sympathetically maintained pain), as a result of increased catecholaminergic activity.

### 6. Genetic factors

The role of genetics in the development of CRPS has been considered. Studies that have been conducted have struggled to find link between CRPS and genetics factors. The biggest reason being the small sample sizes.[10]

Two studies that have been conducted. The first study found that siblings of patients with CRPS were more likely to develop it themselves. The second study showed evidence of familial CRPS, with some families having as much as 5 relatives affected with the condition.[11, 12]

Genes for both major histocompatibility complex (HLA) and tumour necrosis factor have both been linked to the increased likelihood to develop CRPS. The tumour necrosis factor alpha 2 allele was found to lead to an increased production of TNF alpha leading to altered inflammatory response to injury.[5, 10]

## MANAGEMENT

Due to the lack of understanding regarding the pathophysiology of CRPS and multiple features that it presents with makes it a difficult condition to manage. It has been found that the various modalities used to manage CRPS have poor or no evidence for their efficacy in its management[6]. A multidisciplinary approach has been advocated. The broad groups in the management of CRPS include: physical + occupational therapy, pharmacological interventions, invasive interventions and neuro-stimulation.

### Rehabilitation

Both physical therapy (PT) and occupational therapy (OT) have been advocated for the management of CRPS with the goal of functional restoration of the affected limb. These modalities have been found not only to lead to functional restoration but also to improvement of pain in the long term.[13, 14]
PT was shown to have the most dramatic effects regarding improvements CRPS compared to OT, and is thus regarded as the first line management in CRPS.[6]

Two approaches have been described, that is mirror therapy and graded motor imagery.

### 1. Mirror visual feedback (MVF)

It has initially been used successfully in patients with phantom limb pain. These patients have a disruption in the normal interaction between motor intention and the absence of appropriate sensory feedback. In order to overcome this disrupted relationship, a mirror is used where an

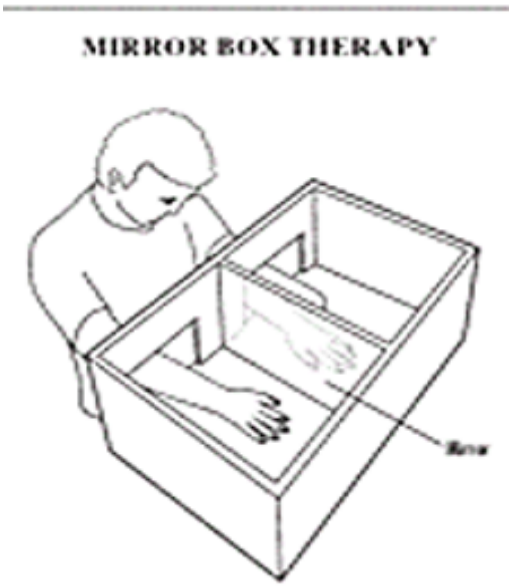
image of the normal limb is superimposed. The patient is then asked to move the normal limb, giving an illusion of movement that is free of pain and discomfort.[8]
These patients have shrinkage of contralateral somatosensory representation of the affected limb. Mirror therapy has been shown to successfully lead to a reduction of pain and improvement of function. Studies have shown that MVF has the greatest benefit in the acute setting with reduction in benefits with increasing chronicity of CRPS.[6, 8]

**2. Graded motor imagery (GMI)**

Graded motor imagery was developed to assist patients with chronic CRPS. The three sequential phases include:

- Limb laterality recognition
- Motor imagery
- MVF

In the first phase, the patients is shown a picture of their limb and has to decide whether it is the right of left limb. The second phase involves the patient seeing a picture of a limb in a particular position and asked to imagine moving the affected limb into the same position. The third and final step is MVF. At the conclusion of this process there should be activation of the premotor and motor cortices and restoration of their orientation. In a study conducted by Moseley et al significant improvement of pain in patients with chronic CRPS using GMI was shown.[15]




**Pharmacological intervention**

Pharmacological management of CRPS throughout the years has involved the use of multiple drugs as a result poorly understood pathophysiology and lack of evidence or poorly done trials. A review article by Perez et al assessed therapeutic interventions used in the management of CRPS. They concluded the following:[13]

- Non-steroidal anti-inflammatory drugs - Insufficient evidence.
- Opioids – Insufficient evidence.
- Antidepressants- No evidence.
- Anticonvulsants- Limited evidence for gabapentin only.
- Transdermal lignocaine- No evidence.
- Corticosteroids- Positive effect

It was found that of the standard therapeutic drugs, corticosteroids are beneficial in the acute setting.[8]

**Less commonly used/emerging drugs include:**

**Calcitonin**

It is a hormone that is produced within the thyroid gland and is known for its analgesic properties. Theories for its mechanism of action include possible anti-inflammatory properties or augmentation of the descending pathway. Two reviews (Salibi et al and Cochrane) showed beneficial outcomes. However in a review by Tran et al[14], it has been found that patients taking calcitonin are at increased risk of developing cancer hence it is not marketed anymore.

**Bisphosphonates**

It has been demonstrated that patients with CRPS develop osteoporosis as a result of increased osteoclastic activity. It has hypothesized that bisphosphonate use will slow down osteoclastic activity and thus lead to a reduction in pain associated with the resorption of bone. Multiple studies and reviews have noted the increased efficacy of bisphosphonates to manage CRPS associated pain. [3, 6, 14, 16]

**Free radical scavengers**

Free radicals are produced as a result of an excessive inflammatory reaction. This possibly contributes to the development of CRPS. N-acetylcysteine, mannitol and dimethyl sulfoxide (DSMO) have been investigated to determine their efficacy in the management of CRPS. Positive results were found for both DSMO with warm CRPS and N-acetylcysteine for cold CRPS.[6, 13]
There was no evidence for the efficacy of mannitol in the management of CRPS.[14]

**NMDA antagonists**

Sub-anaesthetic intravenous ketamine has yielded positive results in terms of managing CRPS pain as a result of central sensitisation. It was also noted that a higher proportion of patients suffered from significant side effects such as: nausea, sedation, hallucinations.[13, 16]

**Anti-hypertensives**

Both phenoxybenzamine and nifedipine have been shown to aid in the management of CRPS especially where there is evidence of altered blood flow. Their benefits have been best illustrated in acute CRPS.[13]

**Vitamin C**

It has been suggested that it use may prevent the development of CRPS in patients that fractures. This is due to its antioxidant effects that limit oxidative stress as a result of inflammation.[13]
Vitamin C given at a dose of 500mg daily for a period of 50 days after injury or surgery was recommended.

A review article by Bruehl et al noted conflicting results for the use of vitamin C to prevent the development of CRPS, with one trial showing an increased incidence in patients that took vitamin C.[3]

## Invasive interventions

### 1. Sympathetic nerve blocks

This could be accomplished by either a stellate ganglion or lumbar sympathetic block. As it was thought that the pain was sympathetically mediated, performing this type of block would not only aid in pain relief but also confirm the diagnosis of CRPS. It would distinguish between sympathetically mediated pain(SMP) and sympathetically independent pain(SIP).[6]
However the evidence to support it has been has been poor. A review conducted by Salibi et al found moderate evidence to support the use of sympathetic blocks.[6] However guidelines that were released for the management of CRPS in Netherlands found no use for routine sympathetic blocks in patient with CRPS.[13]

### 2. Intravenous regional aneasthesia (IVRA)

It is a process whereby a tourniquet is applied and a drug is infused into the limb. This ensures that there is interstitial diffusion and prevents the drug from being systemically distributed. Guanethidine was investigated to determine its effectiveness in the management of CRPS and the results were poor. Studies also looking at other commonly used agents such lignocaine and clonidine were not encouraging as well.[6] The Dutch guidelines noted that there was evidence for the use of ketanserine (serotonin type 2 receptor antagonist)[13]

### 3. Brachial plexus and epidural infusions

One of the indications for a brachial plexus block is intractable pain as a result of CRPS. A continuous regional technique (as long as 3 weeks) is ideally used in this region, as not only does it block the sensory afferents but also the sympathetic efferent. Its use is only supported by limited case series observations. [8]

Epidural infusions have been used in the management of CRPS, the common drug being clonidine with or without bupivacaine. There is moderate evidence to support its use.

### Neurostimulation

This involves the implantation of electrodes into the central nervous system (brain or spinal cord) and stimulation of the tissue. This is based on the gate theory, stimulation of the large diameter afferents in the dorsal horn inhibits the transmission of pain through the small diameter fibres .This has been shown to lead to a reduction of pain and improve quality of life. It is considered a last line treatment option. It’s use has been advocated for use in patients with advanced stages of CRPS.[6]

### Sympathectomy

The use of surgical sympathectomy to relieve CRPS pain has been met with conflicting results. The national Dutch guidelines suggest that the greatest benefits occur when it is done within 3 months of injury[13].
In a review article by Salibi et al, it was noted that surgical sympathectomy has a high failure rate. In addition there is a high rate of post sympathectomy neuralgia[6].

**Approach to a CRPS patient** [13, 17, 18]

Patients that suffer from CRPS may present for surgery that either related to the affected limb or unrelated procedure. An article by Reuben et al listed points to take into consideration, which are:

**1. Timing**

Ideally surgery should be performed when there is complete resolution of CRPS symptoms or at least are adequately managed. The use of sympatholytic agents or blocks is advocated to improve blood flow to the affected limb.

**2. Type of aneasthesia**

General aneasthesia has been postulated to result in relapse or worsen CRPS symptoms.

Where possible the preferred anaesthetic should be regional or neuraxial aneasthesia for the sympatholytic effects and the attenuation of the neuroendocrine response.
Patients presenting for surgery with lower limb CRPS, suggested protocol involves an epidural infusion of local anaesthetic started 12 hours prior to surgery. This infusion should be maintained for 3-6 days.
Stellate ganglion block should be considered in patients presenting for upper limb surgery with concomitant CRPS.

The use of a tourniquet should be minimised or avoided, in order to minimize the reperfusion injury that would lead to the production of free radicals.

In patients with a spinal cord stimulator, neuraxial aneasthesia is not contraindicated but must be done with caution. If neuraxial technique is recommended it should be done under imaging to avoid damaging the leads of the device.
The use of unipolar diathermy is to be avoided. Should it be deemed necessary the grounding plate should be placed outside of the electrical field of the stimulator.

**3. Multimodal analgesia**

Use of multimodal analgesia in targeting multiple receptors to prevent the development of both peripheral and central sensitisation has been advocated. Furthermore the concept of preventative analgesia whereby adequate management of pain throughout the peri-operative period have been shown to reduce the incidence of chronic pain syndromes post operatively.

A case study where ketamine was used as an adjunct anaesthetic agent in patients with refractory CRPS. It found that post operatively all patients returned to their base line preoperative pain levels.
Ketamine was infused at a rate of 50mg/hr, clonidine (augment NMDA receptor blockade) and midazolam (prevent agitation and vivid dreams) were also given at induction

## CONCLUSION

In conclusion complex regional pain syndrome is poorly understood with involvement of multiple factors thus making its management difficult. It is hoped with continued research and better quality studies this will lead improved treatment modalities.

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