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Cochrane Corner – Complex regional pain syndrome: many treatment options, little evidence

Complex regional pain syndrome (CRPS) is a disabling pain disorder whose pathophysiology is not fully understood. Numerous, heterogeneous treatment approaches are available. A current Cochrane Review examines the quality and effectiveness of the evidence.

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The case and the PICO question

The Suva insurance physician, a neurologist, examines Ms. S., a 44-year-old visiting nurse, as part of an insurance medical assessment regarding the protracted course of an uncomplicated radius fracture following a fall from a bicycle. NSAIDs were initially prescribed to alleviate the pain. As there was no improvement, the patient was switched to opiates after three weeks. She also underwent physiotherapy for hand swelling, but this was discontinued due to pain. The employer asked for a medical insurance evaluation after it seemed unlikely that the employee would not be able to return to work after 10 weeks of therapy. The consultation occurred 12 weeks after the accident and the Suva doctor made a diagnosis of suspected "complex regional pain syndrome" (CRPS). The most important differential diagnoses, including neuropathy, osseous/ mechanical causes, infection/inflammation, and psychiatric causes, were ruled out. All four Budapest Criteria and a CRPS severity score (CSS) showing severe clinical manifestations (14 of 16 achievable points) indicate a high probability of CRPS.

The doctor recently read a new Cochrane review on the treatment of CRPS during a recent training and refamiliarized herself with the most recent guidelines in order to make the most appropriate therapeutic recommendation and develops the following PICO question: in people in the early phase of CRPS due to a fracture of the distal upper limb, what evidence-based measures will reduce pain and protect her from permanent functional limitations and disability over the medium and long term?

The clinical picture

CRPS is a chronic and disabling pain disorder typically occurring in distal extremities after trauma or surgery. The main symptom is disproportionately severe and persistent pain as compared to the typical course of pain after similar injuries, accompanied by significant autonomic and inflammatory changes. Other typical manifestations include sensory disturbances, temperature changes, abnormal sweating, trophic changes to the skin and nails, swelling and oedema, and increasing mobility restriction to the distal joints. The pathophysiological mechanisms are complex and not fully understood. The current diagnostic standard is based on both the Budapest Criteria and the exclusion of other diseases with similar symptoms. There is no diagnostic tool that confirms CRPS and despite the large number of measures that are recommended and used for treatment, there is still no consensus on the optimal therapy.

The evidence

The insurance doctor searches the Cochrane Library and finds what she is looking for. The Cochrane Library is the database of the Cochrane Collaboration containing almost 10,000 published Cochrane reviews, including the overview: **Interventions for treating pain and disability in adults with complex regional pain syndrome - an overview of systematic reviews**, Ferraro et al, Cochrane Database of Systematic Reviews 2023.

Such an overview is produced when a number of systematic reviews have been conducted and the results are summarized

in a report. The aim of this “review of reviews” is to systematically and critically evaluate all Cochrane and non-Cochrane reviews for evidence on the treatment of CRPS. This overview assessed the effectiveness, benefits, and safety of the interventions to reduce pain, disability, or both, in adults with CRPS.

Seven databases (up to 10/2022) were searched for Cochrane and non-Cochrane reviews of randomized controlled trials testing interventions for CRPS and measuring pain control and prevention of disability. The authors independently assessed the eligibility of the studies, extracted the data, and assessed the quality of the reviews and the robustness of the evidence using the AMSTAR-2 and GRADE tools, respectively.

The results

The current overview contains five Cochrane and twelve non-Cochrane reviews of the evidence for a wide range of treatments including drugs, surgical procedures, rehabilitation, and complementary/alternative therapies. For the vast majority of interventions only a few published studies were found, usually of low or very low quality. The main findings are as follows:

- Bisphosphonates (drugs to slow down bone resorption) can reduce the intensity of pain shortly after the start of treatment compared to placebo (⊗⊗◯◯). They are likely associated with various side effects (⊗⊗⊗◯).
- Compared with placebo treatment, blockade of the sympathetic nervous system with an anesthetic likely does not lead to a reduction in pain intensity (⊗⊗⊗◯).
- There may be no difference in pain reduction between dimethyl sulfoxide (DMSO) cream and oral N-acetylcysteine. It is unclear whether these treatments work at all (⊗⊗◯◯).
- The brachial plexus block (a form of nerve block) can reduce the intensity of pain more than the so-called bupivacaine stellate block (⊗⊗◯◯).

Many of the more commonly used pharmaceutical, surgical, rehabilitative, and psychological interventions for CRPS found in the reviews were supported by very low quality evidence or no evidence at all. Therefore, the authors cannot say with certainty what effects these treatments have on pain and disability in CRPS.

Robustness of the evidence (Certainty of evidence)
Symbols from ⊗⊗⊗⊗ to ⊗◯◯◯ describe how certain the authors are that the effect reported in the studies corresponds to the true value, i.e., is "true". This means that the observed effect of the review is close to the true effect. For more information on the symbols and their meaning, see below.

Implementation of the results

The implementation of evidence-based treatment for CRPS is a major challenge for clinicians as only a few interventions have been investigated in randomized trials. Most of them have shown no benefit (see table). Many studies were too small, or the methodology was not good enough to reliably rule out an effect. In the absence of moderate- or high-certainty evidence in favor or against the efficacy of an intervention, clinical management is best guided by the risk of treatment-related effects, the potential for drug-drug interactions, possible comorbidities, patient preferences, and financial costs. In line with the methodological guidelines for rare diseases, extrapolation of data from other chronic pain conditions - such as neuropathic pain - is sometimes considered appropriate as these symptoms may be similar. The Royal College of Physicians (RCP) in the UK has produced a guideline for the treatment of CRPS which is the only high-quality guideline available to date. The evidence- and consensus-based RCP guidelines recommend an integrated, individualized, multidisciplinary approach based on four pillars of care, each with equal importance: patient education, pain relief (pharmacological and interventional), physical rehabilitation, and psychological interventions.

Next steps

The insurance doctor feels reassured in her previous treatment approach. With this in mind, she advises Ms. S. and informs the Suva case manager who forwards the assessments and recommendations to the attending physician. The case manager also notifies the employer of Ms. S.'s continued incapacity for work for an unforeseeable duration as well as the plan to review the case on a regular basis.

Table: Treatment modalities used for CRPS with mostly, very little, or no evidence *(table also contains the measures listed above).*

Oral, intravenous, and topical pharmacotherapy approaches

- Anti-inflammatory therapies (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cyclooxygenase-2 (Cox-2) inhibitors)
- Free radical scavengers (e.g., mannitol, vitamin C)
- Immunomodulators (e.g., tumour necrosis factor V inhibitors, immunoglobulins)
- Anticonvulsants (e.g., pregabalin, gabapentin)
- Antidepressants and anxiolytics (e.g., amitriptyline, doxepin)
- Opioids (e.g., morphine, tramadol)
- N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine, memantine)
- Antihypertensives and alpha-adrenergic antagonists (e.g., clonidine, phentolamine)
- Bisphosphonates (e.g., pamidronate, alendronate)
- Calcitonin
- Topical analgesics such as lidocaine patches or creams with local anaesthetic, capsaicin or dimethyl sulphoxide (DMSO)

Interventional procedures

- Intravenous sympathetic nerve block with various anaesthetics
- Sympathectomy (e.g., alcohol or phenol, surgically by excision or electrocoagulation)

Neuromodulation

- Various non-invasive and invasive procedures for pain relief through electrical stimulation of the nervous system. Invasive procedures include the implantation of electrodes in the epidural space of the spinal cord or dorsal root ganglion.

Occupational and physiotherapeutic rehabilitation

- Various approaches, often as a multimodal form of treatment, involving e.g., manual therapy, tactile desensitisation, electrotherapy (including TENS), therapeutic exercises, pain management training

Psychological forms of therapy

- Cognitive behavioural therapy, acceptance and commitment therapy, counselling and relaxation techniques, exposure-based treatments

"Robustness of evidence" terminology (Lietz M 2020)

The authors group carried out a "robustness of evidence" assessment. What does "robustness of evidence" mean?

⊗⊗⊗⊗ High degree of robustness
The authors are very sure that the true effect is close to the observed effect.

⊗⊗⊗◯ Medium degree of robustness
The authors have moderate confidence in the observed effect: The true effect is probably close to the observed effect, but there is a possibility that it is substantially different.

⊗⊗◯◯ Low degree of robustness
The authors' confidence in the observed effect is limited: The true effect may differ substantially from the observed effect.

⊗◯◯◯ Very low degree of robustness
The authors have very little confidence in the observed effect: The true effect is likely to be substantially different from the observed effect.

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