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Masterthesis / Review

Primary prevention of Complex Regional Pain Syndrome: A narrative review

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Abstract

Complex regional pain syndrome (CRPS) is a post-traumatic pain syndrome. The pathophysiology is still partially unknown, making treatment difficult for all care providers. The lack of reliable treatment highlights the need for prevention. Several studies and review articles already showed a positive effect of vitamin C on the incidence of CRPS. This narrative review aims to go beyond the effects of vitamin C and review all the literature discussing possible (non-)pharmacological options to prevent the onset of this disease. This narrative review includes 24 articles reviewing 9 drugs and a few other non-pharmacological options such as garroting, length of surgery and surgical approach. The results confirm the known effects of vitamin C on the incidence of CRPS. Pre-clinical research points towards drugs like ketamine, dexmedetomidine, omega-3 fatty acids and elcalcitonin to possibly prevent CRPS in the future. Larger humane studies are needed to prove the preventive power of these drugs. The need for a multidisciplinary approach is shown by the possible effect of minimally invasive surgery, short garroting time and early mobilization by a home-exercise program.

Introduction

Complex regional pain syndrome (CRPS), formerly better known as reflex sympathetic dystrophy or Sudeck algoneurodystrophy is a chronic pain condition. The international association for study of pain (IASP) describes CRPS as "a syndrome characterized by a continuing regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor and/or trophic findings. The syndrome shows variable progression over time"[1]. Its current name was first used in 1994 when the first criteria for the diagnosis of CRPS were adopted. Multiple revisions of these criteria led to the current Budapest Criteria[2] (Figure 1).

CRPS is often divided into 2 different subtypes. CRPS type 1 occurs without obvious nerve damage while in CRPS type 2, clear nerve damage is present. The condition usually occurs after trauma (fall, sprain, ...) or after surgery[2]. The exact pathophysiology is still unknown, but symptoms point to inflammation, dysfunction of the autonomic system, auto-immune system and central cortical organization. These changes lead to an increased responsiveness of nociceptive neurons in the central nervous systems to their normal or subthreshold input[3]. Interestingly, it is found more often in women than men (ratio 4:1). As of today, no study has found an explanation for this sex difference. The fact that the disease mechanism has not yet been fully elucidated makes it extremely difficult to find a reliable treatment for this condition. The public interest in preventing this disease is clear, given the incidence rate of 6,28-26,2 per 100,000 person-years[4]. All this, combined with the negative effect on recovery after trauma/surgery, makes prevention of the onset of this disease of crucial importance. With this narrative review, we try to give an up to date overview of the evidence regarding the primary prevention of CRPS.

IASP Clinical Budapest Criteria in diagnosing CRPS	
1. Continuing pain that is disproportionate to any inciting event	
2. At least one symptom reported in at least three of the following categories:	
Sensory	Hyperesthesia or allodynia
Vasomotor	Temperature asymmetry, skin color changes, skin color asymmetry
Sudomotor	Edema, sweating changes, sweating asymmetry
Motor/trophic	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
3. At least one sign at time of evaluation in at least two of the following categories:	
Sensory	Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
Vasomotor	Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry
Sudomotor	Evidence of edema, sweating changes or sweating asymmetry
Motor/trophic	Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
4. No other diagnosis can better explain the symptoms and signs	

Fig. 1 — Budapest criteria[2].

Methods

We searched PubMed for articles regarding the prevention of CRPS. Articles were included from the date of inception until July 1st of 2023. Original research material of all types was included. Both clinical and pre-clinical studies were included. The patient population could therefore be either a human or animal group (for pre-clinical studies). There had to be some sort of intervention to specifically prevent the onset of CRPS or its typical symptomatology. The intervention-group had to be compared to a control group that did not receive the earlier specified intervention. Outcomes used had to be either incidence of CRPS or the effect on its specific symptoms (for pre-clinical studies). A full text had to be available, and the article had to be written in English. Given the different names given to CRPS, we also searched for prevention of Sudeck algoneurodystrophy and/or reflex sympathetic dystrophy. We found a total of 247 articles. After removing duplicates, we had 167 studies to screen. After screening by title and abstract we had 136 articles for full text review. For various reasons (Figure 2), we excluded 112 articles.

In total, 24 studies were included in this narrative review. 18 studies discuss pharmacological techniques. 8 of them discuss the use of vitamin C, currently the best researched measure to prevent CRPS. Other options discussed below are gabapentin, calcitonin, clonidine, omega-3-fatty acids, lidocaine, dexmedetomidine, ketamine and aspirin. The other 6 studies discuss non-pharmacological interventions such as certain surgical techniques or other kinds of therapy (for example, light therapy). A concise overview of the included articles can be found in Table I.

Vitamin C

Vitamin C is the best known and best researched preventive measure against CRPS. A 1993 study investigated the effect of vitamin C therapy on post burn wound healing. Vitamin C acts as a natural antioxidant that scavenges hydroxyl radicals and superoxide radicals. This scavenging results in the protection of the capillary endothelium and reduces vascular permeability[5]. Given the impact of vitamin C on inflammation parameters in burn wounds, a Dutch research group led by Paul Zollinger first tested the hypothesis that vitamin C could prevent the onset of CRPS[6]. Between 1996 and 1997, they included 115 patients with wrist fractures that were treated conservatively. Half of these patients received vitamin C (500mg for 50 days), the other half received no vitamin C. After 1 year follow-up, they found a significantly lower incidence of CRPS in the vitamin C group, compared to the

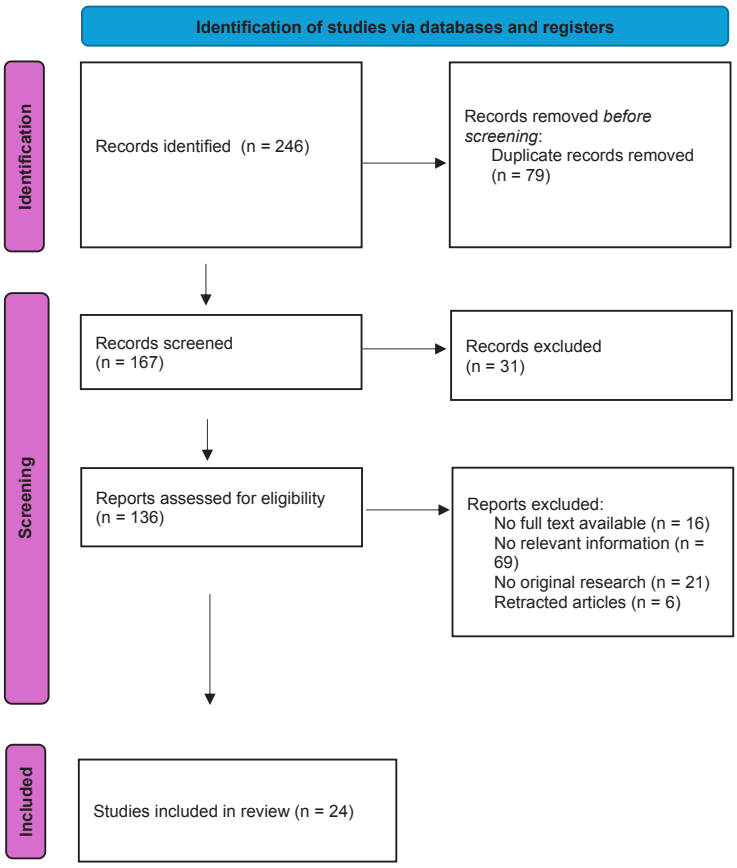

Fig. 2 — Prisma flow diagram of study identification, screening and inclusion[53].

control group (p = 0.04). The same research group conducted a larger trial in 2007 involving 416 patients with wrist fractures (both surgical and conservative treatment)[7]. They divided the patients in 4 groups. 3 groups received vitamin C for 50 days, but in different doses (200mg, 500mg or 1500mg). The fourth group received no vitamin C. Results showed a significantly lower incidence of CRPS in the vitamin C group (p = 0.002, OR = 0.24). Dose analysis showed a significantly lower incidence of CRPS for both the 500mg group (p = 0.007, OR 0.17) and 1500mg group (p = 0.005, OR = 0.17). There was no significant difference for the 200mg group. Given the same odds ratio for both 500mg and 1500mg, they suggested the use of 500mg of vitamin C in the prevention of CRPS after wrist fractures. This research group also published a series of case reports in 2009 of patients who underwent basal thumb prostheses[8]. All patients received 500mg of vitamin C for 50 days after surgery. None of these patients presented with CRPS-like symptoms after surgery. In the same period, a French research group did a before-after study with 392 patients undergoing scheduled foot and ankle surgery[9]. Two chronologically successive groups were created. The first group of 215 patients were not treated with vitamin C while the second group of 177 patients were treated with 1000mg of vitamin C for 45 days after surgery. Follow-up after three months showed a significantly reduced incidence of CRPS in the group treated with vitamin C when compared with the control group (p < 0.001, OR 0.19). These original studies led to the first systematic reviews concluding that vitamin C is effective in the prevention of CRPS after trauma/surgery[10-12]. In 2015, a British research group conducted a randomized controlled trial testing the effectiveness of vitamin C in reducing the incidence of CRPS in a group of 336 patients with distal radius fractures[13]. 50% of the patients received 500mg of vitamin C, the other half received no vitamin C supplementation. They used the DASH-score (Disability of Arms, Shoulder and Head – score) as their primary outcome. They found that vitamin C had no significant effect on the DASH-score. There was also no significant effect on the incidence of CRPS. Of importance, however, is that they used the Atkins criteria to diagnose CRPS and not the widely used Budapest criteria. Another limitation is that the DASH-score is not specific for CRPS (DASH-score is, for example, also high in patients with rotator cuff pathology). Further studies were performed by a Belgian group who did 2 prospective studies on the effect of 1000mg of vitamin C for 40 days after either total knee arthroplasty or foot/ankle surgery[14-15]. Both studies showed a significantly lower incidence of CRPS in the groups treated

Table I. — Overview of included studies.

Clinical studies					
Vitamin C					
Author	Country	Type of study	Patient population	Intervention	Outcome
Hernigou et al. (2021)	Belgium	Prospective RCT	329 patients undergoing foot and/or ankle surgery	121 patients received Vitamin C (40 days 1gr), 208 patients received no Vitamin C after surgery	Significantly lower incidence of CRPS in the Vitamin C group (p= 0.039, OR = 0.19)
Laumonerie et al. (2020)	France	Retrospective cohort study	533 patients undergoing subacromial shoulder surgery	267 patients received Vitamin C (50 days 500mg), 266 patients received no Vitamin C after surgery	Significantly lower incidence of CRPS in the Vitamin C group (p = 0.009, OR = 0.49)
Zollinger et al. (2010)	The Netherlands	Clinical series of case reports	34 patients undergoing basal thumb prostheses	All 34 patients received Vitamin C (50 days 500mg)	No cases of CRPS reported
Hernigou et al. (2021)	Belgium	Prospective RCT	292 patients undergoing total knee arthroplasty	173 patients received Vitamin C (40 days 1gr), 139 patients received no vitamin C	Significantly lower incidence of CRPS in the Vitamin C group (p = 0.008, OR = 0.27)
Zollinger et al. (2007)	The Netherlands	Prospective RCT	416 patients with wrist fractures that were treated in the emergency department (both conservative and surgical treatment)	317 patients received Vitamin C (50 days, 96 received 200mg a day, 114 received 500mg a day and 118 received 1500mg a day), 99 patients received no Vitamin C	Significantly lower incidence of CRPS in the Vitamin C group (p = 0.002, OR = 0.24). Dose analysis shows a significantly lower incidence of CRPS for both the 500mg group (p = 0.007, OR 0.17) and 1500mg group (p = 0.005, OR = 0.17). There was no significant difference for the 200mg group.
Ekrol et al. (2014)	The United Kingdom	Prospective RCT	336 patients with distal radius fractures (both conservative and surgical treatment)	169 patients received Vitamin C (50 days 500mg), 167 patients received no Vitamin C	No significant difference in primary outcome (Disability of Arms, Shoulder and Head, DASH-score). No significant difference in incidence of CRPS.
Besse et al (2009)	France	Before-after study	392 patients undergoing scheduled foot and ankle surgery by a single surgeon	177 patients received Vitamin C (45 days 1000mg), 215 patients received no Vitamin C	Significantly lower incidence of CRPS in the Vitamin C group (p < 0.001, OR 0.19)
Zollinger et al. (1999)	The Netherlands	Prospective RCT	115 patients with conservatively treated wrist fractures	52 patients received Vitamin C (50 days 500mg), 63 patients received no Vitamin C	Significantly lower incidence of CRPS in Vitamin C group (p = 0.04)
Gabapentin					
Sadatsune et al. (2016)	Brazil	Prospective RCT	40 patients undergoing carpal tunnel release surgery under intravenous locoregional anesthesia	20 patients received a single dose of Gabapentin (600mg) before surgery, 20 patients received placebo	No difference in need for sedation, post-operative pain and/or chronic pain syndromes
Akkus et al. (2005)	Turkey	Case report	1 patient with refractory CRPS-like symptoms	Gabapentin (600mg) once a day for a year	Quick resolution of symptoms and no relapse during the follow-up period of 1 year
Elcalcitonin					
Matayoshi et al. (2009)	Japan	Before-after study	59 patients with hemiplegia after stroke	24 patients received rehabilitation and weekly elcalcitonin injections (20 units), 34 patients received rehabilitation	Significantly lower incidence of CRPS in the elcalcitonin group (p = 0.001)
Clonidine and Lidocaine					
Da Costa (2011)	Brazil	Prospective RCT	301 patients undergoing carpal tunnel release	72 patients received general anesthesia, 90 patients received intravenous regional anesthesia (lidocaine 0.5%, 40mL), 66 patients received intravenous regional anesthesia (lidocaine 0.5mL, 40mL) and intravenous clonidine (1mcg/kg), 72 patients received brachial plexus block	No significant difference in the incidence of CRPS between the 4 anesthetic techniques.

Table I. — Overview of included studies/2.

Author	Country	Type of study	Patient population	Intervention	Outcome
Aspirin					
Eraghi et al. (2020)	Iran	Prospective RCT	91 patients with radius fractures undergoing surgical repair	All patients received intravenous regional anesthesia and Acetaminophen every 6 hours. 44 patients received 500mg Aspirin daily for 7 days. 47 received placebo for 7 days.	No significant difference in the incidence of CRPS between the Aspirin group and the control group ($p = 0.479$).
Light therapy					
Zlatkoviv-Svenda et al. (2019)	Serbia	Prospective RCT	52 women with distal radius fracture	The intervention group (n=26) received ice-application, physiotherapy and light therapy for 15 days after plaster removal. The control group received ice-application and physiotherapy for 15 days after plaster removal.	Significantly more pain relief and better range of motion in the intervention group ($p < 0.05$ for both parameters) after two weeks of treatment. Significantly lower incidence of CRPS ($p < 0.05$) in the intervention group after 6 months of follow-up.
Surgical technique					
Mertz et al. (2019)	USA	Retrospective database study	85761 patients undergoing carpal tunnel repair	Compare the incidence of CRPS between patients who underwent endoscopic carpal tunnel repair and open carpal tunnel repair.	Binomial proportion analysis found no significant difference ($p = 0.15$) in the incidence of CRPS between the two surgical techniques.
Sumitani et al. (2013)	Japan	Retrospective database study	185378 patients with a limb fracture undergoing surgical repair	Specify factors that influence the incidence of CRPS.	A correlation was found between the length of anesthesia and the incidence of CRPS ($p < 0.001$).
Boersma et al. (2022)	The Netherlands	Proof-of-concept study	129 patients with distal radius fracture and conservative treatment	All patients received a home-exercise program to study the effect of early mobilization on the incidence of CRPS.	No cases of CRPS were reported.
Pre-clinical studies					
Omega-3 Fatty Acids					
De Oliveria et al. (2021)	Brazil	Experimental RCT in mice	Swiss female mice with induced CRPS type 1 (by garroting one paw)	The intervention group received the normal diet with additional fish oil from 30 days before the ischemic event up until the 15th day after the event, the control group received saline.	A significant reduction in paw edema and less inflammatory cytokines in the intervention group.
Fernandes et al. (2021)	Brazil	Experimental RCT in mice	Swiss female mice with induced CRPS type 1 (by garroting one paw)	The intervention group received the normal diet with additional fish oil from 30 days before the ischemic event up until the 15th day after the event, the control group received saline.	A significant reduction in paw withdrawal frequency was found in the intervention group. A significantly lower level of inflammatory cytokines and lower concentration of TNF was found.
Dexmedetomidine					
Dong et al. (2014)	China	Experimental RCT in rats	60 male rats with induced CRPS type 1 (by garroting one paw)	The intervention group (30 rats) received dexmedetomidine intravenously 10mcg/kg for 7 days after the ischemic event. The control group received saline for 7 days after the ischemic event.	A significant decrease in pain response in the intervention group to both mechanical and cold allodynia compared to the control group. A significant increase in GRK-2 expression in the intervention group compared to the control group.

Table I. — Overview of included studies/3.

Author	Country	Type of study	Patient population	Intervention	Outcome
Ketamine					
Liman et al. (2014)	Hong Kong	Experimental RCT in rats	30 male rats with induced CRPS type 1 (by garroting one paw)	The intervention group (10 rats) received a single dose of intravenous ketamine (100mg/kg) after the ischemic event. A positive control group (10 rats) received a single dose of intravenous methylprednisolone (30mg/kg) after the ischemic event. The control group (10 rats) received a single dose of intravenous saline after the ischemic event	No significant change ($p > 0.05$) in incidence of chronic post-ischemic pain or paw thickness. Significantly higher threshold for mechanical and cold allodynia in the intervention group ($p < 0.05$) compared to the methylprednisolone group and saline group. Significantly lower paw temperature in the intervention group ($p < 0.05$) compared to the methylprednisolone group and saline group.

with vitamin C. Finally, French researchers tested the vitamin C hypothesis in subacromial shoulder surgery[16]. It was performed in a before-after protocol. They found that the group receiving vitamin C had a significantly lower incidence of CRPS. Multivariable regression analysis showed that vitamin C reduced the risk of CRPS by >50%. This led to a new systematic review confirming the positive effect of vitamin C in the prevention of CRPS after trauma and/or surgery[17].

Gabapentin

Gabapentin is a gabapentinoid and is a derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and acts primarily by blocking voltage-dependent calcium channels. Gabapentin reduces dorsal horn neuron excitability and central sensitization in various ways[18-20]. A systematic review showed a reduced incidence of post-operative chronic pain (POCP) by using gabapentin perioperatively[21]. A RCT tested if a single-dose of gabapentin (600mg) before surgery had any effect on the incidence rate of POCP and CRPS in patients undergoing open carpal tunnel release surgery performed under regional intravenous anesthesia (Bier's block using Lidocaine 1%)[22]. Although they did find a numerical reduction in POCP and CRPS, there was no statistical difference. A 2006 case report discusses a case in which a patient spontaneously develops a severe case of CRPS type 1 that was treated with intravenous regional sympathetic blocks[23]. However, the patient suffered from recurring episodes of CRPS-like symptoms that no longer responded to interventional therapy. After introducing gabapentin to his regimen, his symptoms quickly disappeared. The patient took gabapentin in a single dose of 600mg per day for a year after the last episode. He had no recurrence of CRPS-like symptoms since. Given the very low dose of gabapentin used in this patient, it is doubtful gabapentin actively prevents the recurrence of CRPS. The researchers did not disclose what criteria were used for the diagnosis of CRPS type 1 in this patient. These 2 papers are the only published articles looking into the prevention of CRPS by the use of Gabapentin. There is no clear evidence that Gabapentin reduces the incidence of CRPS and should therefore not be advised as a preventative measure.

Calcitonin

Calcitonin was widely used in the treatment of osteoporosis. Furthermore, it was used for a range of pain conditions in the past[24-27]. A few older studies reported no effect on the incidence of CRPS when using calcitonin[28]. However, there is one RCT dedicated to the prevention of CRPS after stroke[29]. This 2009 study tested if weekly injections of elcalcitonin (calcitonin derivative from eel's calcitonin with the same physiological properties) in addition to physiotherapy would prevent CRPS type 1 in hemiplegic patients after a stroke. They showed a statistical reduction in the incidence of CRPS in the group that received the elcalcitonin injections. The prophylactic effect is the strongest when started <4 weeks after stroke. The prophylactic effects were weak when the injections started >6 weeks after stroke. Given the last studies reviewing prophylactic effects of calcitonin in the perioperative period are over 30 years old more studies should be carried out. The importance for these studies is amplified by the promising effects of the 2009 study discussing the prevention of CRPS post-stroke by elcalcitonin injections. Further research should include the prevention of CRPS after surgery and/or trauma. It should be noted however that, as of today, calcitonin is no longer recommended for the treatment of osteoporosis given an increased risk of cancer, albeit low, with long-term use of calcitonin.

(https://www.ema.europa.eu/en/medicines/human/referrals/calcitonin)

Clonidine

We found one article that discussed the possible effect of clonidine perioperatively to prevent the onset of CRPS. A 2011 RCT tried to define the incidence of CRPS after carpal tunnel release with garroting and its relationship with the anesthetic technique[30]. They compared IV regional anesthesia with lidocaine, IV regional anesthesia with lidocaine and clonidine, axillary plexus block and general anesthesia. The results showed no statistical difference between these four anesthetic techniques. They did however see a statistical difference in the incidence of CRPS and the length of garroting (see surgical technique). Given that the only published RCT shows no effect of clonidine on the incidence of CRPS, it should not be used in the prevention of CRPS.

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (present in fish oil) are known for their anti-inflammatory effects. Previous studies have already shown a reduction in the synthesis of pro-inflammatory cytokines in inflammatory diseases[31-32]. We found two pre-clinical studies by a Brazilian research group discussing the effect of omega-3 fatty acids on pain and inflammatory cytokines in a mice model of CRPS type 1. They induced chronic post-ischemia pain by garroting the right hind paw for 3 hours after anesthetizing them with intraperitoneal Pentothal (80mg/kg). The first study started supplementation with either fish oil rich in omega-3, corn oil or saline 30 days before the ischemic event up until 15 days after the ischemic event[33]. Statistical analysis shows that omega-3 supplementation reduces paw edema and alters pro-inflammatory cytokines in the paw muscle 48 hours after the ischemic event. The second study found a significant difference between the saline group and Omega-3 group in paw withdrawal frequency[34]. This effect persisted for over two weeks. They also found a lower concentration of pro-inflammatory cytokines in the paw muscle one day after the ischemic event and a lower concentration of tumor necrosis factor (TNF) in the spinal cord of these mice. These pre-clinical studies show that omega-3 supplementation reduces edema and concentrations of pro-inflammatory cytokines in a post-ischemic CRPS type 1 model in mice. It also shows an antihyperalgesic effect of omega-3 supplementation. However, as of today, there are no clinical human randomized controlled trials evaluating the effect of omega-3 fatty acids on the incidence of CRPS. Therefore, it is not yet advised to use omega-3 fatty acids as a preventative measure perioperatively.

Lidocaine

We found one article discussing the effect of lidocaine on the incidence of CRPS, a 2011 RCT we previously described in the chapter about clonidine[30]. As previously mentioned, there was no relation between the anesthetic technique (intravenous lidocaine, intravenous lidocaine + clonidine, axillary plexus block or general anesthesia) and the incidence of CRPS. They did however find a relation between the garroting time and the incidence of CRPS when using an axillary plexus block or general anesthesia. The incidence of CRPS increased with longer garroting time, implying an effect of ischemia. However, when using an intravenous (IV) anesthetic technique, there was no relation between garroting time and incidence of CRPS. Possibly, there is a positive effect of drugs acting on the site of ischemia. There was no significant difference between the lidocaine and lidocaine + clonidine group.

Dexmedetomidine

Dexmedetomidine is a sympatholytic drug that acts as an agonist of the alpha-2 adrenergic receptor in the brain. It is commonly used for sedation in human and veterinarian medicine. A few studies have shown that a transient decrease in G protein-coupled receptor kinase 2 (GRK2) can produce long-lasting neuroplastic changes in nociceptor function, enhancing inflammatory hyperalgesia[35,36]. A 2014 pre-clinical study investigated the effect of dexmedetomidine on GRK2-expression in the superior cervical ganglion in a rat model of CRPS type 1[37]. The ischemic injury was established by garroting the left forelimb for 3 hours after anesthetizing the rats with intraperitoneal chloral hydrate. They found a decrease of GRK2 expression after ischemic injury in all rats. An increased response to mechanical allodynia was observed in all rats. After daily injection of dexmedetomidine 10 micrograms/kg they found a rapid decrease in the response to mechanical allodynia. The same results were obtained for cold allodynia, with a rapid decrease in pain scores after injection of dexmedetomidine. Histologically a significant decrease in GRK2 expression was seen in the superior cervical ganglion 48 hours after the ischemic event. In the control group, this expression gradually recovered but did not return to normal, even after multiple weeks. In the group receiving dexmedetomidine injections, there is an immediate increase in GRK2-expression with a

return to baseline level 14 days after the ischemic event. This study showed the possible effect of dexmedetomidine on ischemic-induced mechanical and cold allodynia by increasing the GRK2-expression in the superior cervical ganglion in rats. However, given the exact mechanism remains unclear, further studies are required to elucidate the role of GRK2-expression in the sympathetic nervous system. Given there are no human clinical studies and the exact mechanism remains unknown, there is no evidence for a preventative effect of dexmedetomidine on the development of CRPS.

Ketamine

Ketamine is a well-known N-methyl-D-aspartate (NMDA) receptor antagonist and has been shown to produce analgesia by inhibiting pain pathways. It is believed to play an important role in central sensitization, which may induce chronic pain (including CRPS). Ketamine also has an important anti-inflammatory effect[38,39]. A 2015 pre-clinical trial used a rat model of CRPS type 1 to evaluate the effect of ketamine on pain and inflammation[40]. They established ischemic injury by garroting the left hind limb for 3 hours after anesthetizing the rats with pentobarbital. They injected either ketamine (100mg/kg), dexamethasone (30mg/kg) or saline immediately after the removal of the tourniquet. They studied paw thickness, paw temperature, mechanical allodynia, cold allodynia and heat threshold. They detected a significantly lower paw temperature in the ketamine group, compared to the dexamethasone and saline group. They also found that ketamine alleviated the mechanical allodynia and cold allodynia. There was no difference in the heat threshold or paw thickness between the study groups. This study shows the possible positive effect of early treatment with ketamine in a rat model of CRPS type 1. Further clinical studies are warranted to explore the anti-inflammatory and analgesic effect after ischemic injury. Given the lack of clinical studies there is no evidence supporting the use of ketamine in the prevention of CRPS.

Aspirin

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to relief inflammatory symptoms and to relief pain. There is an interest in studying NSAIDs since studies have demonstrated its effect on hyperalgesia and allodynia[41-42]. We found a 2020 RCT comparing the effect of aspirin versus placebo on the prevalence of CRPS in a group of patients with a distal radius fracture[43]. All the patients underwent surgical repair of the fracture and the study protocol was initiated at the emergency department. Patients received either 500mg of aspirin daily or placebo. All the patients received acetaminophen 1g four times a day. Although they found a lower prevalence of CRPS in the aspirin group, this difference was not statistically significant ($p = 0.479$). Further studies, with a larger sample size, are necessary to further investigate the effect of aspirin on the prevalence of CRPS perioperatively. As of today, there is no convincing evidence that aspirin can prevent the onset of CRPS.

Surgical technique

Besides drug interventions, we also tried to identify studies who could define surgical factors influencing the incidence of CRPS. A 2019 retrospective study used US patient care databases from both Medicare and private insurance to define whether the occurrence of CRPS after carpal tunnel repair depends on the surgical technique (open or endoscopic)[44]. They included 85,761 patient records from 2007 until 2016. Binomial proportion analysis found no significant difference ($p = 0.15$) between the two surgical techniques. This study established that the choice between an open or endoscopic technique for carpal tunnel release should not be made over concern of CRPS. A 2014 retrospective study used a nationwide Japanese inpatient database, DPC, to specify factors that influence the risk of developing CRPS[45]. They also searched for possible interventions to reduce the occurrence of CRPS. Included data were from patients with a common pathology (limb fracture), common treatment (surgical repair) and were limited to inpatient data. A total of 185 378 patient records were included. Of this large sample, only 39 patients matched the ICD-10 code criteria for CRPS. These numbers are much lower than the incidence widely found in the literature[46,47], indicating possibly incorrect reporting by the physicians and/or using different criteria for the diagnosis of CRPS. They found a significant increase in CRPS occurrence with a longer duration of anesthesia ($p < 0.001$). The researchers propose the ischemia-reperfusion injury theory as an explanation for this relationship. It is widely accepted that reperfusion of a limb after prolonged occlusion of blood flow can give rise to symptoms like allodynia and hyperalgesia. These symptoms mimic the features of CRPS. If surgeons opt for conservative treatment of fractures, recent literature highlights the importance of a short duration of cast immobilization and active prevention of disuse to prevent the onset of CRPS after a distal radius fracture[48]. A very recent Dutch proof-of-concept study looked into the possible effect of early activity

post-injury on the occurrence of CRPS[49]. They included 129 patients with a distal radius fracture. None of them underwent surgical repair and all of them had a temporary cast immobilization. A home exercise-program was implemented immediately after cast removal. Follow-up phone interviews were organized at >2 months post-injury. According to patients, compliance to the exercise program was 100%. 117 patients (89%) of the patients did not report disproportionate pain. The 12 patients who did report disproportionate pain were assessed during an outpatient visit. None of these patients were diagnosed with CRPS, resulting in an incidence of 0%. It seems that a more active treatment approach lowers the incidence of CRPS. Further prospective studies are needed to study the exact effect of this approach A 2015 retrospective cohort study compared the incidence of CRPS between open shoulder surgery and arthroscopic subacromial shoulder surgery[16]. They found an open approach had a much higher incidence of CRPS (OR 2.19, 95% CI 1.2 – 4.0). Therefore, an arthroscopic approach should be used, if possible, for subacromial shoulder surgery.

Light therapy

It has been proven that light therapy application can provide analgesic effects due to its bio stimulatory effects[50,51]. A 2019 RCT evaluates light therapy application combined with ice-application and optimal exercises in elderly women after distal radius fracture compared to standard therapy (ice-application and physiotherapy)[52]. 52 patients were included and randomly allocated to one of the two study protocols. The intervention group was treated with a combination of ice application, physiotherapy and light therapy. The control group received ice-application and physiotherapy. The results show an improvement in all assessed factors (VAS-score, range of motion) in both groups. However, there was an accelerated pain relief in the intervention group ($p<0.05$) and supination improvement ($p<0.05$) after two weeks of treatment. Six months later, the incidence of CRPS was lower in the intervention group, compared to the control group ($p<0.05$). There was no patient with CRPS in the intervention group, compared to 4 patients with CRPS in the control group. This trial seems to show a positive effect of light therapy on occurrence of CRPS after a distal radius fracture. The limitations of these study are that they had very strict inclusion criteria (only elderly women were included), therefore their data cannot be extrapolated to the entire population. They had a small sample size (52 patients), therefore making it impossible to determine if light therapy only reduces the occurrence of CRPS or completely prevents it. Larger studies are warranted to further study the effect of light therapy. It is a noninvasive procedure and does not interact with other treatment choices. The cost of these therapy sessions is unclear and should be looked into before advising the use of light therapy as a measure to prevent the occurrence of CRPS.

Discussion

This narrative review appraises the efficacy of different preventive strategies of CRPS. As previously mentioned, CRPS is a poorly understood disease. Although much research has already been done, and is still ongoing, the lack of knowledge of the exact pathophysiology makes it difficult to develop proper treatment. Therefore, primary prevention of the disease is a very important topic of research. This importance is amplified by its high incidence. Based on our research strategy we identified and discussed 25 studies on the prevention of CRPS. As expected, most research investigated the possible effect of vitamin C on the incidence of CRPS. Of the 8 studies, 7 showed a significant decrease in the incidence of CRPS with vitamin C intake. The most recent systematic reviews all found a positive effect of vitamin C after trauma/surgery. Therefore, most current guidelines recommend taking vitamin C (500-1000mg/day) to prevent the development of CRPS. With current data, this seems to us a correct recommendation. There are other promising drug options. One of these is elcalcitonin. This product can potentially prevent post-stroke CRPS. Further research on perioperative use is needed before any recommendations can be made. As previously noted, there is an increased risk of cancer, albeit low, when using calcitonin-containing products for an extended period. Therefore, further investigations should focus on the effect of short elcalcitonin treatments. Other promising results come from preclinical studies using mouse or rat models. Both omega-3 fatty acids, dexmedetomidine and ketamine seem to lower inflammation parameters in these models. It is obvious that clinical studies are necessary before making recommendations regarding the use of these drugs to prevent CRPS. The use of the other drug options discussed (gabapentin, clonidine, lidocaine, aspirin) do not seem to have any effect on the prevention of CRPS. During surgery, the negative effect of ischemia-reperfusion injury should be taken into account and the ischemia time with garrot should be kept as short as possible. For a carpal tunnel release, there seems to be no difference between open and endoscopic

surgery. For subacromial shoulder surgery, an arthroscopic approach is preferred. Finally, light therapy appears to be a safe option that does not interfere with other therapies, but further research on effectiveness and cost-benefit has yet to be done before routinely recommending it. We did not look into psychological/psychiatric interventions such as correct treatment of depression and/or anxiety disorders. These could however also have an impact on the incidence of CRPS. A strength of this study is the fact that this is the first narrative review discussing all the possible medicinal/surgical options to prevent the onset of CRPS instead of focusing on vitamin C. Both clinical and pre-clinical studies were included, therefore giving a clear direction for future research. A few articles on clonidine were excluded and not discussed in the paper above given their author was charged with health fraud. A limitation is that we did not look into psychological and/or psychiatric interventions (treatment of depression/anxiety disorders). These could however have a significant impact on the incidence of CRPS. We also did not look into the secondary prevention of CRPS and mostly focused our search on the primary prevention. Another weakness is that we only searched PubMed and possibly did not include all available studies. In short, we recommend the use Vitamin C to prevent the onset of CRPS. Further research should focus on elcalcitonin after surgery/trauma, light therapy and clinical studies using Omega-3-fatty acids, dexmedetomidine or ketamine.

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