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Role of vitamin C in prevention of complex regional pain syndrome (CRPS) after distal radius fractures

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Abstract
Introduction: Complex regional pain syndrome (CRPS) also known as reflex sympathetic dystrophy (RSD) and causalgia is a disorder of a body region, usually of the extremities that is characterized by pain, swelling, limited range of motion. It frequently begins following an injury, surgery, or vascular event such as a stroke. Vitamin C has been proposed to prevent the incidence of complex regional pain syndrome (CRPS).
Aim and Objectives: The aim of this study was to assess the efficacy of vitamin C prophylaxis in the prevention of Complex regional pain syndrome (CRPS) Complex regional pain syndrome (CRPS) in patients after distal end radius fractures.
Materials and Methods: This prospective and randomized study was conducted on 126 patients from August 2018 to July 2020 in the department of orthopaedics, Govt. Medical College Srinagar. In this study the enrolled patients were evaluated from OPD and emergency department. The enrolled patients were distributed in two groups A (66 patients) and B (60 patients). Patients treated with either conservative or surgical management for distal end radius fractures. In group A patients were given vitamin C with standard therapy and group B patients were given standard therapy alone. In both groups the treatment was given for the period of 3 months.
Results: The complex regional pain syndrome (CRPS) was 12.12% in group A and 21.66% in group B.
Conclusion: In this study it has been prevailed that daily administration of 500 mg of vitamin C prophylaxis could reduce the development of complex regional pain syndrome (CRPS) in patients after distal end radius fractures.

Keywords: Vitamin C, complex regional pain syndrome, fracture, distal end radius, aging

Introduction
Complex regional pain syndrome (CRPS) is a disorder of a body region, usually of the extremities that is characterized by pain, swelling, limited range of motion, vasomotor instability, skin changes, and patchy bone demineralization. It frequently begins following an injury, surgery, or vascular event such as a stroke.
Complex regional pain syndrome (CRPS) was reported for the first time in 1865 during the American Civil War in soldiers who were affected by neurologic injuries [1]. It was initially known as causalgia. In the early 20th century, CRPS was known as Sudeck's atrophy, after the German surgeon Sudeck [2], who observed similar clinical features among patients who suffered from orthopaedic injuries without neurologic disorders. Later, CRPS was described as reflex sympathetic dystrophy because it was believed to be caused by an overactive sympathetic nervous system (SNS). The progressive advancement of the knowledge on CRPS pathophysiology led to several additional terminology changes over the years, during which CRPS was referred to as algodystrophy, algoneurodystrophy, neurodystrophy or shoulder-hand syndrome (because of distal symptoms expanding proximally) [3]. The current term, CRPS, was adopted in 1994 by the International Association for the Study of Pain (IASP) [4].
CRPS is a pathological condition characterized by chronic pain for which the duration and intensity are disproportional relative to the trigger event, which is frequently a trauma to the upper or lower limb [5]. This painful disorder includes sensory, autonomic and motor disturbances [6], which cause functional disability and a reduced quality of life [7, 8, 9]. The literature reports two types of CRPS, depending on whether it is associated with nerve damage or not; CRPS-1: no nerve damage, formerly known as reflex sympathetic dystrophy, and

CRPS-2: with nerve damage, formerly known as causalgia [10]. However, it should be noted that there is no evidence supporting that the physiopathology, the therapeutic response, or the clinical presentation differ between both types of CRPS [11]. Accordingly, a bone fracture or a surgery often causes damage to small nerve fibres, but most CRPS diagnosed after a fracture are classified as CRPS-1 [12, 13].

Review of literature

Zollinger PE *et al*. conducted another in 1999 in which 123 adults with 127 conservatively treated wrist fractures were randomly allocated in a double-blind trial to take a capsule of 500 mg vitamin C or placebo daily for 50 days. Each participant's sex, age, side of fracture, dominance, fracture type, dislocation, reduction, and complaints with the plaster cast were recorded, and they were clinically scored for RSD. The follow-up lasted 1 year. Eight patients were withdrawn after randomisation. 52 patients with 54 fractures (male 22%, female 78%; mean age 57 years) received vitamin C and 63 patients with 65 fractures (male 20%, female 80%; mean age 60 years) received placebo. RSD occurred in four (7%) wrists in the vitamin C group and 14 (22%) in the placebo group 15% (95% CI for differences 2-26). Other significant prognostic variables for the occurrence of RSD were complaints while wearing the cast (relative risk 0.17 [0.07-0.41]) and fracture type (0.37 [0.16-0.89]).This prospective, double-blind study shows that vitamin C was associated with a lower risk of RSD after wrist fractures(19) Zollinger PE *et al*. conducted a study on 317 patients with 328 fractures were randomized to receive vitamin C, and 99 patients with 99 fractures were randomized to receive a placebo.. Analysis of the different doses of vitamin C showed that the prevalence of complex regional pain syndrome was 4.2% (four of ninety-six) in the 200-mg group (relative risk, 0.41; 95% confidence interval, 0.13 to 1.27), 1.8% (two of 114) in the 500-mg group (relative risk, 0.17; 95% confidence interval, 0.04 to 0.77), and 1.7% (two of 118) in the 1500-mg group (relative risk, 0.17; 95% confidence interval, 0.04 to 0.75). Early cast-related complaints predicted the development of complex regional pain syndrome (relative risk, 5.35; 95% confidence interval, 2.13 to 13.42). They concluded that Vitamin C reduces the prevalence of complex regional pain syndrome after wrist fractures. A daily dose of 500 mg for fifty days is recommended (20). F. Aïm *et al*. analysed Randomised, placebo-controlled trials of vitamin C to prevent CRPS-I after wrist fractures in the three main databases in 2017. Three randomised placebo-controlled trials in a total of 875 patients were included. Vitamin C supplementation was started on the day of the injury and continued for 50 days. In the group given 500 mg of vitamin C daily, the risk ratio for CRPS-I was 0.54 (95%CI, 0.33–0.91; P = 0.02). Thus, the risk of developing CRPS-I was significantly decreased by prophylactic treatment with 500 mg of vitamin C per day. The heterogeneity rate was 65% (non-significant). They concluded Daily supplementation with 500 mg of vitamin C per day for 50 days decreases the 1-year risk of CRPS-I after wrist fracture.

(1a). Naohiro Shibuya *et al*. evaluated the effectiveness of vitamin C in preventing occurrence of CRPS in extremity trauma and surgery by systematically reviewing relevant studies. The databases used for this review included: Ovid EMBASE, Ovid MEDLINE, CINAHL, and the Cochrane Database. They searched for comparative studies that evaluated the efficacy of more than 500 mg of daily vitamin C. After screening for inclusion and exclusion criteria, they identified 4 studies that were relevant to their study question. Only 1 of these 4 studies was on foot and ankle surgery; the rest concerned the upper extremities. All 4 studies were in favor of this intervention with minimal heterogeneity (Tau2 ¼ 0.00). their quantitative synthesis showed a relative risk of 0.22 (95% confidence interval ¼ 0.12, 0.39) when daily vitamin C of at least 500 mg was initiated immediately after the extremity surgery or injury and continued for 45 to 50 days. A routine, daily administration of vitamin C may be beneficial in foot and ankle surgery or injury to avoid CRPS

[25] Chen, *et al.* performed a systematic review of published literature through April 2014. References from relevant studies were scanned for additional studies.

The search strategy yielded 710 studies, of which 13 were included: 7 on postoperative pain and 6 on CRPS I. In the final analysis, 1 relevant study found a reduction in postoperative morphine utilization after preoperative vitamin C consumption, whereas another showed no difference in postoperative pain outcomes between the vitamin C and control groups. A meta-analysis of 3 applicable CRPS I studies showed a decrease in postoperative CRPS I after perioperative vitamin C supplementation (relative risk=2.25; τ^2=0). It was conclude that There is moderate-level evidence supporting the use of a 2 g preoperative dose of vitamin C as an adjunct for reducing postoperative morphine consumption, and high-level evidence supporting perioperative vitamin C supplementation of 1 g/d for 50 days for CRPS I prevention after extremity surgery. Additional studies are necessary to increase the level of evidence to determine the overall effectiveness and optimum dosage of vitamin C [26] Sunitha *et al*. conducted a literature review to retrieve articles reporting on the use of vitamin C to prevent CRPS. Data collected included sample size, study design type, dose of vitamin C used, and outcome measures of association expressed as relative risk (RR) and odds ratio. A total of 225 articles were obtained from the database search. After the exclusion of duplicates, unrelated articles, editorial letters, and commentaries, 4 articles and 1 systematic review relevant was obtained. Six of the 9 Hill criteria were met, and an earlier meta-analysis showed a quantified reduction in CRPS risk. In conclusion the number of causal/association criteria met was adequate to support the scientific premise of the effect of vitamin C in preventing CRPS after DRF. Furthermore, vitamin C administration is of relatively low cost and has few complications unless administered in large doses [27].

Materials and methods

This prospective and randomized study was conducted on 126 patients from August 2018 to July 2020 in the department of orthopaedics, Govt. Medical College Srinagar. In this study the enrolled patients were evaluated from OPD and emergency department. The enrolled patients were distributed in two groups A (66 patients) and B (60 patients). Patients treated with either conservative or surgical management for distal end radius fractures. In group A patients were given vitamin C with standard therapy and group B patients were given standard therapy alone. In both groups the treatment was given for the period of 3 months.

Inclusion criteria

1. Age more than 18 years
2. Unilateral wrist fractures.
3. Ability to provide informed consent
4. Ability to attend local follow up.
5. All wrist fractures will be included, independent of treatment choice.

6. Nonoperative treatment consisting of the use of a plaster cast, with the fracture being reduced under local anesthesia if necessary.
7. Operative treatment will be applied at the surgeon's discretion.
8. Vitamin C prophylaxis 500 mg/day for 50 days will be initiated from the day of injury.
9. Patients will be asked to start the medication from that moment, on the day of the fracture.

Exclusion criteria

1. Patients with severe kidney failure,
2. Allergy for Vitamin C
3. Pregnancy
4. Multiple Fractures
5. Inability to give informed consent
6. Bilateral fractures
7. History of Renal calculi.
8. History of G6PD deficiency.

Outcome measures

Primary outcomes

Complex regional pain syndrome type 1(CRPS-I): this is characterised by a complex of symptoms and signs including pain, swelling and vasomotor instability. We have included studies which have used established and validated classification criteria including the International Association for the Study of Pain (IASP) criteria (Merskey 1994) as well as studies which predate these criteria or used a non-standard definition of CRPS-I.

Secondary outcomes

1. Pain (activity or rest pain)
   Patient assessment scales such as (but not exclusively limited to) the Visual Analogue scale (VAS) (Revill 1976) and self- reported pain questionnaires.
2. Function

a) Patient functional assessment scales such as (but not exclusively limited to) the Visual Analogue scale (VAS) (Revill 1976) and self-reported questionnaires including the Health Assessment Questionnaire (HAQ) (Fries 1980), the Disability of the Arm, Shoulder and Hand questionnaire (DASH) (Hudak 1996) and the Patient Related Wrist Evaluation (PRWE) (Mac Dermid 2000).
b) Range of motion of wrist in flexion and extension
c) Grip strength
d) Vasomotor responses

3. Quality of life
   Patient quality of life assessment scales such as (but not exclusively limited to) self-reported questionnaires including the EQ-5D (Euro Qol 1990) and the Medical Outcomes study short form 36 (SF-36) (Ware 1993).

Statical analysis

Statistical analysis will be performed with SPSS version 16.0 (SPSS) software on a personal computer. Sample and group sizes will be estimated a priori with use of results of our previous study, a planned power of 90%, and a significance level (α) of 0.05 [3]. Cross tabulation results will be used for demographic classification of the variables under study. The chi-square test, analysis of variance, and the Student t test will be used as applicable for univariate analysis. Measures of association, along with their confidence intervals, will be calculated with the Pearson chi-square test or the Fisher exact test. The probability for entry was set at 0.05, and the probability for removal was set at 0.10.

Results

In this prospective and randomized study the complex regional pain syndrome (CRPS) we enrolled 130 participants among which 4 patients were excluded due to lack of follow-up. The final analysis was conducted on 126 patients. Out of the 126 patients 66 patients were given vitamin C plus standard therapy and 60 patients were given standard therapy alone. In both groups the treatment was given for the period of 3 months. The both the groups had fractures of the distal end of the radius. The mean age of the participants in group A was 52.40 years, whereas in group B the mean age was 49.36 years. The overall prevalence of CRPS in the entire study was in 21 patients among 126 patients that is 16.66. The CRPS occurred in group A was 12.12% (8 patients) and in group B 21.66% (13 patients Vitamin C was significantly associated with a reduction in the likelihood of exhibiting complex regional pain syndrome.

Discussion

The findings of this study documented that vitamin C 500 mg per day supplementation for 3 months was associated with a lower occurrence of CRPS which suggests that vitamin C supplementation is a promising option for prophylactic use in the prevention of CRPS which is a devastating, painful condition causing impairment in function and quality of life. There is a high prevalence of CRPS after fracture of the distal end radius fractures [14-17].

The pathogenesis of CRPS is unclear, but appears to involve the formation of a reflex arc after an inciting event. The arc follows the routes of the sympathetic nervous system and is modulated by cortical centers to produce peripheral vascular disturbances. The pain sensation in response to injury may lead to increased sensitivity of injured axons to epinephrine and other substances released by local sympathetic nerves. The enhanced sensitivity can be blocked by the intravenous administration of sympatholytic agents.

CRPS commonly occurs in either the upper or lower extremities [18, 19, 20, 21] involvement of both upper and lower limbs in the same patient is unusual [22], but possible as it can spread from the site of injury to a different location. Recurrent forms of CRPS have been described. Three stages may occur during the course of CRPS [23-28]. Stage 1 follows an event or without apparent cause, the patient develops pain in a limb. The essential features include burning and sometimes throbbing pain, diffuse uncomfortable aching, sensitivity to touch or cold, and localized edema. The distribution of the pain is not compatible with a single peripheral nerve, trunk, or root lesion. Vasomotor disturbances occur with variable intensity, producing altered color and temperature. The radiograph is usually normal but may show patchy demineralization. The second stage is marked by progression of the soft tissue edema, thickening of the skin and articular soft tissues, muscle wasting, and the development of brawny skin. This may last for three to six months. The third stage is most severe. It is characterized by limitation of movement, the shoulder-hand syndrome (capsular retraction producing a frozen shoulder), contractures of the digits, waxy trophic skin changes, and brittle ridged nails .Bone radiography reveals severe demineralization. The longer the CRPS is in stage 3, the more difficult it is to reverse the clinical course of the disease with any type of intervention. However, patients presenting in stage 3 should still be treated aggressively some experience substantial improvement. Autonomic features

including cyanosis, mottling, increased sweating, abnormal growth of hair, diffuse swelling in non-articular tissue, and coldness may occur in the later stages. Urologic manifestations include detrusor hyperreflexia or areflexia, producing urgency, frequency, incontinence, or urinary retention [29]. Myofascial trigger points are common in the area of trauma or about the shoulder girdle and trapezius [30, 31]. Shoulder complaints occurred more frequently in women in one report, and often represented an associated tendinitis of one or both tendons of the biceps muscle [32]. Although only one extremity may appear to be involved, careful inspection occasionally reveals symmetric findings [33]. The elbow is usually spared. Diagnosis early in the development of CRPS can be difficult due to a lack of objective findings, although description of a throbbing burning pain, paresthesia, and altered skin temperature are helpful. Autonomic testing and scintigraphy may provide an early clue to the diagnosis, while radiologic studies can be helpful later in the course of illness. In addition, the response to treatment is often a very useful diagnostic test. Nonetheless, it is important to keep in mind that the diagnosis of CRPS is made clinically. Fracture of the distal radius may lead to CRPS of the upper extremity. The incidence of this complication is uncertain; reported rates range from less than 1 to 22 % [34, 35].

The prophylactic use of vitamin C after wrist fracture may lower the risk of CRPS.

Vitamin C reduces lipid per-oxidation, scavenges hydroxyl radicals, protects the capillary endothelium, and inhibits vascular permeability. The optimal dose of vitamin C remains uncertain. Doses of 500 to 1500 mg/day may be more effective than lower doses. There appears to be no clinically significant difference between 500 mg and 1500 mg daily. A dose of 500 mg/day was more efficacious than placebo in both randomized trials for post wrist fracture prophylaxis and is the dose that is suggested by the authors of the largest clinical trial [36] and, independently.

Conclusion

In this study results suggest that daily administration of 500 mg of vitamin C prophylaxis could reduce the development of complex regional pain syndrome (CRPS) in patients after distal end radius fractures. Vitamin C (500 mg/day) supplementation thus can be a promising prophylactic option for the prevention of CRPS.

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