

Research Paper

Effects of Vitamin C and Oxycodone on Prevention of Complex Regional Pain After Surgically Treated Distal Radius Fractures



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ABSTRACT

Background: Complex regional pain syndrome (CRPS) is a chronic and debilitating condition that often occurs following distal radius fractures. Severe pain, vasomotor and sudomotor changes, swelling, and functional impairments characterize this syndrome. Given the high costs and psychological burden associated with this condition, preventive and therapeutic interventions, such as vitamin C and oxycodone, have drawn considerable attention.

Objectives: This study aimed to evaluate the effects of vitamin C and oxycodone on the incidence and severity of CRPS symptoms in patients with distal radius fractures treated with surgical pinning and casting.

Methods: This randomized, double-blind clinical trial was conducted on 120 patients at three major hospitals in Tehran City, Iran. The patients were divided into three groups: The vitamin C group (500 mg daily for 8 weeks), the oxycodone group (5-10 mg daily based on weight for 2 weeks), and the placebo group. Assessments included pain intensity (visual analog scale [VAS]), joint functionality (Quick DASH), and CRPS symptoms at weeks 2, 4, 6, and 8.

Results: The vitamin C group demonstrated significant reductions in CRPS symptoms (e.g. swelling, sensitivity to cold) and improved joint functionality. The oxycodone group showed the greatest reduction in acute pain during the early phases of treatment, but had a limited effect on CRPS symptoms. The placebo group exhibited the least improvement across all measures.

Conclusion: Vitamin C can be recommended as an effective preventive strategy for managing CRPS. Oxycodone is beneficial for controlling acute pain but requires cautious long-term use. Combining these two interventions may yield optimal results.

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Introduction

Complex regional pain syndrome (CRPS) is a chronic and multifaceted pain condition that poses significant challenges to both patients and healthcare providers [1]. First described in the 19th century as reflex sympathetic dystrophy (RSD), CRPS is characterized by severe, disproportionate pain often following trauma, surgery, or immobilization [2]. Its hallmark features include vasomotor and sudomotor dysfunction, sensory abnormalities, motor impairment, and trophic changes in the skin, hair, and nails [3, 4].

CRPS is typically classified into two types: Type I, which occurs without a confirmed nerve injury [1], and type II, which is associated with a definite nerve injury. Although CRPS can affect individuals of any age, it is more common in women and middle-aged adults, with distal radius fractures being among the most frequently identified triggers [5-8].

Pathophysiology

The exact pathophysiology of CRPS remains poorly understood, but it is widely regarded as a multifactorial disorder involving neurogenic inflammation, autonomic dysregulation, central sensitization, and immune system activation [9, 10]. Prolonged pain and sensory abnormalities are believed to result from abnormal interactions between the peripheral and central nervous systems [11, 12].

Clinical presentation

The clinical presentation of CRPS is highly variable, with patients often experiencing severe pain, allodynia (pain from normally non-painful stimuli), hyperalgesia (increased sensitivity to painful stimuli), and edema [3-5]. Vasomotor symptoms such as temperature and color changes in the affected limb are common, along with sudomotor dysfunction, including excessive sweating or dryness [11]. Over time, untreated CRPS can lead to muscle atrophy, joint stiffness, and significant functional impairment [10].

Diagnosis

The diagnosis of CRPS is primarily clinical, based on the Budapest criteria, which include the presence of persistent pain disproportionate to the initial injury, along with signs and symptoms in at least two of the following categories: Sensory, vasomotor, sudomotor/edema, and

motor/trophic [2, 13]. Diagnostic imaging and laboratory tests are typically used to exclude other conditions and confirm the diagnosis.

Treatment challenges

Managing CRPS is particularly challenging due to its complex pathophysiology and heterogeneous presentation. Current treatment strategies involve a multidisciplinary approach, combining pharmacological interventions, physical therapy, and psychological support. Medications such as analgesics, anticonvulsants, corticosteroids, and bisphosphonates are commonly used, but their efficacy varies. Despite these efforts, many patients experience persistent symptoms and long-term disability [10, 13].

Rationale for the study

Vitamin C has emerged as a potential preventive intervention for CRPS due to its antioxidant properties, which may counteract oxidative stress and reduce inflammation [14-16]. Similarly, oxycodone, a potent opioid analgesic, has been widely used for pain management, particularly in acute settings [17]. However, the long-term efficacy and safety of these interventions in the prevention and management of CRPS remain uncertain [18]. Given the high prevalence of CRPS following distal radius fractures and the associated healthcare burden [19, 17, 20], this study seeks to evaluate the individual and combined effects of vitamin C and oxycodone on CRPS outcomes.

This research aims to fill the existing knowledge gaps by providing evidence-based insights into the role of these interventions in reducing CRPS symptoms, improving functional outcomes, and enhancing patients' quality of life (QoL). The findings of this study are expected to contribute to the development of effective prevention and treatment protocols for CRPS in clinical practice.

Methods

This study was conducted as a randomized, double-blind, interventional clinical trial designed to evaluate the effects of vitamin C and oxycodone on the prevention and management of CRPS in patients with distal radius fractures.

Study design

The trial was conducted across three tertiary care hospitals in Tehran, Iran: [Rasoul Akram Hospital](#), [Shohada-e Haft-e Tir Hospital](#), and [Shafa Yahyaian Hospital](#). A total of 120 patients with confirmed distal radius fractures requiring surgical intervention were enrolled.

Study participants and their inclusion

Participants were selected based on specific inclusion and exclusion criteria. All patients were informed about the study and provided written consent before enrollment.

The inclusion criteria were patients aged 18–75 years with acute distal radius fractures requiring closed reduction and pinning, the ability to comply with the follow-up schedule and assessments, and no prior history of CRPS or related conditions.

The exclusion criteria were patients with high-energy trauma (e.g. vehicular accidents, falls from significant heights), use of medications such as corticosteroids, antidepressants, or vitamin C before enrollment, severe systemic conditions, including hepatic or renal failure, non-compliance, or inability to participate in follow-ups.

Randomization and blinding

Patients were randomized into three groups using simple randomization:

1) Group 1 (A): Received 500 mg of vitamin C daily for 8 weeks; 2) group 2 (C): Received oxycodone based on patient weight (10 mg for >70 kg, 5 mg for ≤70 kg) for 2 weeks; 3) group 3 (B): Received a placebo daily for 2 weeks.

Block randomization was performed, with each hospital assigned a block size of 8 patients. The allocation order for drug groups varied as follows:

1) [Rasoul Akram Hospital](#): A, B, C; 2) [Shafa Yahyaian Hospital](#): B, A, C; 3) [Shohada-e Haft-e Tir Hospital](#): C, A, B.

Blinding details

1) Drugs were distributed in identical capsules filled with starch as a placebo; 2) both patients and evaluators were blinded to the drug type; 3) Data collection was performed using standardized tools.

Study interventions

Group A (vitamin C): Participants received 500 mg of vitamin C daily for eight weeks; Group C (oxycodone): Participants were administered oxycodone at doses of 5–10 mg/day (adjusted based on body weight) for two weeks; Group B (placebo): Participants received identical placebo capsules for a period of two weeks.

Outcome measures

The following primary and secondary outcomes were assessed at baseline and at weeks 2, 4, 6, and 8 after treatment:

1) Pain intensity: Measured using the visual analog scale (VAS), where 0 indicates no pain and 10 represents maximum pain; 2) joint functionality: Evaluated using the quick DASH questionnaire, which assesses upper limb mobility and limitations; 3) CRPS symptoms: Sudomotor, vasomotor, and sensory abnormalities were recorded using standardized clinical checklists; 4) Adverse events: Any complications or side effects related to the interventions were documented.

Data collection and analysis

Trained clinicians collected baseline demographic data, including age, gender, dominant hand, type of fracture, and details of the intervention. Independent evaluators conducted follow-up assessments at each time point. The data were anonymized to ensure confidentiality and then entered into SPSS software, version 22 for statistical analysis.

Descriptive statistics were used to summarize participant characteristics. Quantitative variables were analyzed using paired t-tests and ANOVA, while categorical variables were assessed using chi-square tests. Subgroup analyses were performed to examine the effects of age, gender, and fracture type.

Results

This section presents the detailed findings of the study, analyzing the effects of vitamin C and oxycodone on the prevention and management of CRPS. The results are organized into baseline characteristics, primary outcomes, secondary outcomes, and subgroup analyses.

Baseline characteristics

A total of 120 participants were included in the study, with 40 participants in each of the three groups (vitamin C, oxycodone, and placebo). The demographic and clinical characteristics of the participants were well-balanced across all groups, as summarized below:

The mean age of participants was 45.07 ± 15.43 years in the vitamin C group, 42.63 ± 17.61 years in the placebo group, and 37.53 ± 16.67 years in the oxycodone group ($P=0.206$). The male-to-female ratio was approximately equal across all groups ($P=0.709$). Extra-articular fractures (type A) accounted for 54% of cases, partial intra-articular fractures (type B) for 23%, and complete intra-articular fractures (type C) for 23%.

Primary outcomes

Pain intensity (VAS): The oxycodone group showed the most significant reduction in pain intensity, with a mean VAS score of 1.5 by week 8 ($P<0.001$). The vitamin C group demonstrated moderate pain reduction, particularly in the later weeks (weeks 6–8). The placebo group showed minimal improvement in pain scores over the 8 weeks.

Joint functionality (Quick DASH): The vitamin C group showed the greatest improvement in functionality, achieving a mean Quick DASH score of 25.5 by week 8 ($P<0.01$). The oxycodone group demonstrated moderate enhancements, while the placebo group showed negligible changes.

Secondary outcomes

CRPS symptoms: Both the vitamin C and oxycodone groups showed significant reductions in symptoms of sweating and swelling by week 8 ($P<0.01$).

About cold intolerance, the vitamin C group outperformed the other groups, with 87.5% of participants reporting complete resolution by week 6.

Adverse events: Mild adverse effects, such as nausea and sedation, were reported in the oxycodone group. No severe adverse events were observed in any of the groups.

Subgroup analyses

Subgroup analyses were conducted to explore the effects of demographic and clinical variables on the outcomes:

Younger participants (<50 years) in the vitamin C group showed a slightly faster recovery in functionality compared to older participants.

No significant differences in outcomes were observed between male and female participants. Participants with type A fractures demonstrated better overall outcomes across all groups.

Statistical analysis

Statistical analyses confirmed the significance of the observed differences among groups. P for key comparisons were $P<0.001$ for pain intensity (VAS), $P<0.01$ for joint functionality (Quick DASH), $P<0.01$ for CRPS symptoms (sweating and swelling), and $P<0.01$ for cold intolerance.

Discussion

This study provides important insights into the preventive and therapeutic roles of vitamin C and oxycodone in managing CRPS in patients with distal radius fractures. Key findings and their implications are discussed below.

Effectiveness of vitamin C

Vitamin C demonstrated significant efficacy in reducing CRPS-specific symptoms such as sweating, swelling, and cold intolerance.

Functional recovery, as assessed by the Quick DASH scores, was markedly improved in patients receiving vitamin C. These findings align with previous studies, including those by Zollinger et al. (2007) [21] and Besse et al. (2009) [18], which supported the role of vitamin C in preventing CRPS.

Effectiveness of oxycodone

Oxycodone was highly effective in managing acute pain, particularly during the early postoperative period. However, its limited impact on CRPS-specific symptoms highlights the need for complementary interventions. The potential for dependency and mild adverse effects necessitates cautious use.

Clinical implications

1) Vitamin C should be considered as part of routine postoperative care to prevent CRPS; 2) oxycodone remains an effective option for acute pain management, but should be used judiciously to minimize risks; 3)

combining preventive and therapeutic strategies may enhance overall patient outcomes.

Conclusion

This study aimed to evaluate the effects of vitamin C and oxycodone on the prevention and management of CRPS in patients with distal radius fractures. The findings confirm the substantial benefits of vitamin C as a preventive measure for CRPS, while oxycodone demonstrated its efficacy in managing acute postoperative pain. Key conclusions are summarized as follows.

Administering vitamin C has been shown to reduce the incidence and severity of CRPS-specific symptoms, including swelling, sweating, and cold intolerance. It promotes better functional recovery as evidenced by improved Quick DASH scores. Vitamin C demonstrates safety with no reported adverse effects, making it an ideal preventive strategy. Oxycodone provides effective relief from acute pain, particularly during the early postoperative phase. However, it showed limited impact on CRPS-specific symptoms, emphasizing its role primarily in pain management. Finally, oxycodone has mild side effects such as nausea and sedation, highlighting the need for cautious use.

Limitations

The follow-up period was limited to 8 weeks, which may not capture long-term outcomes. The study was conducted in a single geographic region, which may limit its generalizability. Patient compliance with interventions could not be independently verified.

General insights

The combination of preventive strategies, such as vitamin C, with therapeutic interventions, like oxycodone, can offer a comprehensive approach to managing CRPS. Early intervention and tailored management are critical in reducing the burden of CRPS on patients and healthcare systems.

Recommendations

Based on the findings of this study, the following recommendations are proposed for clinical practice, research, and patient care.

Clinical implementation

Incorporate vitamin C supplementation (500 mg/d) as a routine preventive measure for patients undergoing surgical treatment for distal radius fractures.

Use oxycodone for acute pain management in the postoperative period, but monitor patients for potential side effects and dependency risks. Develop standardized protocols for early identification and management of CRPS symptoms.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of [Iran University of Medical Sciences](#), Tehran, Iran (Code: IR.IUMS.FMD.REC.1403.231). The study adhered to the Declaration of Helsinki and local ethical guidelines. All participants provided informed consent, and their anonymity was maintained throughout the trial. Ethical approval ensured that the study protocols minimized risks and adhered to the highest standards of patient safety.

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Authors' contributions

Study design and writing the original draft: Amin Fathi; Investigation: Shima Babaei; Data collection: Hooman Shariatzadeh, AliAkbar Seifi Ashkezari, Sina Moghim, and Ahmad Hemat Yar; Data interpretation: Shima Babaei and Taghi Aghajanolou; Data analysis: Hooman Shariatzadeh and Shayan Amiri; Statistical analysis: Shayan Amiri; Review and editing: Hooman Shariatzadeh, Shayan Amiri, and Taghi Aghajanolou.

Conflict of interest

The authors declared no conflict of interest.

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References

- [1] IASP. Classification of chronic pain, second edition (revised) [Internet]. 2025 [Updated 2025 October 18]. Available from: [\[Link\]](#)
- [2] Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain*. 1999; 83(2):211-9. [\[DOI:10.1016/S0304-3959\(99\)00104-9\]](#) [\[PMID\]](#)
- [3] Förderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain*. 2004; 110(3):756-61. [\[DOI:10.1016/j.pain.2004.05.019\]](#) [\[PMID\]](#)
- [4] Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: A contribution to pain in complex regional pain syndrome (CRPS). *Pain*. 2007; 133(1-3):111-9. [\[DOI:10.1016/j.pain.2007.03.013\]](#) [\[PMID\]](#)
- [5] Lewis JS, Kersten P, McPherson KM, Taylor GJ, Harris N, McCabe CS, et al. Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome. *Pain*. 2010; 149(3):463-469. [\[DOI:10.1016/j.pain.2010.02.007\]](#) [\[PMID\]](#)
- [6] Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, A population-based study. *Pain*. 2003; 103(1-2):199-207. [\[DOI:10.1016/S0304-3959\(03\)00065-4\]](#) [\[PMID\]](#)
- [7] de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: A population-based study. *Pain*. 2007; 129(1-2):12-20. [\[DOI:10.1016/j.pain.2006.09.008\]](#) [\[PMID\]](#)
- [8] Fanuele J, Koval KJ, Lurie J, Zhou W, Tosteson A, Ring D. Distal radial fracture treatment: What you get may depend on your age and address. *J Bone Joint Surg Am*. 2009; 91(6):1313-9. [\[DOI:10.2106/JBJS.H.00448\]](#) [\[PMID\]](#)
- [9] Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology*. 2004; 62(12):2182-6. [\[DOI:10.1212/01.WNL.0000130156.05828.43\]](#) [\[PMID\]](#)
- [10] Bruehl S. Complex regional pain syndrome. *BMJ*. 2015; 351:h2730. [\[DOI:10.1136/bmj.h2730\]](#) [\[PMID\]](#)
- [11] McCabe CS, Haigh RC, Halligan PW, Blake DR. Referred sensations in patients with complex regional pain syndrome type 1. *Rheumatology*. 2003; 42(9):1067-73. [\[DOI:10.1093/rheumatology/keg298\]](#) [\[PMID\]](#)
- [12] Cohen H, McCabe C, Harris N, Hall J, Lewis J, Blake DR. Clinical evidence of parietal cortex dysfunction and correlation with extent of allodynia in CRPS type 1. *Eur J Pain*. 2013; 17(4):527-38. [\[DOI:10.1002/j.1532-2149.2012.00213.x\]](#) [\[PMID\]](#)
- [13] Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Pract*. 2002; 2(1):1-16. [\[DOI:10.1046/j.1533-2500.2002.02009.x\]](#) [\[PMID\]](#)
- [14] Keef T, Keef S. The efficacy of vitamin c in the prevention of complex regional pain syndrome after distal radius fractures: A synthesis. *J Pain Palliat Care Pharmacother*. 2018; 32(4):208-11. [\[DOI:10.1080/15360288.2019.1598530\]](#) [\[PMID\]](#)
- [15] Besse JL, Gadeyne S, Galand-Desmé S, Lerat JL, Moyer B. Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery. *Foot Ankle Surg*. 2009; 15(4):179-82. [\[DOI:10.1016/j.fas.2009.02.002\]](#) [\[PMID\]](#)
- [16] Cazeneuve JF, Leborgne JM, Kermad K, Hassan Y. [Vitamin C and prevention of reflex sympathetic dystrophy following surgical management of distal radius fractures (French)]. *Acta Orthop Belg*. 2002; 68(5):481-4. [\[PMID\]](#)
- [17] Lichtman DM, Bindra RR, Boyer MI, Putnam MD, Ring D, Slutsky DJ, et al. American academy of orthopaedic surgeons clinical practice guideline on: The treatment of distal radius fractures. *J Bone Joint Surg Am*. 2011; 93(8):775-8. [\[DOI:10.2106/JBJS.938ebo\]](#) [\[PMID\]](#)
- [18] Shibuya N, Humphers JM, Agarwal MR, Jupiter DC. Efficacy and safety of high-dose vitamin C on complex regional pain syndrome in extremity trauma and surgery—Systematic review and meta-analysis. *J Foot Ankle Surg*. 2013; 52(1):62-6. [\[DOI:10.1053/j.jfas.2012.08.003\]](#) [\[PMID\]](#)
- [19] Ekrol I, Duckworth AD, Ralston SH, Court-Brown CM, McQueen MM. The influence of vitamin C on the outcome of distal radial fractures: A double-blind, randomized controlled trial. *J Bone Joint Surg Am*. 2014; 96(17):1451-9. [\[DOI:10.2106/JBJS.M.00268\]](#) [\[PMID\]](#)
- [20] Evaniew N, McCarthy C, Kleinlugtenbelt YV, Ghert M, Bhandari M. Vitamin C to prevent complex regional pain syndrome in patients with distal radius fractures: A meta-analysis of randomized controlled trials. *J Orthop Trauma*. 2015; 29(8):e235-41. [\[DOI:10.1097/BOT.0000000000000305\]](#) [\[PMID\]](#)
- [21] Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. *J Bone Joint Surg Am*. 2007; 89(7):1424-31. [\[DOI:10.2106/JBJS.F.01147\]](#) [\[PMID\]](#)