



Review

Vitamin C Could Prevent Complex Regional Pain Syndrome Type I in Trauma and Orthopedic Care? A Systematic Review of the Literature and Current Findings

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Abstract

The aim of this systematic review is to evaluate the efficacy of Vitamin C (VC) in preventing Complex Regional Pain Syndrome type I (CRPS-I) in fractures or surgery of the upper and lower extremities.

During December 2020, Scopus and PubMed search was performed to analyze VC supplementation in preventing CRPS-I after trauma and orthopedic care, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guideline. Patient, Intervention, Comparison, Outcomes, Study Design model, and a modified version of the Coleman Methodology Score were used to analyze the included studies. The research was limited from 1990 to December 2020. Initial screening results identified 649 studies. After reviewing each study, six clinical studies were included in the study.

A total of 2026 patients of whom 632 male and 1394 female were collected in our systematic review. During the entire follow-up period, the occurrence of CRPS-I was evaluated in 1939 patients. Five of the six analyzed studies were favoring prophylactic use of the 500-1000 mg daily dose of VC for 45-50 days after orthopedic or trauma care for prevention of CRPS-I. Only one study found no benefit in VC supplementation compared with placebo to prevent CRPS-I.

Analysis of the literature suggests that a daily 500-1000 mg VC supplementation may reduce the onset of CRPS-I in trauma of upper/lower extremities and in orthopedic surgery.

Keywords: Ascorbic acid, chronic pain, complex regional pain syndrome, reflex sympathetic dystrophy, vitamin C.

Please cite this article as "Giustra F, Bosco F, Alessandro A, Artiaco S, Bistolfi A, Masse A. Vitamin C Could Prevent Complex Regional Pain Syndrome Type I in Trauma and Orthopedic Care? A Systematic Review of the Literature and Current Findings. Med Bull Sisli Etfal Hosp 2021;55(2):139-145".

Complex regional pain syndrome type I (CRPS-I), formerly known as reflex sympathetic dystrophy, is a chronic, complex, multifaceted disease common after fractures or surgery of upper/lower extremities. It has an incidence rate of 5.46 per 100.000 person-years.^[1] Unlike CRPS-II (also known as causalgia) characterized by a mayor nerve injury, CRPS-I exhibits impaired function (hyper-activation) of the

sympathetic nervous system without direct organic damage. Clinical development presents a "hot phase" with edema, erythema, and pain caused by circulatory disturbance and a "cold phase" characterized by bone demineralization, limited range of movement of the affected joint, tendons stiffness, and retraction. The prognosis of this syndrome is good if treated in the first period of onset but gives poor

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Submitted Date: December 30, 2020 **Accepted Date:** January 22, 2021 **Available Online Date:** July 02, 2021

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results if treated in the chronic phase. At present, there is not a specific therapy based on the etiopathogenesis of this syndrome but only symptomatic treatments and psychological counseling. Vitamin C (VC) is a free radical scavenger capable of stabilizing reactive oxygen species (ROS), which can damage the membrane lipids of endothelial cells in the micro circulation.^[2] The “hot phase” of CRPS-I is characterized by inflammation and microangiopathy with damage to the endothelial barrier that can cause increased pain and swelling.^[3] The exact mechanism of action of VC is not clear and its use for the prevention of CRPS-I is debated. In several studies, VC administration appears to be effective in preventing CRPS-I, although in others the clinical results have been contradictory.^[4] VC is fairly inexpensive, accessible to many, with no substantial adverse effects. The purpose of this systematic review is to analyze the efficacy of VC in the prevention of CRPS-I in trauma and scheduled surgery of the extremities.

Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.^[5] We evaluated current evidence of the role of VC to prevent CRPS-I in trauma and orthopedic care. To reduce the risk of possible bias in these systematic review two authors (FB and FG) performed the search and evaluated the articles independently. A third author (AA) was involved to solve any disagreement.

Screening Strategy

Patient, Intervention, Comparison, Outcomes, Study design model tool was used for asking focused clinical questions according to PRISMA guidelines.

- Patient (P): Patients undergone trauma or orthopedic care
- Intervention (I): The preventing role of oral ascorbic acid (VC)
- Comparison (C): VC group versus control group
- Outcomes (O): Occurrence of CRPS-I
- Study design model (S): Randomized controlled trials, quasi-experimental study (before and after), retrospective comparative study.

The inclusion criteria of the studies examined were articles published in English, French and Spanish languages, studies published within the past 30 years, full text of the articles should be available, participants underwent orthopedic or trauma care. We excluded from our research radiological and diagnostic studies, case reports, editorials, technical notes, preclinical studies, and review articles.

Selection Criteria and Selection of Research

During December 2020, a literature research of PubMed and Scopus database was performed using the following mesh terms: ([VC] OR [Ascorbic Acid]) AND ([complex regional pain syndrome] OR [reflex sympathetic syndrome] OR [chronic pain] OR [algodystrophy] OR [Sudek* atrophy] OR [Sudek* dystrophy]). The research was limited from 1990 to December 2020. Initial screening results identified 649 studies, among which 609 were included after excluding repeated studies. The title and abstract of all the articles were reviewed. Furthermore, full text of each selected article was retrieved. After reviewing each study according to the inclusion and exclusion criteria, six clinical studies that analyzed the role of VC in preventing complex regional pain syndrome after trauma and orthopedic care were included in the analysis. Bibliography of each article was analyzed to find further relevant publication. The corresponding PRISMA flow chart is shown in Figure 1.

Data Extraction

A data collection tool was created by the authors extracting the following data: Author and publication year, study design, number of groups, evaluation time points, CRPS-I diagnostic criteria used, dose of VC, sample size patients, sample size sex, sample size mean age, occurrence of CRPS-I, P-value studies, time of treatment initiation, duration of treatment, topic of orthopedic-trauma care, and type of orthopedic-trauma care (Tables 1, 2).

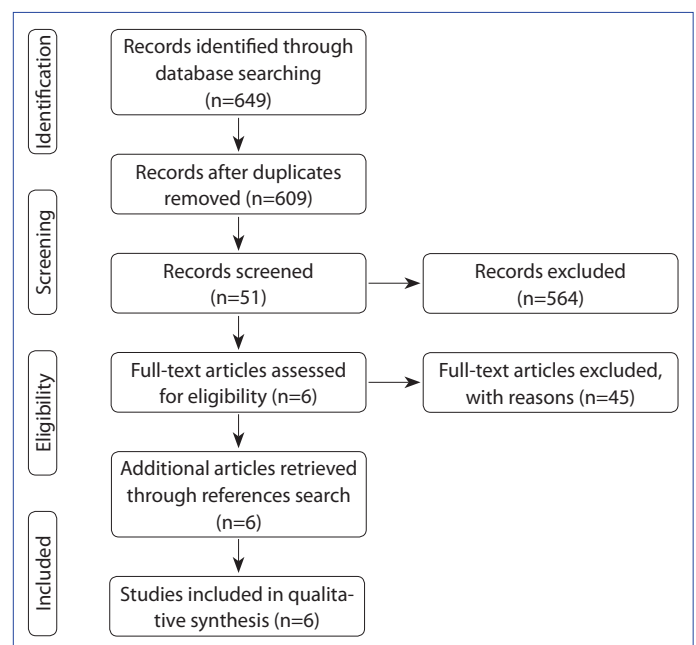


Figure 1. Preferred Reporting Items for Systematic review and Meta-Analysis flow diagram of articles screened, selected, and included in the systematic review.

Table 1. Description of the included studies with vitamin C used to prevent the development of CRPS-I after fractures or surgery of upper/lower extremities

Author and publication year	Study design	Number of groups	Evaluation time points	CRPS-I diagnostic criteria used	Dose of vitamin C (mg)	Sample size patients		Occurrence of CRPS-I		P-value studies	Time of treatment initiation	Duration of vitamin C treatment (days)	Topic of Orthopedic Trauma care	Type of Orthopedic Trauma care		
						n TOT	Vitamin C group n (%)	Control n (%)	n TOT						Vitamin C group n/n TOT (%)	Control n/n TOT (%)
Zollinger et al. (1999)	Randomized controlled study	2	7, 30, and 45 days, 4 and 6 months, 1 year	Veldman Criteria	500 mg	115	52 (43.7)	63 (52.9)	115	4/52 (7.7)	14/63 (22.2)	0.040	D0	50	Wrist fracture	Non-operative, n=115
Cazeneuve et al. (2002)	Quasi-experimental study (before and after)	2	10, 20, 30 and 90 days	Not specified	1000 mg	195	95 (48.7)	100 (51.3)	195	2/95 (2.1)	10/100 (10)	Not calculated	D0	45	Wrist fracture	Surgical, n=195
Zollinger et al. (2007)	Randomized controlled study	4	1 year	Veldman Criteria	200 mg	195	96 (49.2)	99 (50.8)	195	4/96 (4.2)	10/99 (10.1)	0.122	D0	50	Wrist fracture	Non-operative, n=291 Surgical, n=37
Besse et al. (2009)	Quasi-experimental study (before and after)	2	10, 21, 45 days and then every 3 months	IASP criteria	1000 mg	420	235 (56)	185 (44)	420	4/235 (1.7)	18/185 (9.7)	0.005	D0	45	Foot and ankle surgery	Surgical, n=420
Ekrol et al. (2014)	Randomized controlled study	4	6 weeks, 1 year	Atkins criteria	500 mg (displaced fractures) 500 mg (non-displaced fractures)	186 150	94 (50.5) 75 (50)	92 (49.5) 75 (50)	138 111	11/70 (15.7) 3/54 (5.6)	11/68 (16.2) 3/57 (5.3)	1 1	D0	50	Wrist fracture	Non-operative, n=252 Surgical, n=84
Laumonerie et al. (2019)	Retrospective comparative study	2	6, 12, 24 weeks	IASP criteria	500 mg	533	267 (50.1)	266 (49.9)	533	18/267 (6.7)	36/266 (13.5)	0.02	D0	50	Subacromial shoulder surgery	Surgical, n=533

CRPS-I: Complex regional pain syndrome type I; mg: Milligram; n: Number (of patients); nTOT: Total number (of patients); IASP: International Association for the Study of Pain; D0: Day of the trauma.

Table 2. Main demographic characteristics of patients collected from comprehensive research of literature

Author and publication year	Sample size patients			Sample size sex				Sample size mean age, y.o.	
	Vitamin C group		Control	Vitamin C group		Control		Vitamin C group	Control
	n (%)	n (%)	n (%)	M, n	F, n	M, n	F, n	Mean±SD	Mean±SD
Zollinger et al. (1999)	52 (43.7)	63 (52.9)	11	13	41	50	57	57	60
Cazeneuve et al. (2002)	95 (48.7)	100 (51.3)	28	32	67	68	57	57	55
Zollinger et al. (2007)	96 (49.2)	(50.8)	16	20	80	79	63±17	63±15	61±18
	114 (53.5)	99 (46.5)	21		93				
	118 (54.4)	(46.6)	18		100				
Besse et al. (2009)	235 (56)	185 (44)	55	48	180	137	62±18	51±16	47±17
Ekrol et al. (2014)	94 (50.5)	92 (49.5)	27	20	67	72	58±20	51±19	62±18
	75 (50%)	75 (50)	17	26	58	49			54±21
Laumonerie et al. (2019)	267 (50.1)	266 (49.9)	140	140	127	126	59±9.4		61±10.9

y.o.: years old; n: number (of patients), %: percentage, M: male, F: female, SD: standard deviation

Evaluation of Methodological Quality

Studies included in this systematic review were assessed independently by two authors regarding the quality evaluation lists using a modified version of the Coleman Methodology Score (mCMS), modified by Ramponi et al.^[6,7] If the authors did not specifically report the data necessary to determine the mCMS (i.e., procedure for assessing outcomes, and diagnostic certainty), data were extracted when possible and calculated by two independent authors (FB and FG) of the current manuscript. Disagreements were solved by AA.

Results

Our original search identified six studies included in this systematic review that collected a total of 2026 patients, of whom 632 males and 1394 females (male/female ratio, 0.3). In 1939 patients, the occurrence of CRPS-I during the entire follow-up period was evaluated. Oral VC supplementation was received by 1101 patients (mean age of 58±4.6 years) while 838 patients received a placebo or no treatment (mean age of 57±5.5 years). Main demographic characteristics are listed in Table 2.

To evaluate the efficacy of VC on preventing CRPS-I a study conducted by Zollinger et al.^[8] in 1999 was published. In this randomized controlled study, 115 patients with distal radius fractures were assigned to a group receiving a 500 mg daily dose of oral VC (n=52) or to a placebo group (n=63). A 50-day course of daily VC or placebo was administered starting from the day of the trauma. All patients were treated conservatively, and the evaluation times were 7, 30, and 45 days 4 and 6 months, and 1 year from the event. CRPS-I was diagnosed with the clinical criteria described by Veldman et al.^[9] VC has been shown to be effective in preventing CRPS-I secondary to wrist fracture at 1 year from the event (7% vs. 22%, p=0.040). In 2002, Cazeneuve et al.^[10] have made a quasi-experimental study (before and after) of two groups of 195 patients with distal radius fractures. Group I enrolled 100 patients who did not receive any VC supplementation. Group II included 95 patients who received 1 g of VC for 45 days, starting with the day of injury. All patients were surgically treated and examined up to 10, 20, 30, and 90 days after injury. Diagnostic criteria of CRPS-I were not described in the article. The onset of CRPS-I was lower among in patients in Group II in all follow-up controls (2.1% vs. 10%). Eight years after their first study, Zollinger et al.^[11] reported a multicenter, randomized controlled study. They evaluated 427 patients with wrist fractures treated surgically or conservatively. They allocated patients at random to daily dose of 200, 500, or 1500 mg of oral VC or to a placebo for 50 days, starting on the day of the trauma with a 1-year evaluation time point. The incidence of CRPS-I was

diagnosed by Veldman et al. criteria as in a 1999 study. Separate statistical analysis showed that only the 500 and 1500 mg doses significantly reduced the risk of CRPS-I a 1-year from the injury ($p=0.014$ and $p=0.022$, respectively). Besse et al.^[12] published a quasi-experimental study (before and after) of two groups of 420 patients to evaluate the efficacy of oral VC in preventing CRPS-I after foot and ankle surgeries. All patients were assigned to a group ($n=235$) that receiving 1 g of VC supplementation or to a placebo group ($n=185$) on the 1st post-operative day and continuing for 45 days. Patients were examined up to 10, 21, 45 days, and then every 3 months. They used the International Association for the Study of Pain criteria (IASP criteria) to diagnose CRPS-I.^[13] In this study, CRPS-I turned out significantly less common in oral VC group than in placebo group in all follow-up controls ($p=0.005$). In 2014, Ekrol et al.^[14] have made a randomized controlled study in which have been enrolled 336 patients. They analyzed the not displaced fractures separately from the displaced ones and randomized patients to receive 500 mg of VC or placebo daily for 50 days after the fracture. Evaluation time points were 6 weeks and 1 year after the trauma. The incidence of CRPS-I was diagnosed by Atkins et al. criteria.^[15] There was no significant difference in the frequency of CRPS-I at 1 year between the two treatment groups ($p=1$ for both groups). In this study, oral VC supplementation failed to reduce the risk of CRPS-I. Recently, Laumonerie et al.^[4] published a retrospective comparative study to determine whether oral VC supplementation was associated with reduced risk of CRPS-I after subacromial shoulder surgery (SaSS). Group I enrolled 266 patients did not receive 500 mg of VC supplementation. Group II included 267 patients who received 1 g of VC for 45 days, starting with the day of surgical procedure. Patients were examined up to 6, 12, and 24 weeks after surgery. CRPS-I was diagnosed with the clinical IASP criteria. The incidence of CRPS-I over a 6-month period was significantly lower among patients in Group II ($p=0.02$). Thus, they recommend preventive care with VC when possible for SaSS.

Finally, five studies were favoring prophylactic use of the 500-1000 mg daily dose of VC for 45-50 days after orthopedic or trauma care for prevention of CRPS-I. Although, Ekrol et al.^[14] reported in their study that administration of VC confers no benefit to patients with a displaced or not displaced fracture of the distal aspect of the radius after 1-year follow-up. A comprehensive evaluation of each article analyzed in this systematic review is available as supplementary material in Table 1.

Discussion

VC for CRPS-I prevention in trauma and orthopedic issues is a topic of considerable debate.^[16] Most studies in the lit-

erature have analyzed the efficacy of this antioxidant supplementation in patients with wrist fractures. The American Academy of Orthopedic Surgeons (AAOS) in their 2009 clinical practice guidelines recommended supplementation of daily 500 mg of VC for 50 days to prevent the occurrence of CRPS-I after distal radius fractures. They classified this recommendation as moderate strength.^[17] In 2018, the Royal College of Physicians in the UK updated its guidelines for the prevention of CRPS-I in wrist fracture. The authors reported that 500 mg of VC per day for the first 6 weeks after injury would help reduce this complication.^[18] In 2016, Aïm et al.^[19] in their meta-analysis reported that the incidence of CRPS-I, in patients with distal wrist fractures treated with daily administration of VC, was significantly reduced. The daily dose of VC and duration of treatment in the included studies were the same as suggested by AAOS in their guideline. Dosages below 500 mg were not effective.^[11] In literature, the use of VC to prevent CRPS-I has not been limited only to wrist fractures, but some authors have evaluated its effectiveness in post-traumatic and scheduled surgery of the upper and lower extremities.^[4,12] Shibuya et al.^[20] in their analysis included studies that examined wrist fractures and foot/ankle surgery. They reported that daily VC supplementation could be useful in lower extremities trauma or surgery to reduce the occurrence of CRPS-I. In 2019, Laumonerie et al.^[4] evaluated the efficacy of VC to prevent CRPS-I in shoulder surgery, concluding that VC administered for 50 days after surgery is helpful in preventing CRPS-I after SaSS.

CRPS-I is a multifactorial and debilitating complication that is not fully understood to date. It has similar clinical manifestations to other pathologies characterized by chronic pain such as transient osteoporosis of the hip, marrow edema syndrome, and regional migratory osteoporosis.^[21,22] There is no effective treatment available. VC is easily accessible, fairly inexpensive, and relatively safe in healthy patients. However, some adverse effects have been reported when administered in high dosages. The most common complications are fatigue and lethargy.^[23] Taylor et al.^[24] in their study showed that a dose of up to 1300 mg/d of VC raised the risk for calcium oxalate nephrolithiasis. Nevertheless, previous studies reported no significant correlation between VC intake and kidney stone development.^[25,26] Higher doses of VC have been correlated with renal failure (2.5-45 g) or hemolysis in patients with known glucose-6-phosphate dehydrogenase deficiency (40-80 g).^[27,28] None of the studies included in this review reported complications with VC supplementing in a daily dosage of 200-1500 mg, except for Cazeneuve et al.^[10] The authors documented two cases of gastrointestinal intolerance in the VC group; however, these two patients who discontinued VC did not develop CRPS-I. In our review, five out of six

included studies independently demonstrated a low risk of CRPS-I with a daily VC administration. Only Ekrol et al.^[14] found no favorable effect of taking VC compared with placebo in preventing CRPS-I.

Some potential limitations in our review process need to be analyzed. First, the main problem was related to the limited number of included studies. Three of the six studies analyzed had a low risk of selection bias considering that they had a double-blind, randomized design. Two studies were quasi-experimental (before-and-after), where the two groups analyzed had similar characteristics. However, as reported by Malay and Chung,^[29] with advances in technology, there is less likelihood that the treatment provided to the two groups could have been the same, which may have led to biased results. Laumonerie et al.^[4] had a retrospective nature without randomization. Not all studies had the same follow-up, and in some of them, data were not fully reported or not reported at all. Although several clinical and radiological tests are available for the diagnosis of CRPS-I,^[30,31] the gold standard remains exclusively clinical^[32] with an elevated risk of biases. Zollinger et al.,^[8,11] in their two studies, used the Veldman's et al.^[9] criteria, but in the first, a diagnosis of CRPS-I was made if four of six symptoms were presented, whereas in the second, it was diagnosed if four of five symptoms were checked. Ekrol et al.^[14] used the Atkins et al.^[15] criteria for the clinical diagnosis of CRPS-I. Besse et al.^[12] and Laumonerie et al.^[4] based the diagnosis of CRPS-I on the IASP criteria, which are currently the most widely used. However, IASP criteria are based on expert consensus rather than a detailed analysis of the scientific literature.^[33] Cazeneuve et al.^[10] in their study did not specify applied diagnostic criteria and, unlike other studies, did not use a placebo in the control group. All articles did not clarify whether physical therapy was used in patients diagnosed with CRPS-I. This could lead to possible outcome bias because these treatments can lead to pain relief. Finally, the participants' compliance with daily prescribed VC was not mentioned in the study.

Conclusion

At present, according to our research, a daily administration of 500-1000 mg of VC could reduce the development of CRPS-I in trauma of upper/lower extremities and in orthopedic surgery. Further double-blind, randomized clinical trials are needed to investigate the beneficial effect of VC, overcoming the limitations of the previous studies. Furthermore, it may be useful to discover the exact action of VC mechanism in preventing CRPS-I and to develop an objective, not just clinical, diagnosis of CRPS-I to reduce the risk of high biases.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Financial Disclosure: The authors declare that this study received no financial support.

Authorship Contributions: Concept – F.G., F.B.; Design – A.A., A.M.; Supervision – A.B., S.A.; Fundings – A.M.; Materials – None; Data collection &/or processing – F.G., F.B.; Analysis and/or interpretation – F.G., F.B., A.A.; Literature search – F.G., F.B.; Writing – F.G., F.B., A.A.; Critical review – S.A., A.B., A.M.

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