Published in final edited form as:

J Hand Surg Am. 2014 November ; 39(11): 2251–2257. doi:10.1016/j.jhsa.2014.08.009.

Testing the validity of preventing chronic regional pain syndrome with vitamin C after distal radius fracture

Sunitha Malay, MPH¹ [Clinical Research Coordinator] and Kevin C Chung, MD, MS² [Professor of Surgery]

¹Section of Plastic Surgery, Department of Surgery, University of Michigan Health System, Ann Arbor, MI

²Section of Plastic Surgery, Department of Surgery, The University of Michigan Health System, Ann Arbor, MI

Abstract

Purpose—The American Academy of Orthopaedic Surgeons (AAOS) recommends the use of vitamin C to prevent complex regional pain syndrome (CRPS) for patients with distal radius fractures (DRF). We hypothesized that the evidence for supporting this recommendation is weak, based on epidemiological principles of association and causality. The specific aim of this project was to test the validity of this recommendation.

Methods—We 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 and odds ratio. We then applied Hill criteria to evaluate the relationship between vitamin C and CRPS.

Results—We obtained 225 articles from the database search. After the exclusion of duplicates, unrelated articles, editorial letters, and commentaries, we found 4 articles and one systematic review relevant to our topic. Six of the nine Hill criteria were met, and an earlier meta-analysis showed a quantified reduction in CRPS risk. However, criteria like biological plausibility, specificity, and coherence were not met.

Conclusions—The number of causal/association criteria met was adequate to support the scientific premise of the effect of vitamin C in preventing CRPS after distal radius fracture. Furthermore, vitamin C administration is of relatively low cost and has few complications unless administered in large doses. Owing to sufficient epidemiological evidence availability, the AAOS recommendation of vitamin C to prevent CRPS has practical merit.

Level of evidence—Therapeutic, Level II.

Keywords

Bradford Hill criteria; CRPS; Distal radius; prophylactic; Vitamin C

INTRODUCTION

Distal radius fractures (DRFs) are common injuries in two groups of Americans.(1) Young adults experience complex fractures after high impact trauma and elderly individuals sustain fractures after a fall owing to their fragile bones. Neurovascular, bone, and soft tissue complications can follow DRF.(2) Among the neurovascular complications, complex regional pain syndrome (CRPS) is of special concern because of its chronic and disabling nature. The reported incidence of CRPS varies greatly from 1%–37% after DRFs (3–5) and 3% – 10% in patients with volar locking plate fixation after DRFs.(2,6,7) Use of vitamin C as a therapy to prevent the onset of CRPS in patients with DRFs is a topic of considerable debate.(8–10)

The American Academy of Orthopedic Surgeons (AAOS) develops evidence-based clinical practice guidelines to help surgeons better treat patients. These guidelines counsel surgeons on the treatment options, management of accompanying injuries, postoperative therapy, and complications. In a 2009 clinical practice guideline, the AAOS recommended 500 mg of vitamin C every day for 50 days after DRF to prevent occurrence of CRPS.(11) The strength of this recommendation was categorized as “moderate,” which means the evidence for such a recommendation was gathered from level II or level III studies with consistent findings or a single level I study in favor or against the intervention.(11) In other words, it means that the “benefits exceed the potential harm and that practitioners can follow the recommendation but remain alert to new information and be sensitive to patient preferences.”(11)

Vitamin C is readily accessible, relatively inexpensive, and does not have any substantial harmful effects. No matter how innocuous, owing to the lack of strong recommendation, such an arbitrary use may not be advantageous to prevent CRPS. Therefore it is imperative to evaluate if any relationship exists between vitamin C and CRPS prevention. With an estimated prevalence rate of 21/100,000 and substantial work absences, CRPS poses a considerable financial impact on the health care system.(12, 13) The aim of this paper was to critically examine the available studies to evaluate the AAOS recommendation based on epidemiological principles. We hypothesized that there was not enough scientific evidence to warrant the prophylactic use of vitamin C against CRPS.

METHODS

Literature search

The authors searched Medline, Embase, and Scopus databases for relevant articles using the keywords “vitamin C” or “ascorbic acid” and “complex regional pain syndrome” or “reflex sympathetic dystrophy.” An experienced, masters of public health researcher performed the search, with support from the university medical librarians. Affected condition was not limited to DRF alone, but included other conditions where vitamin C was used to prevent CRPS development. We did not use any limit on the language of articles.

Hill criteria

In 1965 Hill, an epidemiologist, outlined the minimal conditions required to establish a causal relationship between an exposure and its effect. We applied these criteria to determine the relationship between vitamin C and CRPS similar to health research in other medical specialties.(14–16) Strength of association, consistency, specificity, temporality, biological gradient (dose response relationship), biological plausibility, coherence, experimental evidence, and analogy constitute the 9 Hill criteria.(17) We determined a criterion to be met when a definition and explanation of it provided by Hill were valid with vitamin C and CRPS based on the available evidence. We did not find any information about the number of criterion to be met for an association to be considered causal, but we observed that if majority of criteria were met, the authors considered the association to be causal.(14–16) In addition, there was a lack of information about the weightage of individual criterion. In the preparation of this manuscript, the authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. (18)

RESULTS

Literature search

We obtained 225 articles from three databases searched. We performed title and abstract search after the exclusion of duplicates. We excluded all unrelated articles, editorial letters, and commentaries. Four studies and one systematic review related to the use of vitamin C and CRPS were available for final review. Among the four studies, three were conducted in DRF patients and one was conducted in patients undergoing foot and ankle surgery. (8,19–21) We included the foot and ankle surgery article to add to the sample size for our analysis. The systematic review comprised of the above four original studies.(22) The type of study design, dose of vitamin C used, sample size, and CRPS outcome expressed as measures of association (relative risk and odds ratios) in these studies are presented in Table 1.

Hill Criteria

Strength of association—The stronger association between the two variables indicates an increased likelihood of them being in a causal relationship as identified by the measures of association (odds ratio, relative risk). The criterion strength of association is met for vitamin C and CRPS. Included studies in our review are summarized as below. Zollinger et al found that conservatively treated DRF patients randomized to vitamin C group (500 mg/day), and placebo group developed CRPS in 7% and 22%, respectively.(19) A relative risk ratio of 0.34 and odds ratio of 0.29 were observed in group treated with vitamin C compared to group with placebo.

Cazeneuve et al showed that the incidence of CRPS in the vitamin C group (1000 mg/day) was 2% versus 10% in the control group of DRF patients treated with pinning.(20) A relative risk ratio of 0.2 and an odds ratio of 0.2 were observed.

Zollinger et al randomized three groups of surgically treated and casted DRF patients to receive 200mg, 500mg, and 1500mg/day of vitamin C for 45 days.(8) The overall incidence of CRPS in the vitamin C group was 2%, whereas in placebo group it was 10% ($P=.002$). An overall relative risk ratio of 0.24 and odds ratio of 0.20 were observed.(8)

Besse et al gave a group of patients undergoing foot and ankle surgery 1000 mg/day of vitamin C for 45 days.(21) CRPS occurred in 2% of patients among the vitamin C group and 10% of patients in the control group who were treated earlier but did not receive vitamin C. A relative risk ratio of 0.18 and an odds ratio of 0.16 were observed. All the above four studies found a statistically significant lowered incidence of CRPS with vitamin C use.

Consistency—The ability of an association to be repeatedly evident when investigated by different groups at various occasions and diverse settings proves it to be consistent. In other words, consistency is a search for repeatability of results. The criterion consistency is met for vitamin C and CRPS. Overall risk ratios of 0.34, 0.20, 0.24, and 0.18(8,19–21) were observed in studies conducted by various investigators in diverse settings using different study designs. Thus, reduction of CRPS risk with vitamin C intervention was observed to be consistent across all studies.

Biological gradient—With increasing amount of exposure or causal factor, the effect also increases proportionately. The higher the dose, the more is the effect. The criterion of biological gradient is met for vitamin C and CRPS. The incidence of CRPS in three groups of DRF patients who received a daily vitamin C dose of 200mg, 500mg and 1500mg was 4.2%, 1.8%, and 1.7% respectively.(8) With an increase in vitamin C dose, there was an increased reduction of CRPS indicating a dose response relationship. Although, the effect remained almost same with 500mg and 1500mg, there was a marked decrease in the incidence compared to the group that received 200mg.

Experimental evidence—Associations obtained from animal models in laboratory studies or other clinical trials can be considered to interpret causal relationships. Laboratory experiments and randomized clinical trials allow the researchers to control exposures, monitor, and thus estimate true associations between the two investigating elements. The criterion of experimental evidence was met for vitamin C and CRPS. Zollinger et al. conducted two randomized clinical trials that effectively demonstrated a reduced incidence of CRPS with vitamin C intake in DRF patients.(8, 19) In addition, vitamin C was extensively tested and demonstrated positive effects in several healing processes such as burn injuries in humans and fracture healing and skeletal muscle injuries in animal models such as rats.(8, 23–26)

Temporality—The cause should always precede the development of effect, implying temporality. The criterion of temporality was met. Administration of vitamin C reduced the CRPS occurrence, and in this instance, CRPS prevention occurred after the vitamin C intervention.

Biological plausibility—The association is said to be biologically plausible when there is a theoretical explanation between the cause and the effect based on the existing scientific knowledge. The criterion of biological plausibility was not met for vitamin C and CRPS. The exact pathophysiological mechanism for the development of CRPS is not well understood.(9) Likewise, the action mechanism of vitamin C in the prevention of CRPS is not elucidated according to the current scientific knowledge. Despite the fact that vitamin C

is a known antioxidant and helps in hydroxylation reactions,(27) its role in CRPS prevention remains unknown.

Coherence—Coherence means that the interpretation of relationship should not conflict the established facts about the characteristics of the intervention and the effect. That implies other possible theories or hypotheses should not disagree. The criterion of coherence was not met for vitamin C and CRPS. The natural history and biology of CRPS has several proposed theories. Similarly, various concepts were postulated to explain the role of vitamin C in CRPS prevention. Owing to the existence of numerous theories, it is unlikely that they are in accordance with each other to explain the relationship.

Specificity—This criterion means that ideally, an effect should have only one cause. Presence of a single cause enhances its credibility to be a causal factor. The criterion of specificity was not met. CRPS is also treated with opioids, antidepressants, anesthetics, and physiotherapy.(13) Additionally, use of vitamin C is not specific to prevent CRPS alone. Vitamin C has been used with success to promote recovery in burns, skeletal muscle injuries, and fractures.(23–26)

Analogy—When similar associations are proven to be causal, then by analogy, the association in question is more likely to be a causal association. The analogy criterion was met for vitamin C and CRPS. Randomized studies found that dimethylsulfoxide (DMSO) significantly reduced the pain in CRPS-1.(28–30) DMSO is a free radical scavenger. The association of DMSO and CRPS prevention has been proven to be causal. Pathogenesis of CRPS involves free radical formation which may be destroyed by vitamin C.(15,31,32)

DISCUSSION

We tested our hypothesis that there was not enough evidence for AAOS recommendation of vitamin C as a prophylactic against CRPS occurrence. Our analysis of studies showed that six of the nine Hill criteria were met. Therefore we rejected our hypothesis. There were a few caveats in the methodology and conduct of the included studies. In addition, criteria like biological plausibility, specificity, and coherence were not met. However, technological advancements may present new findings that will help us better evaluate these criteria. In addition, Hill neither mandated any criterion as an absolute requirement nor the number of criteria to be met. Application of Hill criteria in this context was intended to validate the vitamin C preventive effect of CRPS but not to impart clinical implication. Because available evidence permitted only a “moderate” recommendation, the AAOS suggested future research on the effect of nonsurgical adjuvant modalities such as vitamins, minerals, and physical therapy.(11) Practice of the AAOS recommendation for administration of vitamin C to DRF patients is therefore a reasonable approach until further higher level evidence becomes available.

A systematic review of studies with vitamin C use as an intervention to prevent CRPS in extremities from four databases yielded a total of 414 studies.(22) Four studies met the strict inclusion and exclusion criteria for final review. Meta-analysis of the four inclusive studies showed an overall relative risk of 0.22 (95% CI = 0.12, 0.39) for CRPS development with

500mg of vitamin C per day administered for 45–50 days following the injury or surgery. (22) A statistically significant ($P<.001$) fivefold reduction in the incidence of CRPS was observed. All the studies were in favor of prophylactic use of vitamin C for CRPS prevention.

Based on the available knowledge, the biological mechanism for the preventive action of vitamin C against CRPS is not evident. Specificity that corresponds to a one to one relationship is not frequently encountered unlike in an infectious disease context where a specific pathogen is known to cause a particular disease. For the coherence criterion, there should be a compatible association between the existing theories and knowledge available for it to be coherent. Owing to the multiple possible mechanisms for the vitamin C action and ambiguity of CRPS biological spectrum, and clinical diagnosis, it is not evident that if the theories were compatible or contradictory.

We found several limitations in the included studies. At first, there was a lack of a reference standard to diagnose CRPS. Currently, clinical diagnosis of CRPS is based on either the International Association for the Study of Pain (IASP) criteria or the Veldman criteria.(8,33) However, the current IASP criteria lack adequate specificity and therefore are likely to lead to over-diagnosis. (33) The Veldman criteria were developed and are widely used in Netherlands to diagnose CRPS but can also be inconsistent.(8,19) Zollinger et al. conducted 2 studies using Veldman criteria. In one study a CRPS diagnosis was made if 4 out of 6 symptoms were present, whereas, in a study 10 years later a CRPS diagnosis was made if 4 out of 5 symptoms were present.(8,19) Besse et al. used IASP criteria to diagnose CRPS. (21) Thus estimation of exact prevalence of CRPS becomes imprecise. Therefore, the reduction in the CRPS incidence achieved by the investigators in the above studies is debatable. Second, there was no mention if the investigators checked to see if the study participants actually took the pills provided to them leading to compliance issues.(9)

Third, the studies had study design issues, such as selection bias. Zollinger et al. introduced a large potential of selection bias because only 416 of the 2137 eligible patients were enrolled.(8) Additionally, a low prevalence of CRPS 5% versus 22% in their previous study was observed. Two of the included studies were quasi experimental before-and-after studies, in which the control group was a similar group treated at an earlier time without the intervention. With technological advancements, there is a less likelihood of treatment provided to the two groups being same, which might lead to biased results. Physical therapy provides some relief for CRPS in patients with DRFs. However, the articles lacked the information if physical therapy was used for their study participants. This could lead to possible confounding of the results.(34)

Fourth, the dosages of vitamin C used in the studies were 200mg, 500mg, 1000mg, and 1500 mg.(8,19–21) These dosages are above the recommended reference daily intake for vitamin C which is 60 mg.(27) The effect of such high doses of vitamin C is uncertain. For instance, recent trials with up to 1300mg/day of vitamin C dose showed that large doses of vitamin C resulted in an increased risk for calcium oxalate nephrolithiasis.(35, 36) However, earlier studies demonstrated no significant association between vitamin C intake and kidney stone formation.(37, 38)

We suggest that future studies should incorporate robust study designs to overcome the limitations of earlier studies and thus be able to deliver solid conclusions. Additionally, studies should be conducted to determine the exact dosage of vitamin C that can be safely administered to achieve the desired protective effect. Level-I evidence derived from such studies can further strengthen the validity of the AAOS recommendation of vitamin C use to prevent CRPS after a DRF.

Acknowledgments

Research reported in this publication was supported in part by grants from the National Institute on Aging and National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR062066) and from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (2R01 AR047328-06) and a Midcareer Investigator Award in Patient-Oriented Research (K24 AR053120) (to Dr. Kevin C. Chung). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Shauver MJ, Yin H, Banerjee M, et al. Current and future national costs to medicare for the treatment of distal radius fracture in the elderly. *J Hand Surg Am.* 2011; 36(8):1282–1287. [PubMed: 21705154]
2. Berglund LM, Messer TM. Complications of volar plate fixation for managing distal radius fractures. *J Am Acad Orthop Surg.* 2009; 17(6):369–1377. [PubMed: 19474446]
3. Jellad A, Salah S, Ben Salah Frih Z. Complex regional pain syndrome type I: incidence and risk factors in patients with fracture of the distal radius. *Arch Phys Med Rehabil.* 2014; 95(3):487–492. [PubMed: 24080349]
4. Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. *J Bone Joint Surg Br.* 1990; 72(1):105–110. [PubMed: 2298766]
5. Dijkstra PU, Groothoff JW, ten Duis HJ, et al. Incidence of complex regional pain syndrome type I after fractures of the distal radius. *Eur J Pain.* 2003; 7(5):457–462. [PubMed: 12935798]
6. Arora R, Lutz M, Hennerbichler A, et al. Complications following internal fixation of unstable distal radius fracture with a palmar locking-plate. *J Orthop Trauma.* 2007; 21(5):316–322. [PubMed: 17485996]
7. Rozental TD, Blazar PE. Functional outcome and complications after volar plating for dorsally displaced, unstable fractures of the distal radius. *J Hand Surg Am.* 2006; 31(3):359–365. [PubMed: 16516728]
8. Zollinger PE, Tuinebreijer WE, Breederveld RS, et al. 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):1424–1431. [PubMed: 17606778]
9. Amadio PC. Vitamin C reduced the incidence of reflex sympathetic dystrophy after wrist fracture. *J Bone Joint Surg Am.* 2000; 82(6):873. [PubMed: 10859108]
10. Shah AS, Verma MK, Jebson PJ. Use of oral vitamin C after fractures of the distal radius. *J Hand Surg Am.* 2009; 34(9):1736–1738. [PubMed: 19896015]
11. New AAOS guideline addresses distal radius fractures. 2009 at <http://www.aaos.org/Research/guidelines/DRFguideline.asp>.
12. Sandroni P, Benrud-Larson LM, McClelland RL, et al. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain.* 2003; 103(1–2):199–207. [PubMed: 12749974]
13. Maihofner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. *Eur J Neurol.* 2010; 17(5):649–660. [PubMed: 20180838]
14. Stahl S, Stahl AS, Meisner C, et al. Critical analysis of causality between negative ulnar variance and Kienbock disease. *Plast Reconstr Surg.* 2013; 132(4):899–909. [PubMed: 24076682]

15. Davidson TM, Smith WM. The Bradford Hill criteria and zinc-induced anosmia: a causality analysis. *Arch Otolaryngol Head Neck Surg.* 2010; 136(7):673–676. [PubMed: 20644061]
16. van Diepen AT, Jassal SV. A qualitative systematic review of the literature supporting a causal relationship between exit-site infection and subsequent peritonitis in patients with end-stage renal disease treated with peritoneal dialysis. *Perit Dial Int.* 2013; 33(6):604–610. [PubMed: 24335122]
17. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* 1965; 58(5): 295–300. [PubMed: 14283879]
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009; 62:1006–1012. [PubMed: 19631508]
19. Zollinger PE, Tuinebreijer WE, Kreis RW, et al. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet.* 1999; 354(9195):2025–2028. [PubMed: 10636366]
20. Cazeneuve JF, Leborgne JM, Kermad K, et al. Vitamin C and prevention of reflex sympathetic dystrophy following surgical management of distal radius fractures. *Acta Orthop Belg.* 2002; 68(5):481–484. [PubMed: 12584978]
21. Besse JL, Gadeyne S, Galand-Desme S, et al. Effect of vitamin C on prevention of complex regional pain syndrome type I in foot and ankle surgery. *Foot Ankle Surg.* 2009; 15(4):179–182. [PubMed: 19840748]
22. Shibuya N, Humphers JM, Agarwal MR, et al. 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):62–66. [PubMed: 22985495]
23. Yilmaz C, Erdemli E, Selek H, et al. The contribution of vitamin C to healing of experimental fractures. *Arch Orthop Trauma Surg.* 2001; 121(7):426–428. [PubMed: 11510911]
24. Sarisozen B, Durak K, Dincer G, et al. The effects of vitamins E and C on fracture healing in rats. *J Int Med Res.* 2002; 30(3):309–313. [PubMed: 12166348]
25. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg.* 2000; 135(3):326–331. [PubMed: 10722036]
26. Kearns SR, Daly AF, Sheehan K, et al. Oral vitamin C reduces the injury to skeletal muscle caused by compartment syndrome. *J Bone Joint Surg Br.* 2004; 86(6):906–911. [PubMed: 15330035]
27. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA.* 2002; 287(23):3116–3126. [PubMed: 12069675]
28. Geertzen JH, de Bruijn H, de Bruijn-Kofman AT, et al. Reflex sympathetic dystrophy: early treatment and psychological aspects. *Arch Phys Med Rehabil.* 1994; 75(4):442–446. [PubMed: 8172505]
29. Zuurmond WW, Langendijk PN, Bezemer PD, et al. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand.* 1996; 40(3):364–367. [PubMed: 8721469]
30. Perez RS, Zollinger PE, Dijkstra PU, et al. Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol.* 2010; 10:20. [PubMed: 20356382]
31. Huygen FJ, De Bruijn AG, De Bruin MT, et al. Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm.* 2002; 11(1):47–51. [PubMed: 11930962]
32. Bielski BH, Richter HW, Chan PC. Some properties of the ascorbate free radical. *Ann N Y. Acad Sci.* 1975; 258:231–237.
33. Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. *International Association for the Study of Pain. Pain.* 1999; 81(1–2):147–154. [PubMed: 10353502]
34. Frolke JP. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? *J Bone Joint Surg Am.* 2007; 89(11):2550–2551. author reply 1–2. [PubMed: 17974902]
35. Traxer O, Huet B, Poindexter J, et al. Effect of ascorbic acid consumption on urinary stone risk factors. *J Urol.* 2003; 170(2 pt 1):397–401. [PubMed: 12853784]

36. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol.* 2004; 15(12):3225–3232. [PubMed: 15579526]
37. Curhan GC, Willett WC, Rimm EB, et al. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. *J Urol.* 1996; 155(6):1847–1851. [PubMed: 8618271]
38. Curhan GC, Willett WC, Speizer FE, et al. Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol.* 1999; 10(4):840–845. [PubMed: 10203369]

Figure 1.
Flowchart of database search for vitamin C use to prevent CRPS

Table 1
Studies with Vitamin C use to prevent the development of CRPS* after distal radius fractures

Author (Year)	Type of study	Study Design	Vitamin C dose	Sample size		Mean Age (y)		CRPS diagnostic Criteria used	Relative risk ratio (RR)	Odds Ratio (OR)
				Experimental	Control	Experimental	Control			
Zollinger et al. (1998)	DRF study	Double blind, randomized	500 mg	54	65	57	60	Veldman criteria	0.34	0.29
Cazeneuve et al. (2002)	DRF study	Quasi experimental (before and after)	1000 mg	95	100	57	55	Not specified	0.2	0.19
Zollinger et al. (2007)	DRF study	Double blind, randomized	200 mg	96	99	63	61	Veldman criteria	0.04	0.22
			500 mg	114		63			0.017	
			1500 mg	118		62			0.016	
Besse et al. (2009)	Foot and Ankle surgery study	Quasi experimental	1000 mg	235	185	51	47	IASP criteria	0.18	0.16

CRPS- Complex Regional Pain Syndrome
IASP-International Association for the Study of Pain
y-years

Table 2

Causal inference assessment of vitamin C and CRPS using Hill criteria

Hill Criteria	Criteria Met
Strength of association	Yes
Consistency	Yes
Temporality	Yes
Experimental evidence	Yes
Analogy	Yes
Biological gradient	Yes
Biological plausibility	No
Coherence	No
Specificity	No

CRPS- Complex Regional pain Syndrome