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Vitamin C in Complex Regional Pain Syndrome in Patients with Distal Radius Fracture

Vitamina C na síndrome da dor complexa regional em pacientes com fratura distal do rádio

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Abstract

Objective To evaluate the effect of vitamin C in preventing complex regional pain syndrome (CRPS) in patients with fracture of the distal end of the radius (FDER).

Methods The present study included FDER patients with an indication for surgical treatment and aged over 18 years. We evaluated the age group, gender, dominant side, presence of comorbidities, affected side, trauma mechanism, and the surgical technique. Participants were randomized into 2 groups: placebo ($n = 64$), which received microcrystalline cellulose, and intervention ($n = 58$), treated with 1 g/day of vitamin C in a single dose for 60 days, starting immediately after surgery.

Results The average incidence of neuropathic pain was 17% higher in the placebo group than in the vitamin C one during the evaluation period ($p = 0.008$). The average visual analog scale (VAS) for pain was 1.22 points higher in the placebo group regardless of evaluation moment ($p = 0.001$). The CRPS at 12 and 24 weeks were statistically more frequent in the placebo group ($p = 0.014$ and 0.007, respectively).

Conclusion Vitamin C has an effect on preventing neuropathic pain and CRPS, as well as on controlling postoperative pain control.

Keywords
- ascorbic acid
- chronic pain
- complex regional pain syndromes
- radius fractures

Resumo

Objetivo Avaliar o efeito da vitamina C na prevenção da síndrome da dor complexa regional (SDCR) em pacientes com fratura da extremidade distal do rádio (FEDR).

Métodos Foram incluídos pacientes com FEDR com indicação de tratamento cirúrgico e idade acima de 18 anos, sendo avaliados faixa etária, gênero, dominância, presença de comorbidades, lado acometido, mecanismo do trauma e técnica cirúrgica. Os participantes foram randomizados em dois grupos: placebo ($N = 64$), que recebeu celulose microcristalina, e intervenção ($N = 58$) , que recebeu 1 g/dia de vitamina C, em dose única durante 60 dias, iniciando no pós-operatório imediato.

Palavras-chave
- ácido ascórbico
- dor crônica
- fraturas do rádio
- síndrome da dor regional complexa

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Resultados A incidência de dor neuropática foi em média 17% maior no grupo placebo do que no grupo vitamina C nas semanas avaliadas ($p = 0,008$). A escala visual análoga (EVA) foi em média 1,22 pontos maior no grupo placebo independente do momento de avaliação ($p = 0,001$). A SDCR, em 12 e 24 semanas, foi estatisticamente mais frequente no grupo placebo ($p = 0,014$ e 0,007 respectivamente).
Conclusão A vitamina C tem efeito na prevenção da dor neuropática e da SDCR, bem como no controle da dor pós-operatória.

Introduction

Distal radius fractures (DRFs) are the most common fractures. They present a clear bimodal pattern in children under 15 and adults over 50, who are at increased risk of fracture. Treatment includes closed reduction and cast immobilization or surgery.[1]

In the immediate postoperative period, direct nociceptor activation in the inflammatory response and potential injury to nerve structures clinically presents with pain during rest at the surgical site and adjacent regions, in addition to pain triggered by touch or movement, indicating peripheral sensitization.[2]

Complex regional pain syndrome (CRPS) is a complication featuring chronic and persistent pain with no cellular damage. It presents as autonomic and sensory pain, and motor, trophic, and vasomotor abnormalities leading to limb dysfunction.[3,4] The incidence of CRPS in patients with DRF is approximately 4%.[4] Some studies reported incidences from 1 to 37%, with a direct impact on quality of life, well-being, and work capacity.[5,6] Its clinical presentation varies from type I to II, respectively without or with evidence of nerve damage.[3,4]

Several recent clinical studies have shown that vitamin C administration to patients with CRPS, acute and post-herpetic neuralgia, and cancer-related pain significantly results in pain relief and improves the quality of life. It is also a powerful antioxidant that neutralizes free radicals and reduces oxidative stress, potentially contributing to treating inflammation and chronic pain.. It has proven safe and effective in relieving acute and chronic pain, including in outpatient, surgical, and oncology patients, and may decrease opioid use.[7,8]

Vitamin C plays a complex and multifaceted role in pain modulation, primarily through its antioxidant properties, regulation of inflammation, and support of connective tissue health. However, further research is required to fully elucidate its direct influence on pain and define specific guidelines for its clinical application.

The present study aimed to evaluate vitamin C's efficacy in preventing neuropathic pain and CRPS onset in patients with DRF undergoing surgical treatment and assess its impact on postoperative pain control.

Materials and Methods

This randomized, double-blind clinical study included patients with DRF undergoing surgical treatment at the orthopedics and traumatology service of a tertiary hospital.

The sample included patients over 18 years old admitted from April 2023 to April 2024 with DRF and indication for surgical treatment. We excluded pediatric subjects, polytraumatized patients, bilateral fractures, subjects with chronic renal failure, a history of kidney stones, ipsilateral DRF, diagnosis of neuropathic pain, history of glucose-6-phosphate dehydrogenase deficiency and hyperoxaluria, vitamin C allergy, under vitamin C or multivitamin treatment, or not agreeing to participate in the research protocol.

We evaluated the following clinical aspects: age range, gender, dominant side, presence of comorbidities, affected side, trauma mechanism, and surgical technique used. The radiographic evaluation consisted of images in anteroposterior and lateral views of the injured wrist submitted to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification.

An online research tool (https://www.randomizer.org/) was used to randomize the participants into two groups. The placebo group ($n = 64$) received microcrystalline cellulose, and the intervention one ($n = 58$) received 1 g/day of vitamin C[9] in a single dose for 60 days starting immediately after surgery. A medical team member prescribed the medication, without informing the patient and the main researcher. The latter was did the 24-week monitoring.

All patients followed the same analgesia protocol, with dipyrone 1 g every 6 hours as the first choice of common analgesic agent and, in case of allergy, paracetamol 750 mg every 6 hours with a weak opioid. For the opioids, the first choice was tramadol 100 mg every 12 hours and, for allergic patients, codeine 30 mg was the second one. The patients received instructions to take the medications based on pain intensity.

At admission, the Quick Disabilities of the Arm, Shoulder, and Hand (Quick-DASH, *d*) questionnaire assessed upper limb functionality.[10] This tool consists of 11 questions to assess physical function during the last week. Its score ranges from 0 to 5 for each item, and the final score ranges from 0 to 100. Furthermore, all patients underwent an evaluation for depression and anxiety using the Hospital Anxiety and Depression Scale (HADS).[11]

We performed clinical, functional, and radiographic evaluations at five points, at 2, 4, 6, 12, and 24 weeks. The patient, the attending surgeon, and the main researcher were blinded to randomization, with the last one being responsible for clinical follow-up and radiological fracture healing assessment.

At each follow-up appointment, we asked patients to assess their pain intensity at that moment using a visual analog scale (VAS), a one-dimensional tool with a line ranging from 0 to 10 points, indicating "no pain" and "worst pain imaginable", respectively. We also assessed the presence of treatment-related complications and CRPS signs and symptoms using the Budapest criteria.[12]

At the 12th-week evaluation, we defined the presence of neuropathic pain with the *Douleur neuropathique 4* (DN4) questionnaire, consisting of seven items referring to symptoms and three to the physical examination. Each item scores one for positive answers and zero for negative answers. A total score equal to or greater than four suggests neuropathic pain.[13]

In the 24th week of follow-up, patients underwent a new clinical evaluation using the same tools along with VAS for pain quantification.

Those diagnosed with CRPS underwent drug treatment with pregabalin or gabapentin, continued the follow-up in the service, and received a referral for monitoring by a physical therapy team.

The Excel 2013 (Microsoft Corp.) software stored the collected data, while the analysis used the Statistical Package Social Sciences (SPSS, IBM Corp.) for Windows, version 22.0. The significance level of the tests was 5%.

The description of qualitative characteristics used absolute and relative frequencies, while chi-square or exact tests (Fisher's or likelihood ratio) determined any association. The description of quantitative characteristics used summary measures (mean, standard deviation [SD], median, and quartile values), and the unpaired Student's t-test or Mann-Whitney test performed group comparisons. The presentation of VAS scores and the presence of neuropathic pain at the five points relied on summary measures, absolute and relative frequencies, respectively compared groups and times using generalized estimating equations (GEEs) with normal distribution, identity link function, binomial distribution, and logical link function, assuming a first-order autoregressive correlation matrix (AR[1]) between the evaluation moments of the same patient. Next, Bonferroni's multiple comparisons revealed differences between groups and times.

The Research Ethics Committee evaluated and approved this study under number CAAE 63013922.1.0000.0040.

Results

The sample consisted of 137 patients, of whom 122 completed the 24-week follow-up, including 55 women (45.1%) and 67 men (54.9%) with an average age of 48.1 years. ►**Table 1** details the characteristics of each group.

The behavior of the groups was statistically similar for neuropathic pain and VAS throughout the evaluation ($p_{Interaction} > 0.05$). Neuropathic pain presented statistical differences between groups at all times ($p_{Group} = 0.013$). Moreover, the average VAS differed between groups regardless of the evaluation moment ($p_{Group} = 0.001$) and throughout time in both groups ($p_{Time} < 0.001$), as shown in ►**Table 2**.

The frequency of neuropathic pain was on average 17% higher in the placebo group than in the vitamin C group during the study period ($p = 0.008$). The average VAS was 1.22 points higher in the placebo group regardless of the evaluation time ($p = 0.001$) and presented a statistically significant decrease throughout the weeks in both groups ($p < 0.05$). However, no statistically significant differences occurred between consecutive evaluations, i.e., 4 to 6 weeks, 6 to 12 weeks, and 12 to 24 weeks ($p > 0.05$), as can be seen in ►**Table 3**.

In the 12th and 24th weeks, CRPS was statistically more frequent in the placebo group ($p = 0.014$ and 0.007, respectively). The Quick-DASH score at 24 weeks was statistically lower in the vitamin C than in the placebo group ($p = 0.040$), as shown in ►**Table 4**.

Fracture severity per AO classification had no statistically significant association with CRPS and neuropathic pain ($p > 0.05$).

Patients with neuropathic pain at 12 weeks had a statistically higher HADS score ($p = 0.048$), with a similar difference in the 24 weeks without statistical significance ($p = 0.220$).

Discussion

Patients treated with vitamin C had superior postoperative pain control compared with those receiving placebo. This supplementation was shown to significantly reduce pain intensity, which may be attributed to its effect on modulating inflammation and reducing oxidative stress. These results suggest that vitamin C can be an effective intervention for improving postoperative pain management, which is consistent with the literature.

Evidence suggests that ascorbic acid (vitamin C) administration may have analgesic properties in some clinical conditions.[7] This is an essential micronutrient with evidence supporting its role in several metabolic processes related to mental health, stress response, bone formation, tissue repair, collagen production, and pain perception.[8,14] It influences the inflammatory response, potentially modulating the production of inflammatory cytokines and the activity of immune cells, reducing pain-associated inflammation.[7]

Vitamin C is a water-soluble antioxidant with high levels in the central nervous system that exceed serum concentrations by 10-fold.[15–17] It is a powerful antioxidant and anti-inflammatory agent, constituting a cofactor for adrenal steroidogenesis and catecholamine biosynthesis. It can also increase endomorphin and endorphin synthesis, and it is a cofactor for the biosynthesis of amidated opioid peptides.[7,8]

Evidence suggests that N-methyl-D-aspartate (NMDA) receptors largely mediate the nociceptive response of ascorbic acid, specifically by interacting with ionotropic glutaminergic receptors. There is good evidence regarding the involvement of NMDA receptors in pain modulation, as they reduce transmission and exert antinociceptive action.[15,17,18]

As described in a review by Fukushima and Yamazaki, the increased demand for ascorbic acid in surgical settings potentially results from oxidative stress. Therefore,

Table 1 Description of personal and clinical characteristics according to groups and statistical test results

Variable	Group		Total ($N = 122$)	*p*-value
	Placebo ($N = 64$)	Vitamin C ($N = 58$)		
Age (years)				
mean ± SD	47.9 ± 15.4	48.3 ± 15.5	48.1 ± 15.4	0.909**
median (25p; 75p)	47 (37.3; 63.8)	48.5 (36.8; 60.8)	47.5 (37; 63)	
Gender, n (%)				
Female	29 (45.3)	26 (44.8)	55 (45.1)	0.957
Male	35 (54.7)	32 (55.2)	67 (54.9)	
Dominant side, n (%)				
Right	62 (96.9)	54 (93.1)	116 (95.1)	0.422*
Left	2 (3.1)	4 (6.9)	6 (4.9)	
Comorbidities, n (%)				
None	46 (71.9)	40 (69)	86 (70.5)	0.682#
SAH	6 (9.4)	7 (12.1)	13 (10.7)	
DM	1 (1.6)	4 (6.9)	5 (4.1)	
SAH + DM	5 (7.8)	3 (5.2)	8 (6.6)	
Psychiatric disorders	2 (3.1)	1 (1.7)	3 (2.5)	
Other	4 (6.3)	3 (5.2)	7 (5.7)	
Injured side, n (%)				
Right	33 (51.6)	22 (37.9)	55 (45.1)	0.131
Left	31 (48.4)	36 (62.1)	67 (54.9)	
Trauma mechanism, n (%)				
Low energy	27 (42.2)	29 (50)	56 (45.9)	0.387
High energy	37 (57.8)	29 (50)	66 (54.1)	
AO, n (%)				
Extra-articular	31 (48.4)	13 (22.4)	44 (36.1)	**0.008**
Partial articular	6 (9.4)	5 (8.6)	11 (9)	
Articular	27 (42.2)	40 (69)	67 (54.9)	
Treatment, n (%)				
Closed reduction (Kirschner wire)	45 (70.3)	34 (58.6)	79 (64.8)	0.177
ORIF	19 (29.7)	24 (41.4)	43 (35.2)	
HADS				
mean ± SD	8.1 ± 6.6	7.7 ± 6.4	7.9 ± 6.5	0.768£
median (25p; 75p)	7 (3; 12)	7 (3; 10)	7 (3; 11)	

Abbreviations: AO, AO/OTA classification; DM, diabetes mellitus; HADS, hospital anxiety and depression scale; ORIF, open reduction and internal fixation; SAH, systemic arterial hypertension; SD, standard deviation. **Notes:** Chi-square test; *, Fisher's exact test; #, Likelihood ratio test; **Unpaired Student's t-test; £, Mann-Whitney test.

postoperative patients require daily doses higher than those recommended, and the administration of exogenous vitamin C is associated with better surgical outcomes.[19] Studies showed that its administration is also associated with a reduced need for postoperative opioid analgesics.[20]

The significant positive impact of vitamin C in preventing neuropathic pain and CRPS onset presented here is consistent with the literature. Patients receiving it showed a notable reduction in the incidence and intensity of neuropathic pain and a lower occurrence of CRPS compared with the placebo group. These effects may be attributed to the ability of vitamin C to reduce inflammation and oxidative stress, critical factors in the development and maintenance of these painful conditions.

Free radicals play a critical role in generating pain in several diseases, including neuropathic and inflammatory conditions. Antioxidants may participate in modulation inhibition and attenuate injury-induced mechanical allodynia. Their combination has a greater antiallodynic effect on neuropathic pain processing in the spinal cord.[21]

Table 2 Description of neuropathic pain and VAS for pain according to groups, evaluation times, and result comparisons

Variable	Group		p_{Group}	p_{time}	$p_{interaction}$
	Placebo ($N = 64$)	Vitamin C ($N = 58$)			
Neuropathic pain			**0.013**	0.091	0.355
12 weeks					
DN4 <4	45 (70.3)	50 (86.2)			
DN4 ≥4	19 (29.7)	8 (13.8)			
24 weeks					
DN4 <4	47 (73.4)	53 (91.4)			
DN4 ≥4	17 (26.6)	5 (8.6)			
VAS			**0.001**	<**0.001**	0.147
2 weeks					
mean ± SD	3.9 ± 3.1	2.8 ± 2.4			
median (25p; 75p)	5 (0; 7)	2 (1; 5)			
4 weeks					
mean ± SD	3.5 ± 2.9	1.7 ± 2.2			
median (25p; 75p)	3 (0; 6)	1 (0; 3)			
6 weeks					
mean ± SD	3 ± 3.2	1.4 ± 2.1			
median (25p; 75p)	2 (0; 6)	0 (0; 2)			
12 weeks					
mean ± SD	2.1 ± 2.9	1.3 ± 2			
median (25p; 75p)	0 (0; 3.8)	0 (0; 2)			
24 weeks					
mean ± SD	1.8 ± 2.8	0.9 ± 1.6			
median (25p; 75p)	0 (0; 2)	0 (0; 2)			

Abbreviations: AR(1), first-order autoregressive correlation matrix; DN4, *Douleur neuropathique 4* questionnaire; GEE, generalized estimating equation; SD, standard deviation; VAS, visual analog scale. **Notes:** GEEs with binomial distribution and logit link function; GEEs with normal distribution and identity link function; both models assumed an AR(1) correlation matrix between times.

Table 3 Neuropathic pain e EVA results from multiple comparisons between groups and times

Variable	Comparison		Men difference	SE	*p*-value	95% CI	
						Inferior	Superior
Neuropathic pain (%)	Placebo and Vitamin C		17.0	6.4	**0.008**	5.0	30.0
VAS	Placebo and Vitamin C		1.22	0.37	**0.001**	0.50	1.94
	2–4 weeks		0.76	0.18	<**0.001**	0.25	1.28
	2–6 weeks		1.20	0.24	<**0.001**	0.53	1.87
	2–12 weeks		1.71	0.27	<**0.001**	0.95	2.47
	2–24 weeks		2.08	0.29	<**0.001**	1.26	2.90
	4–6 weeks		0.44	0.18	0.175	−0.08	0.95
	4–12 weeks		0.94	0.24	**0.001**	0.27	1.62
	4–24 weeks		1.31	0.27	<**0.001**	0.55	2.08
	6–12 weeks		0.51	0.18	0.059	−0.01	1.02
	6–24 weeks		0.88	0.24	**0.002**	0.21	1.55
	12–24 weeks		0.37	0.18	0.443	−0.15	0.89

Abbreviations: CI, confidence interval; SE, standard error; VAS, visual analog scale. **Notes:** Bonferroni's multiple comparisons.

Table 4 Statistical analysis results of CRPS and Quick-DASH according to groups at different assessment times

Variable	Group		Total ($N = 122$)	*p*-value
	Placebo ($N = 4$)	Vitamin C ($N = 58$)		
CRPS at 12 weeks				
No	57 (89.1)	58 (100)	115 (94.3)	**0.014***
Yes	7 (10.9)	0 (0)	7 (5.7)	
CRPS at 24 weeks				
No	56 (87.5)	58 (100)	114 (93.4)	**0.007***
Yes	8 (12.5)	0 (0)	8 (6.6)	
Quick-DASH at 24 weeks				
mean ± SD	15.2 ± 25.5	5.9 ± 13	10.8 ± 21	**0.040£**
median (25p; 75p)	0 (0; 25)	0 (0; 16)	0 (0; 16)	

Abbreviations: CRPS, complex regional pain syndrome; Quick-DASH, quick disabilities of the arm, shoulder and hand; SD, standard deviation. **Notes:** *Fisher's exact test; #Likelihood ratio test; **Unpaired Student's t-test; £Mann-Whitney test.

Studies revealed that ascorbic acid protects cortical neurons from the toxic effects of NMDS mediated by its receptors.[15] Brain ascorbic acid levels have an association with the activity of these receptors and increasing their concentration may benefit patients with risk for neurological complications.[15,17,22,23]

Randomized clinical trials investigated the effects of vitamin C on CRPS incidence in patients undergoing wrist and ankle surgery. In these studies, the doses ranged from 0.2 to 1.5 g/day for 45 to 50 days after surgery. Its administration resulted in lower CRPS incidences, with doses $\geq$ 0.5 g/day as the most effective.[9,24–26] Previous research has indicated surgical patients require supplementation doses higher than 0.5 g/day to restore their normal status.[7,19]

Vitamin C supplementation has been associated with improved functional outcomes, including decreased pain and risk of CRPS after orthopedic surgery.[27]

Contrary to our results and the literature data previously described, Ekrol et al.[24] found no significant difference in the DASH score, CRPS incidence, or fracture consolidation over 1 year, concluding that vitamin C administration has no benefit for patients with DRF.

A meta-analysis of seven randomized controlled trials demonstrated that oral vitamin C supplementation can reduce the risk of CRPS type I but did not improve functional outcomes in orthopedic patients.[28]

One limitation of this study was the number of participants. Although the minimum sample size was determined to be 850 individuals, we obtained promising results with 122. This can be attributed to a more pronounced therapeutic effect than previously considered, to the intra- and intergroups variability, or to the high adherence to the intervention protocol. In some situations, a significant clinical difference between groups can translate into statistical significance even with a smaller sample size. It is worth highlighting that despite the promising results, this limitation may have impacted on the robustness and generalizability of the findings. As such, studies a larger sample size are recommended for confirmation and external validation.

Conclusion

The present study demonstrated that vitamin C can have a positive influence on the prevention of neuropathic pain, CRPS, as well as control of postoperative pain and inflammation in patients with DRF.

Authors' Contribution

Each author contributed individually and significantly to the development of the present article: FASA: research project preparation, patient assessment, data collection, data analysis, manuscript writing, paper reviewing and editing, and intellectual study conception; RMB: patient assessment, data collection, data analysis, paper review; YAA: data analysis, research project preparation, paper writing, reviewing, and editing, and intellectual study conception; PMBBF: data analysis, research project preparation, paper writing and reviewing, and intellectual study conception; RBC: data analysis and paper writing, reviewing, and editing.

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Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Raudasoja L, Aspinen S, Vastamäki H, Ryhänen J, Hulkkonen S. Epidemiology and Treatment of Distal Radius Fractures in Finland-A Nationwide Register Study. J Clin Med 2022;11(10): 2851. Doi: 10.3390/jcm11102851

2 Silva HLND, Tanaka GO, Pinheiro TB, Abdouni YA. Prevalence of Neuropathic Pain in Patients with Fracture of the Distal Extremity

of the Radius Treated with Volar Locking Plate. Rev Bras Ortop 2022;57(06):924–929. Doi: 10.1055/s-0041-1736526
3 Li Z, Smith BP, Tuohy C, Smith TL, Andrew Koman L. Complex regional pain syndrome after hand surgery. Hand Clin 2010;26 (02):281–289. Doi: 10.1016/j.hcl.2009.11.001
4 Romero JO, Soto IB, González RT, Choque FE, Hernandez JAZ, Atanasio JMP. Factors associated with complex regional pain syndrome in surgically treated distal radius fracture. Acta Ortop Bras 2017;25(05):194–196. Doi: 10.1590/1413-785220172505165544
5 Tajerian M, Clark JD. New Concepts in Complex Regional Pain Syndrome. Hand Clin 2016;32(01):41–49. Doi: 10.1016/j.hcl.2015.08.003
6 Roh YH, Lee BK, Noh JH, et al. Factors associated with complex regional pain syndrome type I in patients with surgically treated distal radius fracture. Arch Orthop Trauma Surg 2014;134(12): 1775–1781. Doi: 10.1007/s00402-014-2094-5
7 Carr AC, McCall C. The role of vitamin C in the treatment of pain: new insights. J Transl Med 2017;15(01):77. Doi: 10.1186/s12967-017-1179-7
8 Zelfand E. Vitamin C, Pain and Opioid Use Disorder. Integr Med (Encinitas) 2020;19(03):18–29
9 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(07):1424–1431. Doi: 10.2106/JBJS.F.01147
10 Silva NCd, Chaves TC, Santos JBd, et al. Reliability, validity and responsiveness of Brazilian version of QuickDASH. Musculoskelet Sci Pract 2020;48:102163. Doi: 10.1016/j.msksp.2020.102163
11 Botega NJ, Bio MR, Zomignani MA, Garcia C Jr, Pereira WAB. Transtornos do humor em enfermaria de clínica médica e validação de escala de medida (HAD) de ansiedade e depressão. Rev Saude Publica 1995;29(05):355–363. Doi: 10.1590/s0034-89101995000500004
12 Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8(04):326–331. Doi: 10.1111/j.1526-4637.2006.00169.x
13 Santos JG, Brito JO, Andrade DCd, et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain 2010;11(05):484–490. Doi: 10.1016/j.jpain.2009.09.014
14 Luo TD, Marois AJ, Smith TL, Willey JS, Emory CL. Ascorbic Acid and Its Clinical Role in Orthopaedic Surgery. J Surg Orthop Adv 2018;27(04):261–268
15 Saffarpour S, Nasirinezhad F. Functional interaction between N-methyl-D-aspartate receptor and ascorbic acid during neuropathic pain induced by chronic constriction injury of the sciatic nerve. J Basic Clin Physiol Pharmacol 2017;28(06):601–608. Doi: 10.1515/jbcpp-2017-0015
16 Harrison FE, Bowman GL, Polidori MC. Ascorbic acid and the brain: rationale for the use against cognitive decline. Nutrients 2014;6(04):1752–1781. Doi: 10.3390/nu6041752
17 Azevedo Filho FASd, Castro YMCd, Cerqueira MP, Rodrigues TA, Ali-Abdouni Y, Fucs PMM. Use of ascorbic acid (vitamin C) and alpha tocopherol (vitamin E) as adjuvants in the treatment of neuropathic pain. Br J P 2025;8:e20250005. Doi: 10.5935/2595-0118.20250005-en
18 Nasirinezhad F, Hosseini M, Salari S. Anti-allodynic Efficacy of NMDA Antagonist Peptide and Noradrenaline Alone and in Combination in Rodent Neuropathic Pain Model. Korean J Pain 2015; 28(02):96–104. Doi: 10.3344/kjp.2015.28.2.96
19 Fukushima R, Yamazaki E. Vitamin C requirement in surgical patients. Curr Opin Clin Nutr Metab Care 2010;13(06):669–676. Doi: 10.1097/MCO.0b013e32833e05bc
20 Jeon Y, Park JS, Moon S, Yeo J. Effect of Intravenous High Dose Vitamin C on Postoperative Pain and Morphine Use after Laparoscopic Colectomy: A Randomized Controlled Trial. Pain Res Manag 2016;2016:9147279. Doi: 10.1155/2016/9147279
21 Park JM, Kim CK, Lee HC, et al. Antiallodynic effects of vitamin C and vitamin E in chronic post-ischemia pain rat model. Korean J Anesthesiol 2013;65(05):442–448. Doi: 10.4097/kjae.2013.65.5.442
22 Ballaz S, Morales I, Rodríguez M, Obeso JA. Ascorbate prevents cell death from prolonged exposure to glutamate in an in vitro model of human dopaminergic neurons. J Neurosci Res 2013;91(12): 1609–1617. Doi: 10.1002/jnr.23276
23 Shah SA, Yoon GH, Kim HO, Kim MO. Vitamin C neuroprotection against dose-dependent glutamate-induced neurodegeneration in the postnatal brain. Neurochem Res 2015;40(05):875–884. Doi: 10.1007/s11064-015-1540-2
24 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):1451–1459. Doi: 10.2106/JBJS.M.00268
25 Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354(9195): 2025–2028. Doi: 10.1016/S0140-6736(99)03059-7
26 Cazeneuve JF, Leborgne JM, Kermad K, Hassan Y. Vitamin C and prevention of reflex sympathetic dystrophy following surgical management of distal radius fractures. Acta Orthop Belg 2002;68 (05):481–484
27 Oakes B, Bolia IK, Weber AE, Petrigliano FA. Vitamin C in orthopedic practices: Current concepts, novel ideas, and future perspectives. J Orthop Res 2021;39(04):698–706. Doi: 10.1002/jor.24947
28 Hung KC, Chiang MH, Wu SC, et al. A meta-analysis of randomized clinical trials on the impact of oral vitamin C supplementation on first-year outcomes in orthopedic patients. Sci Rep 2021;11(01): 9225. Doi: 10.1038/s41598-021-88864-7