

# Effects of Multiple Intravenous Doses of Perioperative Vitamin C on Pain Management Following Total Hip Arthroplasty

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**Purpose:** Although the benefits of numerous intravenous vitamin C doses during the perioperative phase on postoperative pain following total hip arthroplasty for whether patients could have pain relief for a longer period of time have not yet been tested, a single dose of vitamin C can assist control pain after the procedure on the first post-operative day.

**Methods:** One hundred patients undergoing total hip arthroplasty (THA) at our institution were enrolled in this prospective, double-blind, placebo-controlled, randomized experiment. These patients were randomized to either the control group or the vitamin C group. While the control group received an equivalent daily dose of a placebo, the vitamin C group received an intravenous injection of 3g of vitamin C every day during the perioperative period. Ten milliliters of morphine were injected subcutaneously as a rescue analgesic for patients who complained of discomfort following surgery. The amount of morphine used for rescue analgesia and the levels of inflammatory markers were the main outcomes that we evaluated. Additionally, we evaluated postoperative pain and hip joint recovery using the Visual Analog Scale (VAS) as secondary outcomes.

**Results:** In the vitamin C group, the subcutaneous morphine injection dosage was considerably lower (0–24h  $6.1\text{mg} \pm 2.7\text{mg}$  vs  $4.0\text{mg} \pm 2.9\text{mg}$ ,  $p = 0.000$ , total use  $8.3\text{mg} \pm 3.1\text{mg}$  vs  $6.6\text{mg} \pm 3.9\text{mg}$ ,  $p = 0.018$ ). During the perioperative term, the vitamin C group experienced better hip motion and lower VAS pain levels at rest and during exercise.

**Keywords:** vitamin C, total hip arthroplasty, postoperative pain, visual analog scale, pain

For severe osteoarthritis and other hip conditions, total hip replacement (THA) is a very successful procedure. Many patients report moderate-to-severe discomfort following the operation, despite its advantages. Although opioid analgesics are good at relieving pain, side effects including postoperative nausea and vomiting (PONV) might make it difficult to use them. Complications from inadequate pain management can include depression, anxiety, pneumonia, and an increased risk of myocardial infarction. In order to facilitate early functional exercises following surgery, which are essential for recovery, effective pain management is also essential.

Although opioids are commonly used to relieve postoperative pain, they can produce respiratory depression, which poses a substantial risk to individuals with a history of obstructive sleep apnea or airway difficulties. This emphasizes the need for safer pain treatment options for these individuals.

Vitamin C is required for collagen synthesis and connective tissue function, both of which are important for wound healing, according to research. Vitamin C acts as an antioxidant, stabilizing and reducing reactive oxygen species (ROS) by eliminating pro-inflammatory components from tissues. Its analgesic benefits stem from its capacity to neutralize ROS, which protects cells, tissues, and neurons from oxidative stress. Vitamin C may also increase the production of natural pain relievers and act as a cofactor in the synthesis of neurotransmitters and peptide hormones, such as opioid

peptides. It is also associated with the control of genes and transcription factors, which contribute to its pain-relieving properties.<sup>1</sup>

Vitamin C may be a safe and useful supplemental treatment for both acute and chronic pain, according to studies. For instance, it has been demonstrated that giving patients 2g of vitamin C intravenously reduces both postoperative pain and morphine use following laparoscopic cholecystectomy.<sup>2</sup> In a similar vein, giving 3g of vitamin C during tonsillectomy successfully reduced postoperative pain and the need for analgesics without causing any negative side effects.<sup>3</sup> Additionally, it has been demonstrated that complex regional pain syndrome after orthopedic treatments can be avoided with a daily dosage of 500 mg of vitamin C for 50 days after surgery.<sup>4</sup> Vitamin C is readily accessible and reasonably priced, and unlike opioids, it does not cause respiratory depression or the uncommon bleeding hazards linked to NSAIDs.<sup>3</sup>

A single intravenous injection of vitamin C may alleviate discomfort on the first day following total hip replacement, according to our team's earlier research.<sup>5</sup> But it is not enough. We need patients to relieve pain in a longer time, so we decided to explore whether multiple doses intravenous vitamin C could relieve pain management following total hip arthroplasty in a longer time.

## Materials and Methods

To conduct the study, a randomized, double-blind, prospective, and placebo-controlled experiment was employed. Our institution's Clinical Trials and Biomedical Ethics Committee is accustomed to it. Prior to their involvement, the anniversary actor gave accounting abreast consent. Additionally, the abstraction was preregistered with the Chinese Clinical Trials Registry on March 22, 2023, beneath allotment cardinal ChiCTR2300069613.

## Study Design

The abstraction was structured as a prospective, double-blind randomized controlled balloon involving 100 patients appointed for unilateral primary total hip arthroplasty (THA). The experiment was started from March 24, 2023. The sample measurement was based on the after-effects from a basic study. Participants were assigned to two groups applying an accidental cardinal table.

The sample measurement aimed to ascertain a 30% aberration in VAS affliction array amid the groups afterward administering vitamin C. With an alpha akin of 0.05 and an ability of 80% ( $1-\beta$ ), an absolute of 50 patients per accumulation was bent to be sufficient.

Double-blinding was carefully maintained throughout the trial. An absolute investigator activated a computer-generated randomization account to accredit patients to either the abstraction or ascendancy accumulation aloft their admission. These accumulation assignments were accurate in a computer system. During the surgical procedure, additional researchers administered either the appointed biologic or a placebo, ensuring the surgeon was blind to the patient's accumulation assignment. Additionally, the board was amenable to accessing postoperative abstracts, and assuming statistical analyses were added to the accumulation allocations. Patients were abreast of their accumulation assignments three days after the surgery at the end of the study.

## Surgery and Perioperative Management

All first-time overall hip arthroplasty (THA) sufferers had been randomly assigned to one in all corporations in a 1:1 ratio, the use of a computer-generated random quantity list. Admission (three days previous to surgical operation): Data gathered covered age, sex, BMI, preoperative exercising and resting ache scores, hip variety of motion, in addition to CRP and IL-6 levels. Patients acquired doses of celecoxib (200 mg) as a pre-analgesic at the day earlier than surgical operation.

## Intraoperative

All surgical techniques had been accomplished through a unmarried healthcare professional.

THAs had been done beneathneath widespread anesthesia through a surgical group that covered a senior healthcare professional (PK) and researchers, utilising a posterolateral approach. All sufferers acquired the identical cementless acetabulum (top acetabulum composition; DePuy Synthes, USA) and femur components (Corail stem; DePuy Synthes).

Group A: After induction of anesthesia, sufferers acquired an intravenous injection of 3g of vitamin C (Tianjin Jinyao Pharmaceutical, away from light) dissolved in 500 ml of regular saline, and injections of vitamin C in line with day 24 hours after surgical operation. Group B: Following anesthesia induction, sufferers acquired an intravenous injection of 3 g of placebo and 500 ml of regular saline, and injections of vitamin C in line with day 24 hours after surgical operation.

During anesthesia induction, each corporations required 10 mg of dexamethasone.

Post-operative: Throughout the perioperative period, the healthcare professional administered periarticular local infiltration analgesia. After awakening from widespread anesthesia, sufferers had been given ice packs across the incision. To control postoperative ache, sufferers acquired two hundred mg of celecoxib two times day by day. If ache becomes intolerable, 10 mg of morphine hydrochloride become administered subcutaneously as a rescue analgesic. Enoxaparin (0.2 mL) become given 12 hours post-surgical operation to save your venous thromboembolism (VTE), accompanied through 0.4 mL day by day till discharge. After discharge, sufferers acquired 10 mg of rivaroxaban as soon as day by day for 2 weeks. Additionally, all sufferers acquired intravenous mixed anesthesia.

## Randomization

The random number table for enrolling all patients in this study was generated in Microsoft Excel on a computer. Patients were divided into two groups based on the random number table. The first researcher was unaware of the group allocation and study design, and prepared opaque envelopes for all patients. On the day of the surgery, the second researcher randomly assigned patients to the control group and the vitamin C group. Before the surgery, the second researcher ensured that the anesthesiologists and nurses who had not participated in the study in any other form had prepared the appropriate amount of vitamin C and placebo in our hospital pharmacy. After the patient was under general anesthesia, 24 hours after the surgery, and 48 hours after the surgery, the corresponding items were brought to the operating room or injection room. The third researcher evaluated all the study results but was unaware of the patient group allocation. The fourth researcher analyzed all the data but was also unaware of the group allocation.

## Patient Recruitment

### Inclusion Criteria

1. The affected person has to meet category reputation I–III in line with the American Society of Anesthesiologists.
2. Patients need to be present to process their first unilateral overall hip arthroplasty at West China Hospital of Sichuan University.
3. Patients have to be identified with both hip arthritis or femoral head necrosis (Ficat III or IV) following unilateral number one overall hip replacement.

### Exclusion Criteria

1. Patients who do now no longer have osteoarthritis or femoral head necrosis (Ficat III or IV) and are at expanded danger for detrimental occasions because of corticosteroid use.
2. Patients who have been on long-time period diet vitamin C therapy three.
3. Individuals requiring number one bilateral hip surgical procedure or overall hip revision four.
4. Patients with pre-present heart, liver, lung, or kidney diseases.
5. Individuals with posterior acetabular wall defects or Crowe stage III or four dysplastic osteoarthritis.
6. A record of any hip surgeries, whether or not arthroscopic or open.
7. A record of hip infections.
8. A record of immoderate alcohol consumption.
9. Individuals with intellectual illness, cognitive impairment, or individuals who frequently use psychotropic capsules or are opioid-dependent.
10. Uncontrolled hypertension.

11. Presence of diarrhea.
12. Narcotic dependence.
13. Diagnosis of neuromuscular diseases.
14. Recent thrombotic occasions (eg, myocardial infarction, stroke, deep vein thrombosis, or pulmonary embolism).
15. Inability to talk verbally.
16. Allergies or contraindications to opioids, celecoxib, and diet Vitamin C.
17. Patients the usage of any analgesics (eg, NSAIDs, opioids, or acetaminophen) frequently or within 3 days prior to the scheduled surgical procedure.
18. Patients with renal insufficiency and improved creatinine levels.
19. Individuals who refuse to offer knowledgeable consent.

## Statistical Analysis

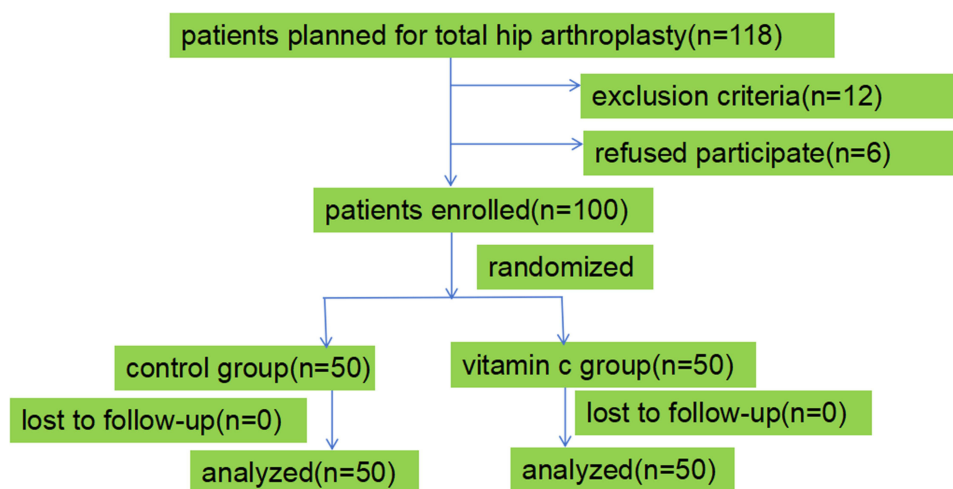
Statistical evaluation become accomplished the usage of SPSS 25.0 software. Continuous variables had been expressed as mean  $\pm$  well-known deviation. The unbiased samples t-take a look at become applied to examine dimension indexes that observed an everyday distribution. For variables that had been now no longer commonly distributed, the Mann-Whitney U take a look at become implemented for non-stop data, whilst specific variables had been evaluated the usage of both the Chi-rectangular take a look at or Fisher's genuine take a look at. A importance level ( $\alpha$ ) of 0.05 becomes set for two-sided tests, with p-values underneath 0.05 appeared as statistically significant.

## Demographic Information About Patients

In this study, a total of 118 patients were initially enrolled. Eighteen patients were excluded due to failure to meet the inclusion criteria or refusal to provide consent. The remaining 100 patients were allocated into two groups, with no patients being lost to follow-up (Figure 1). Prior to the surgery, both groups exhibited comparable baseline demographic and clinical characteristics (Table 1).

## Primary Outcome

The number one final results changed into to assess whether or not intravenous nutrition C management at some stage in the perioperative length of general hip substitute surgical procedure decreased postoperative morphine consumption. Morphine utilization changed into in comparison among the 2 group at some stage in the primary 24 hours post-surgical procedure and in the course of the hospitalization length. The consequences confirmed that sufferers with the vitamin C group required substantially much less morphine in comparison to the ones with the manipulate group at some stage in the perioperative length (Table 2).



**Figure 1** Flow diagram of patients' selection and exclusion.

**Table 1** Baseline Demographic and Clinical Characteristics of Patients

	Control(n=50)	Vitamin C(n=50)	P Value
Age	52.67±5.39	52.91±6.01	0.834
Gender(women/men)	25/25	28/22	0.689
Height(cm)	163.31±4.89	164.13±4.75	0.397
Weight(kg)	57.53±6.81	56.97±6.53	
BMI(kg/cm <sup>2</sup> )	22.60±2.40	22.70±1.50	0.803
Diagnostic			0.267
DDH-OA	35	31	
ONFH	13	12	
OA	2	7	
ROM (°)(flex)	90.92±6.21	91.11±5.89	0.876
ROM (°)(ext)	0.74±1.53	0.83±1.66	0.779
ROM (°) (abd)	25.28±6.99	24.89±5.34	0.755
IL-6	4.82±0.45	4.96±0.81	0.288
CRP	5.34±0.8	5.27±0.76	0.655
VAS post-op	4.72±0.33	4.76±0.37	0.570

**Table 2** Postoperative Morphine Consumption

	Control(n=50)	Vitamin C(n=50)	P Value
Morphine consumption was observed at 0–24 h after surgery (mg)	6.1±2.7	4.0±2.9	0.000
Total Morphine use after surgery(mg)	8.3±3.1	6.6±3.9	0.018

## Secondary Outcome

The group receiving vitamin C exhibited significantly lower pain scores both at rest and during movement than the control group during the postoperative period (Table 3–4).

**Table 3** The Average Postoperative VAS Pain Scores During Motion of Patients in Both Groups

	Control(n=50)	Vitamin C(n=50)	P Value
VAS-Pos2h-motion	5.56±0.48	4.75±0.43	0.000
VAS-Pos6h-motion	5.06±0.64	4.61±0.53	0.000
VAS-pos12h-motion	4.91±0.53	4.52±0.49	0.000
VAS-pos24h-motion	4.47±0.76	4.03±0.69	0.003
VAS-pos48h-motion	4.02±0.58	3.69±0.55	0.004
VAS-pos72h-motion	3.94±0.62	3.54±0.53	0.005

**Table 4** The Average Postoperative VAS Pain Scores at Rest of Patients in Both Groups

	Control(n=50)	Vitamin C(n=50)	P Value
VAS-Pos2h-rest	3.03±0.69	2.73±0.65	0.027
VAS-Pos6h-rest	2.85±0.62	2.50±0.53	0.003
VAS-Pos12h-rest	2.79±0.51	2.39±0.46	0.000
VAS-Pos24h-rest	2.62±0.54	2.27±0.43	0.001
VAS-Pos48h-rest	1.95±0.14	1.80±0.16	0.000
VAS-pos72h-rest	1.51±0.42	1.34±0.35	0.030

### Inflammation Markers

During the postoperative period, the vitamin C group also exhibited significantly lower levels of IL-6 and CRP (Table 5).

### Postoperative Functional Recovery

During the postoperative period, the vitamin C group demonstrated significantly improved ROM flexion (Table 6). The two groups did not differ significantly in terms of ROM in the hip extension and abduction.

### Complications

During the postoperative hospitalization, both groups had similar rates of nausea, vomiting, and wound complications (Table 7). Although the vitamin C group showed a tendency towards a reduction in postoperative nausea and vomiting,

**Table 5** Expression of Inflammatory Markers

	Control(n=50)	Vitamin C(n=50)	P Value
IL-6-24h	60.98±8.41	53.61±9.75	0.000
IL-6-48h	49.55±9.16	42.17±6.03	0.000
IL-6-72h	33.21±7.33	30.14±6.84	0.033
CRP-24h	37.49±2.88	30.33±6.94	0.000
CRP-48h	49.74±4.69	44.17±4.74	0.000
CRP-72h	54.16±5.31	50.33±4.12	0.000

**Table 6** Postoperative Functional Recovery and Length of Stay

	Control(n=50)	Vitamin C(n=50)	P Value
Hip ROM (°)			
ROM (°) (Flex)24h	94.82±4.13	98.66±4.51	0.000
ROM (°) (Flex)48h	97.82±3.74	100.50±3.98	0.001
ROM (°) (Flex) 72h	101.13±2.47	103.16±3.64	0.002
ROM (°)(ext)24h	-0.27±0.79	-0.29±0.52	0.881
ROM (°)(ext)48h	-0.25±0.72	-0.22±0.58	0.819
ROM (°)(ext)72h	-0.13±0.47	-0.08±0.53	0.795

(Continued)

**Table 6** (Continued).

	Control(n=50)	Vitamin C(n=50)	P Value
ROM (°) (abd)24h	31.95±1.79	32.31±1.97	0.341
ROM (°) (abd)48h	34.17±2.32	34.34±2.26	0.711
ROM (°) (abd)72h	34.87±2.64	35.08±2.71	0.696

**Table 7** Postoperative Complications

	Control(n=50)	Vitamin C(n=50)	P Value
PONV	4/50	2/50	0.678
Metoclopramide	2/4	1/2	1
Surgical site infection	0	0	-
Dislocation	0	0	-
Venous thrombotic events	0	0	-
Gastrointestinal hemorrhage	0	0	-
Nausea	13	10	0.635

this distinction turned into now no longer statistically significant. No patients in either group experienced postoperative venous thromboembolic events or falls.

## Discussion

To the pleasant of our knowledge, that is the primary examine to research the efficacy of multi-dose vitamin C as a part of a multimodal analgesic routine in general hip arthroplasty (THA). The key locations of this examine became that the addition of multi-dose vitamin C to multimodal analgesia brought about statistically massive discounts in morphine intake, VAS ache rankings, and upgrades in purposeful restoration at some point of the postoperative period. Vitamin C has been proven to relieve ache in loads of conditions.<sup>6–11</sup> For example, research have tested that intravenous management of 2g of vitamin C can lessen postoperative ache and morphine intake in sufferers present process laparoscopic cholecystectomy.<sup>2</sup> Similarly, a 3g infusion of vitamin C at some point of tonsillectomy has been stated to lower postoperative ache and analgesic use with none aspect results.<sup>3</sup> Additionally, vitamin C can mitigate the hazard of persistent ache following acute injury, and a routine of 500 mg of vitamin C each day for fifty days after surgical treatment has been proven to save you complicated nearby ache syndrome following orthopedic procedures.<sup>3</sup> Effective post-operative ache control is crucial for selling restoration and allowing early discharge.<sup>4</sup> Vitamin C was used in many conditions before the surgery, in Sivro M's article, they have proved that the injection of vitamin C could relieve pain after surgery.<sup>5</sup> In orthopedic field, vitamin C could relieve pain in older patients after intramedullary nailing of trochanteric fractures, although they received 2 g of ascorbic acid in 500 ml normal saline intravenously half an hour before the incision, and 1 g of ascorbic acid in 500 ml saline intravenously for 2 days postoperatively.<sup>5</sup> Postoperative ache following general hip arthroplasty (THA) is usually much less severe,<sup>4–12</sup> and thus, vitamin C, as a moderate analgesic, has been explored. Vitamin C exerts its analgesic results via more than one mechanisms: primarily, its antioxidant homes allow it to scavenge reactive oxygen species (ROS), thereby defensive cells, tissues, and nerves from oxidative damage. Furthermore, it could beautify ache alleviation through selling the manufacturing of endogenous compounds concerned in ache modulation. Vitamin C additionally features as a cofactor with inside the synthesis of neurotransmitters and peptide hormones, together with amideated opioid peptides. Additionally, vitamin C impacts the expression of genes and transcription elements that alter its analgesic results.<sup>1</sup> Also, Vitamin C can relieve pain by modifying redox changes in



NMDA receptors to regulate the neurotransmission of glutamate and dopamine.<sup>6</sup> Vitamin C can promote the conversion of dopamine into norepinephrine to relieve pain. In addition, and vitamin C is involved in cholinergic and GABAergic transmission to relieve pain.<sup>6</sup> While preceding studies has highlighted the ache-relieving homes of vitamin C in diverse diseases,<sup>13–18</sup> it's also mentioned that its brief half-lifestyles limits its sustained efficacy. However, as tested in our preceding examine, single-dose of vitamin C can efficiently lessen ache, lower opioid intake, decrease inflammatory markers, and enhance variety of movement inside 24 hours postoperatively. Therefore, we selected to manage multi-dose vitamin C to evaluate its capacity for easing ache at some point of the postoperative period. The consequences have been steady with our hypothesis, demonstrating that multi-dose vitamin C efficiently alleviated ache with inside the post-operative phase. Our examine had numerous capacity limitations. First, all sufferers on this examine underwent total hip arthroplasty (THA) beneath popular anesthesia, which might also additionally range from the analgesic protocols utilized in different clinical facilities or regions. As a result, we can not expect whether or not sufferers present process surgical treatment with spinal anesthesia could enjoy the identical consequences found on this examine. Additionally, our studies became limited to the hospitalization period, and we have been not able to assess long-time period consequences or headaches after discharge. Future research with a bigger pattern length and prolonged follow-up are vital to comprehensively investigate those aspects.<sup>19</sup> Then, maximum of the sufferers in our examination have been rather young, so we plan to research the results of multi-dose vitamin C in older populations in destiny studies. Lastly, because of the subjective bias of the vas pain score, morphine consumption at 24 hours after surgery and during hospitalization was assessed.

Our previous study has proved that single dose vitamin C can relieve pain in the pre-operative 1st day of total hip arthroplasty, but this is not enough, we need to relieve postoperative pain during the postoperative period, so we decided to inject multi-dose vitamin C.<sup>7</sup> This scientific examine confirmed that multi-dose intravenous vitamin C injection ended in decreased opioid intake and decrease VAS ache rankings following total hip arthroplasty (THA). Additionally, it became related to reduced inflammatory markers and a development with inside the variety of movement after the procedure. In the future, we will explore longer follow-up to explore the clinical outcome of vitamin C.

## Ethics approval and consent to participate

The full name of the ethics committee that reviewed my study (West China Hospital Committee), all patients informed consent was obtained, and the declaration of Helsinki was followed.

## Funding

This work was supported by the National Natural Science Foundation (No.82172414).

## Disclosure

The authors declare no competing interests in this work.

## References

1. Carr AC, McCall C. The role of vitamin c in the treatment of pain: new insights. *J Transl Med*. 2017;15(1):77. doi:10.1186/s12967-017-1179-7
2. Kanazi GE, El-Khatib MF, Yazbeck-Karam VG, Hanna JE, Masri B, Aouad MT. Effect of vitamin c on morphine use after laparoscopic cholecystectomy: a randomized controlled trial. *Can J Anaesth*. 2012;59(6):538–543. doi:10.1007/s12630-012-9692-x
3. Ayatollahi V, Dehghanpour Farashah S, Behdad S, Vaziribozorg S, Rabbani Anari M. Effect of intravenous vitamin c on postoperative pain in uvulopalatopharyngoplasty with tonsillectomy. *Clin Otolaryngol*. 2017;42(1):139–143. doi:10.1111/coa.12684
4. 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):1424–1431. doi:10.2106/JBJS.F.01147
5. Sivro M, Ð O, Lazović F, Papović A. The effect of intravenous vitamin C administration on postoperative pain and intraoperative blood loss in older patients after intramedullary nailing of trochanteric fractures. *Eur Geriatr Med*. 2024;16(1):237–243. doi:10.1007/s41999-024-01131-6
6. Hung KC, Lin YT, Chen KH, et al. The effect of perioperative vitamin c on postoperative analgesic consumption: a meta-analysis of randomized controlled trials. *Nutrients*. 2020;12(10):3109. doi:10.3390/nu12103109
7. Han G, Gan Y, Wang Q, Sun S, Kang P. Effect of perioperative single dose intravenous vitamin c on pain after total hip arthroplasty. *J Orthop Surg Res*. 2024;19(1):712. doi:10.1186/s13018-024-05193-x
8. Giustra F, Bosco F, Aprato 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. *Sisli Etfal Hastan Tip Bul*. 2021;55(2):139–145. doi:10.14744/SEMB.2021.82335



9. Seth I, Bulloch G, Seth N, et al.. Effect of perioperative vitamin c on the incidence of complex regional pain syndrome: a systematic review and meta-analysis. *J Foot Ankle Surg.* **2022**;61(4):748–754. doi:10.1053/j.jfas.2021.11.008
10. 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
11. Meena S, Sharma P, Gangary SK, Chowdhury B. Role of vitamin c in prevention of complex regional pain syndrome after distal radius fractures: a meta-analysis. *Eur J Orthop Surg Traumatol.* **2015**;25(4):637–641. doi:10.1007/s00590-014-1573-2
12. Chen S, Roffey DM, Dion CA, Arab A, Wai EK. Effect of perioperative vitamin c supplementation on postoperative pain and the incidence of chronic regional pain syndrome: a systematic review and meta-analysis. *Clin J Pain.* **2016**;32(2):179–185. doi:10.1097/AJP.0000000000000218
13. 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):62–66. doi:10.1053/j.jfas.2012.08.003
14. Böttger F, Vallés-Martí A, Cahn L, Jimenez CR. High-dose intravenous vitamin c, a promising multi-targeting agent in the treatment of cancer. *J Exp Clin Cancer Res.* **2021**;40(1):343.
15. Zeng Y, Liu Z, Xu F, Tang Z. Intravenous high-dose vitamin c monotherapy for sepsis and septic shock: a meta-analysis of randomized controlled trials. *Medicine (Baltimore).* **2023**;102(42):e35648. doi:10.1097/MD.00000000000035648
16. Wilson MK, Baguley BC, Wall C, Jameson MB, Findlay MP. Review of high-dose intravenous vitamin c as an anticancer agent. *Asia Pac J Clin Oncol.* **2014**;10(1):22–37.
17. Zhao X, Liu M, Li C, et al.. High dose vitamin c inhibits PD-L1 by ROS-pSTAT3 signal pathway and enhances T cell function in TNBC. *Int Immunopharmacol.* **2024**;126:111321. doi:10.1016/j.intimp.2023.111321
18. Shen ZY, Chen YR, Wang MC, Chang SS. High-dose vitamin c -induced acute oxalate nephropathy in a renal transplant recipient: a case report and literature review. *Asian J Surg.* **2023**;46(5):2223–2224. doi:10.1016/j.asjsur.2022.11.112
19. Ye S, Wang L, Wang Q, Li Q, Alqwbani M, Kang P. Comparison between ultrasound-guided pericapsular nerve group block and local infiltration analgesia for postoperative analgesia after total hip arthroplasty: a prospective randomized controlled trial. *Orthop Surg.* **2023**;15(7):1839–1846. doi:10.1111/os.13777

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