SYSTEMATIC REVIEW

The Impact of Vitamin C on Analgesic, Anti-inflammatory, and Hemostatic Outcomes After Total Hip and Knee Arthroplasty: A Systematic Review and Meta-Analysis

Shideh Moftakhari Hajimirzaei, MD; Masumeh Bagherzadeh Cham, PhD; Mohammadreza Dolikhani, MD; Seyed Morteza Tabatabaee, MD; Adel Ebrahimpour, MD

Research performed at Department of Orthopedic Surgery, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Objectives: Vitamin C has anti-inflammatory, antioxidant, and analgesic properties, yet its specific impact on perioperative and postoperative outcomes after total hip and knee arthroplasty remains unclear.

Methods: A PRISMA-compliant, PROSPERO-registered systematic review and meta-analysiss was conducted. Randomized controlled trials (RCTs) evaluating oral or intravenous vitamin C in primary hip or knee arthroplasty were searched in MEDLINE, Embase, Web of Science, and Scopus up to May 2025.

Risk of bias was evaluated using the Cochrane RoB tool. Meta-analyses were performed with RevMan version 5.4.1. Effect sizes were expressed as weighted mean differences (WMDs) with 95% confidence intervals (CIs). The certainty of evidence was assessed using the GRADE approach. Statistical heterogeneity was examined using the I^2 statistic ($I^2 \geq 50\%$ indicating substantial heterogeneity) and the chi-square test. A fixed-effect model was applied when $I^2 < 50\%$; otherwise, a random-effects model based on the DerSimonian and Laird method was used.

Results: Of 4,776 records, 3,585 titles/abstracts were screened and 19 full texts assessed; ten RCTs (n=1,162) met inclusion for qualitative synthesis, and three were pooled quantitatively.

Vitamin C administration significantly reduced total morphine use after surgery (WMD = −1.41 mg; 95% CI [−2.32, −0.50]; P = 0.002; I^2 = 0%). It also lowered C-reactive protein (CRP) levels (WMD = −11.32 mg/L; P = 0.0007) and interleukin-6 (IL-6) concentrations (WMD = −8.27 pg/mL; P < 0.0001) at 24 hours, although these effects diminished by 48 hours. No significant differences in postoperative pain scores were observed at either 24 or 48 hours.

Conclusion: This review indicates that vitamin C may be associated with reduced opioid consumption, attenuation of inflammatory responses, and decreased perioperative blood loss among patients undergoing joint arthroplasty. However, the overall strength of evidence remains limited due to heterogeneity in dosage, timing, and routes of administration across the included studies.

Level of evidence: II

Keywords: Ascorbic acid, IL-6, Inflammation, Opioid consumption, Pain, Total hip arthroplasty, Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) effectively relieve pain, restore joint function, and improve quality of life in patients with advanced joint disease. The rates of these procedures are projected to increase by 139% and 176%, respectively, by 2040.[1-3]

Pain and blood loss are significant perioperative challenges following knee and hip arthroplasty.[4-6] The procedure may elicit an exaggerated systemic inflammatory response, potentially progressing to systemic inflammatory response syndrome (SIRS).[7,8] This cascade contributes to postoperative pain, nausea, vomiting

Corresponding Author: Adel Ebrahimpour, Department of Orthopedic Surgery, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Email: a.ebrahimpour@sbmu.ac.ir

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(PONV), deep vein thrombosis (DVT), and wound-related complications.[9] Glucocorticoids such as dexamethasone are frequently administered preoperatively to mitigate postoperative pain and systemic inflammation.[10] However, glucocorticoid therapy in high doses or with prolonged use increases the risk of postoperative gastrointestinal bleeding and hyperglycemia.[11]

Vitamin C has emerged as a potentially safer alternative to glucocorticoids, exerting anti-inflammatory and analgesic effects by scavenging free radicals and attenuating oxidative stress and inflammation.[12] Furthermore, vitamin C stimulates the expression of genes encoding analgesic proteins and serves as a cofactor in the synthesis of analgesic neurotransmitters and peptide hormones.[13] It has been shown to effectively alleviate pain and inflammation in various clinical settings, including herpes zoster, bone fractures, and abdominal surgeries.[14,15]

As a potent antioxidant, vitamin C protects cells from reactive oxygen species (ROS)-induced damage[12,16] and helps reduce bleeding by stabilizing the vascular endothelium.[17] This hemostatic effect has also been demonstrated in non-orthopedic surgical settings.[18,19]

Although the antioxidant and anti-inflammatory properties of vitamin C have been demonstrated in various surgical settings, its specific effects in total knee and hip arthroplasty remain uncertain. This systematic review and meta-analysis aim to evaluate the role of vitamin C in reducing postoperative pain, opioid consumption, inflammatory markers, blood loss, and enhancing recovery, where reported. The objective is to clarify the potential of vitamin C as a safe and effective adjunct in joint replacement surgery.

Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (CRD420251085555).

Search strategy

The MEDLINE, Embase, Web of Science, and Scopus databases were searched up to May 12, 2025, using a combination of MeSH terms, Emtree terms, and relevant keywords, including "hip joint," "knee joint," "ascorbic acid," "vitamin C," "replacement," and "arthroplasty." Supplementary Table 1 provides details of the database-specific search strategies, Boolean operators, and initial record yields before deduplication [Supplementary Table 1].

All retrieved articles were imported into EndNote (version 21) using no restrictions on language or publication date, and duplicate records were removed. Gray literature was also searched. In addition, the ISRCTN registry, the National Institutes of Health Clinical Trials Register, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal were searched to identify unpublished or ongoing studies.

Selection criteria

Two reviewers (SM and MB) independently screened all retrieved records, and any disagreements were resolved by consensus with a third reviewer (AE). Inclusion criteria consisted of randomized controlled trials (RCTs) involving adults (≥18 years) undergoing hip or knee arthroplasty, in which the intervention group received vitamin C at any perioperative stage compared with placebo or other control interventions. Exclusion criteria included review articles, case reports or case series, retrospective studies, conference abstracts without full-text availability, unpublished or duplicate articles, and studies in which vitamin C was administered as part of multivitamin supplementation in all groups.

Outcomes were categorized as perioperative and postoperative measures. Perioperative outcomes included surgical and anesthesia-related parameters, such as propofol dosage and intraoperative blood loss. Postoperative outcomes encompassed pain management, analgesic consumption, inflammatory response (C-reactive protein [CRP], interleukin-6 [IL-6], and erythrocyte sedimentation rate [ESR]), and functional recovery, measured by range of motion (ROM).

Risk of bias assessment

The risk of bias (RoB) for all included studies was independently assessed by S.M.T. and S.M. using the Cochrane RoB (RoB 1) tool for randomized trials. Any disagreements were resolved through discussion with M.D. (third reviewer). Seven domains were evaluated, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias (e.g., small sample size < 30). Each domain was rated as having a low, high, or unclear risk of bias.[20] A study was considered to have an overall low risk of bias only if all domains were rated as low risk. If one or two domains raised some concerns (i.e., unclear risk), the overall judgment was categorized as "some concerns." The overall risk was rated as "high" if any single domain had a high risk or if three or more domains were unclear. The results were visualized using RoBVis traffic-light and summary plots.

Data Extraction and Synthesis

S.M. and M.D. independently extracted the data using a standardized Excel form. For each study, the following information was collected: author and year of publication, study design, group-level demographics, intervention details (vitamin C dose, route, timing, and duration), comparator, follow-up duration, mean ± SD values for the visual analog scale (VAS), morphine consumption (mg), C-reactive protein (CRP, mg/L), interleukin-6 (IL-6, pg/mL), blood loss (mL), and range of motion (ROM). When data were missing or unclear, the corresponding study investigators were contacted for clarification. Any discrepancies were resolved by a third reviewer (A.E.). In addition, the reference lists of all included studies were screened to identify any additional eligible records.

Statistical analyses were performed using RevMan version 5.4.1. Meta-analyses were conducted when three or more studies reported the same outcome. The weighted mean difference (WMD) was calculated as the effect size, since all studies used identical outcome measures. Heterogeneity was assessed using the chi-square test and the I^2 statistic, with $I^2 \geq 50\%$ indicating substantial heterogeneity. A fixed-effect model was applied when $I^2 < 50\%$; otherwise, a random-

effects model based on the DerSimonian and Laird method was used. Effect sizes were interpreted according to Cohen's conventions: small (<0.4), medium (0.4–0.7), and large (>0.7). Sensitivity analyses were not performed because each outcome included only three studies.

Subgroup analysis

A subgroup analysis was conducted based on the duration of follow-up, which included 24 hours, 48 hours, and the interval between day 1 and day 2.

Certainty of evidence

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[21] This framework evaluates five domains of evidence quality: risk of bias, inconsistency, imprecision, indirectness, and publication bias. Specific reasons for downgrading were as follows: substantial heterogeneity ($I^2 > 50\%$) for inconsistency, a 95% confidence interval (CI) crossing the clinical significance threshold for imprecision, and variations in vitamin C dosage for indirectness. The overall quality of evidence was categorized as high, moderate, low, or very low, and the strength of recommendations as strong or weak (conditional). The detailed GRADE assessments are presented in [Supplementary Tables 2–5].

Results

Study Selection

A total of 4,776 records were identified through a comprehensive search of the selected electronic databases. After removing 1,191 duplicates, 3,585 records remained for title and abstract screening. Of these, 3,266 articles were excluded for not meeting the predefined inclusion criteria. The full texts of 19 articles were assessed for eligibility, leading to the exclusion of nine studies: two were pilot trials, five investigated multivitamin interventions, and two administered vitamin C to both study groups. Consequently, 10 randomized controlled trials (RCTs)[22-31] met all eligibility criteria and were included in the systematic review. Among these, three RCTs[26,27,30] were eligible for inclusion in the meta-analysis. The study selection process is illustrated in Figure 1, following the PRISMA guidelines. No relevant unpublished studies were identified through searches of the gray literature [Figure 1].

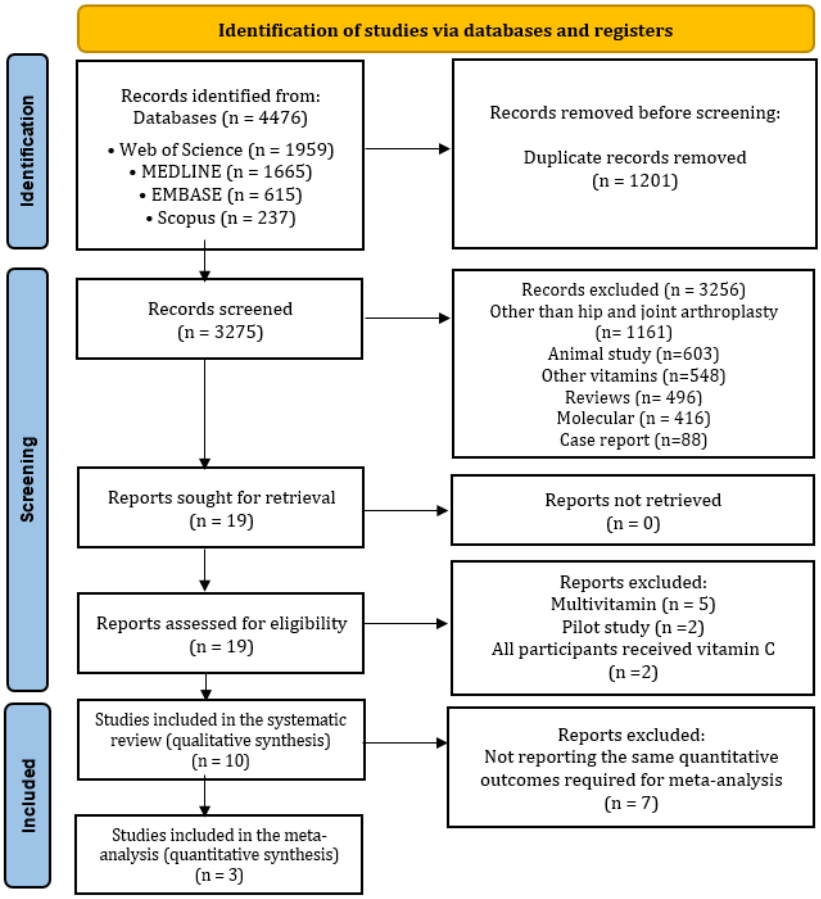

Figure 1. PRISMA flowchart for selecting eligible studies. RCT: randomized controlled trial

Study characteristics

The studies published between 2010 and 2025 included a total of 1,162 participants (557 in the intervention group and 605 in the control group). Among the ten randomized controlled trials (RCTs), seven involved patients undergoing total knee arthroplasty (TKA), and three involved patients undergoing total hip arthroplasty (THA).

Vitamin C administration varied substantially across studies in terms of dosage (ranging from 0.0067 g/kg to 15 g/day), route (intravenous in six studies, oral in three, and combined in one), and timing (intraoperative in three studies, postoperative in three, both in three, and preoperative only in one). Control groups received either saline or active comparators such as melatonin or dexamethasone.

This heterogeneity in intervention protocols may have affected the observed outcomes and limited the ability to make direct comparisons across trials. Follow-up durations ranged from the immediate postoperative period to one year [Table 1, 2].

Table 1. Demographic information of studies.

Author	Year	Country	Orthopedic procedure	Sample size (F/M)		Age (mean±SD)		Groups		Type of anesthesia	Other medicine
				Intervention	Control	Intervention	Control	Intervention	Control		
Hosseini-Monfared et al[18]	2025	Iran	TKA	45 (50/9)	65 (49/10)	68.61 ±6.83	70.24±5.81	3 doses of Vit C IV	an equivalent volume of saline	Spinal anesthesia	Tranexamic acid Cefazolin enoxaparin
Jiang et al[19]	2025	China	THA	35 (23/12) 38 (23/15)	34 (15/19)	57.69±11.03 56.42±10.34	56.41±8.92	Vit C IV followed by oral 10 mg dexamethasone	None of The interventions	General anesthesia	Tranexamic acid Cefuroxime Clindamycin Enoxaparin
Han et al[20]	2025	China	THA	50 (25/25)	50 (28/22)	52.91±6.01	52.67±5.39	Vit C IV followed by infusion within 24 hours postoperatively	3 g placebo	General anesthesia	Celecoxib Enoxaparin Rivaroxaban Morphine
Han et al[21]	2024	China	THA	50 (32/18)	50 (28/22)	54.40 ± 6.23	53.28 ± 7.14	Vit C IV Injection	3 g placebo	General anesthesia	Celecoxib Enoxaparin Rivaroxaban Morphine
LeBurn et al[22]	2024	USA	TKA	86 (49/37)	86 (46/40)	67.8 ± 8.4	66.8 ± 9.0	Vit C tablet	5 mg melatonin	Neuraxial and general anesthesia	
Ramon et al[23]	2023	Germany	TKA	45	65	Not Available	Not Available	High dose Vit C IV	Same infusion without Vit C	Not Available	
Li et al[24]	2021	China	TKA	15 (13/2)	21 (20/1)	69.1 ± 7.4	67.2 ± 5.7	Vit C IV	equivalent dose of normal saline)	General anesthesia combined with a lumbar sciatic nerve block	

Table 1. Continued

Jacques et al[25]	2021	Belgium	TKA	153 (92/61)	139 (97/42)	68 ± 8.7	71 ± 8.4	Oral Vit C	Placebo	Spinal or general anesthesia	Cefazolin Thromboembolic prophylaxis
Behrend et al[26]	2019	Switzerland	TKA	48 (30/18)	47 (28/19)	66.5	68	Vit C tablet	placebo	Not Available	
Lee et al[27]	2010	Korea	TKA	16 (14/2)	16 (15/1)	69.8±4.3	70.8±4.0	High dose Vit C	saline	General anesthesia	

F/M = female/male; SD = standard deviation; et al. = and colleagues; TKA = total knee arthroplasty; THA = total hip arthroplasty; Vit C = vitamin C; IV = intravenous; mg = milligram; g = gram; USA = United States of America.

Table 2. Details of RCTs on vitamin C use in joint arthroplasty, including outcomes, dosage, timing, and follow-up

Author	Year	Outcome measure	Time V-C	Vitamin C dosage (daily)	Time of administration (days)	Follow up
Hosseini-Monfared et al	2025	Blood loss (Hemoglobin level drop), transfusion rate, WOMAC,FJS,OKS,KOOS	Intra-operation Post-operation	1 gr in 10 ml	At the beginning surgery, after the tourniquet release, first 6 hours after TKA	6 month
Jiang et al	2025	VAS postoperative morphine use, inflammatory markers, blood glucose level, fibrinolysis indicators, Harris scores, DVT.PTE, PONV, transfusion rate, length of hospitalization, wound complications, periprosthetic fracture, hip dislocation, 30-day mortality, 90-day readmission	Intra-operation post-operation	1 gr intravenous then orally	15-30 mints before operation, for 2 weeks after discharge	2 weeks
Han et al	2025	Postoperative morphine injection, inflammatory factors, VAS ROM	Intra-operation post-operation	3 gr in 500 ml saline	After induction 24 hr. after surgery	72 hr. post-operation
Han et al	2024	Postoperative morphine injection, inflammatory factors, VAS, ROM	Intra-operation	3 gr in 500 ml saline	After induction intraoperatively	48 hr. post-operation
LeBurn et al	2024	PSQI, LEAS, VAS, VR-12MCS VR-12PCS	Post-operation	125 mg	6 weeks	6 weeks, 90 days

Table 2. Continued

Ramon et al	2023	Inflammatory markers (ESR, CRP)	Post-operation	15 gr parenteral	First four hours after surgery	Eighth postoperative day
Li et al	2021	Propofol dosage	Intra-operation	0.0067g/kg	Single dose	During surgery
Jacques et al	2021	CRPS	Post-operation	1 gr oral vitamin	40 days after surgery	12 months
Behrend et al	2018	ROM AF WOMAC FJS-12 vitamin C plasma concentration	Pre-operation	1 gr	Preoperative day to 50 days	12 months
Lee et al	2010	Myocardial enzymes (CPK, Troponin)	Intra-operation	0.06 g/kg in 100 ml saline and 0.02 g/kg in 30 ml saline	Intra-operation before tourniquet deflation 20 mints after deflation	8 hr. post-operation

AF, Arthrofibrosis; CPK-MB, Creatine Phosphokinase-Myocardial Band; CRP, C Reactive Protein; CRPS, Complex Regional Pain Syndrome; DVT, Deep Vein Thrombosis; ESR, Erythrocyte Sedimentation Rate; FJS, Forgotten Joint Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; OKS, Oxford Knee Score; LEAS, Lower Extremity Activity Scale; PTE, Pulmonary Thromboembolism; PONV, Postoperative Nausea and Vomiting; ROM, Range Of Motion; PSQI, Pittsburgh Sleep Quality Index; VR-12 MCS, Veterans Rand 12 Mental Component Score; VR-12 PCS, Veterans Rand 12 Physical Component Score; SD, Standard Deviation; VAS, Visual Analog Scale; WOMAC, Western Ontario and Mc Master Universities Osteoarthritis. Index.

Risk of bias

Most studies were judged to have a low risk of bias, with four out of ten trials rated as entirely low risk. Jacques et al. (2021) showed a high risk of performance, detection, and reporting bias.[24] Three studies with fewer than 30 participants per group raised concerns regarding potential bias.[24,25,28] All studies demonstrated a low risk of attrition and reporting bias [Figures 2,3].

Key outcomes

Surgical and Anesthesia-Related Outcomes

•Propofol Requirements:

Li et al. (2021) reported that in patients undergoing total knee arthroplasty (TKA), induction doses, recovery time, and perioperative hemodynamic parameters were comparable between the experimental and control groups. However, patients receiving vitamin C required 12% less propofol during maintenance (P = 0.04).[25]

•Blood Loss:

Two studies investigated the effect of vitamin C on postoperative blood loss, yielding conflicting results. Hosseini-Monfared et al. (2025) reported that in patients undergoing total knee arthroplasty (TKA), vitamin C supplementation reduced the postoperative hemoglobin drop by 0.48 g/dL (11.69 vs. 11.21 g/dL, P = 0.031) and significantly decreased total blood loss (463.6 vs. 732.1 mL, P < 0.001).[31] In contrast, Jiang et al. (2025) found no statistically significant difference in total blood loss among patients undergoing total hip arthroplasty (THA) who received vitamin C, dexamethasone, or placebo (871.4 vs. 832.2 mL, P = 0.50).[30]

Pain Management and Analgesic Consumption

Vitamin C supplementation was consistently associated with reductions in postoperative pain and opioid consumption, particularly in studies that employed standardized dosing regimens and outcome measures.

•Pain:

Three studies involving 307 THA patients (135 in the vitamin C group) have evaluated postoperative pain using the VAS.[26,27,30] Although individual studies reported promising results, the meta-analysis showed no significant reduction in pain on day 1 (WMD = –0.34; 95% CI [–0.97 to 0.30]; P = 0.30; I^2 = 93%), day 2 (WMD = –0.05; 95% CI [–0.65 to 0.54]; P = 0.86; I^2 = 94%), or overall (WMD = –0.01; 95% CI [–0.26 to 0.24]; P = 0.95; I^2 = 91%). Pain slightly increased between postoperative days 1 and 2 (WMD = 0.22; 95% CI [0.11 to 0.33]; P < 0.0001; I^2 = 0%). The certainty of the evidence ranged from low to moderate. Overall, these findings indicate no significant benefit of vitamin C supplementation for early postoperative pain following total hip arthroplasty (THA). Details of the GRADE Summary of Findings (SoF) for pain are presented in Supplementary Table 2, including domain ratings, reasons for downgrading (inconsistency and dose heterogeneity), and direction of effect. For continuous outcomes, a negative WMD favors vitamin C. [Figure 4, Supplementary Table 2].

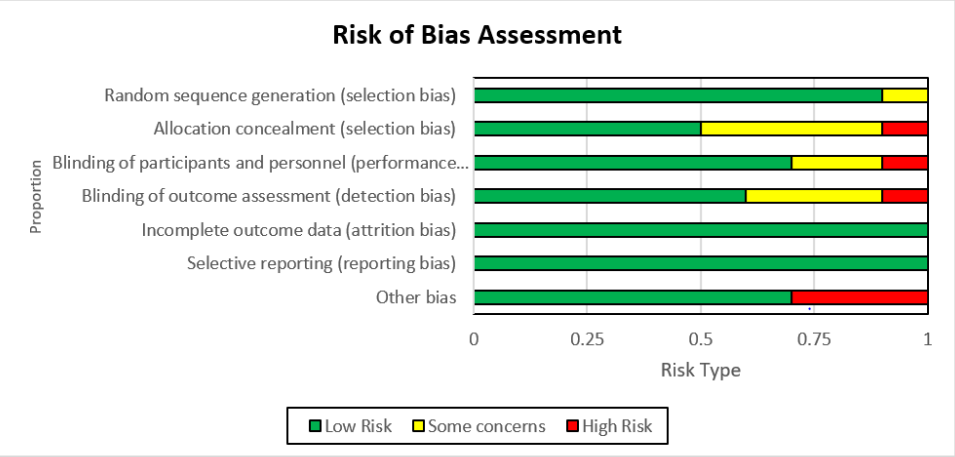

Figure 2. Risk of bias graph for included RCTs, generated using the Cochrane RoB 2.0 tool. Judgments for each domain are presented as percentages across all studies

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
Behrend 2019	+	-	-	-	+	+	+
Han 2024	+	+	+	+	+	+	+
Han 2025	+	+	+	+	+	+	+
Hosseini-Monfared 2025	+	+	+	+	+	+	+
Jacques 2021	-	X	X	X	+	+	X
Jiang 2025	+	+	+	+	+	+	+
LeBrun 2024	+	-	+	+	+	+	+
Lee 2010	+	-	-	-	+	+	X
Li 2021	+	+	+	+	+	+	X
Ramàn 2023	+	-	+	-	+	+	+

X : High risk - :Some concerns + : Low risk

Figure 3. Risk of bias summary for included RCTs, generated using the Cochrane RoB 2.0 tool. Judgments for each domain are shown for each individual study

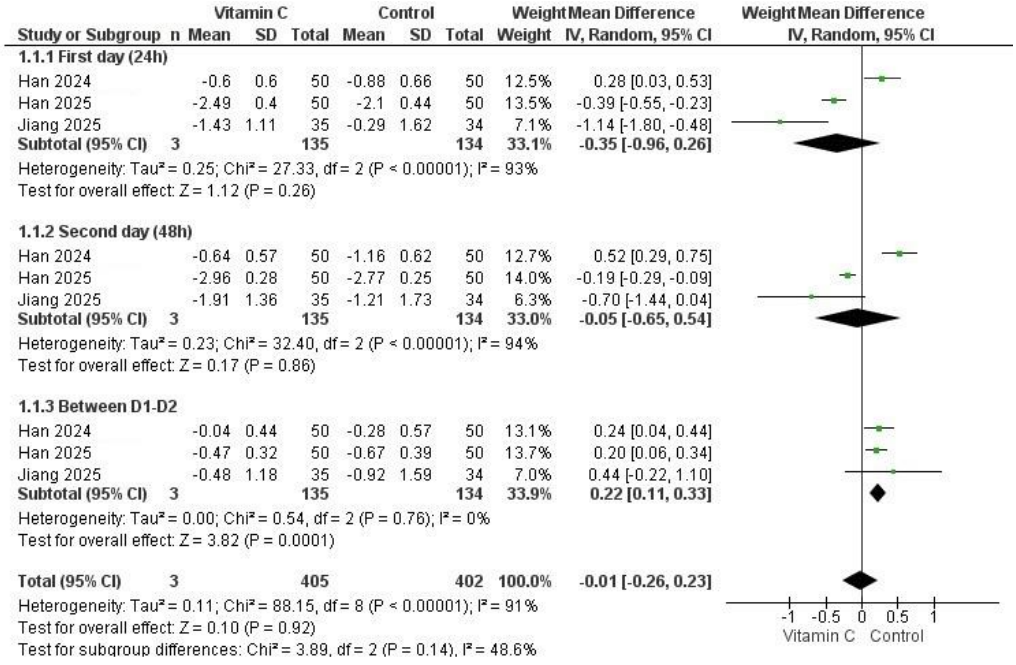

Figure 4. Forest plot of visual analogue scale (VAS) pain scores comparing vitamin C and control groups on postoperative first day (24h), second day (48h), and the change between day 1 and day 2. Effect size = Weighted Mean Difference (WMD) with 95% CI; N: number of articles; CI = Confidence Interval; IV = Inverse Variance; SD = Standard Deviation; D = Day

•Morphine Consumption:

The meta-analysis of three studies involving 307 patients undergoing total hip arthroplasty (THA) demonstrated that vitamin C supplementation significantly reduced total morphine consumption (WMD = −1.41 mg; 95% CI [−2.32 to −0.50]; P = 0.002; I^2 = 0%), with moderate-certainty evidence [Figure 5].

Supporting studies showed reduced 24-hour use with single-dose vitamin C (Han et al. 2024: 4.9 mg vs. 5.8 mg; P values = 0.043) and greater reductions with multiple doses (Han et al. 2025: 4.0 mg vs. 6.1 mg at 24h, P values < 0.001; 6.6 mg vs. 8.3 mg during postoperative period, P values = 0.018).[26,27] Jiang et al. (2025) reported a synergistic effect when vitamin C was combined with dexamethasone.[30] Supplementary Table 3 summarizes the column definitions and GRADE assessments related to opioid use. The certainty of evidence was downgraded for indirectness due to variability in vitamin C dosing across studies. For continuous outcomes, a negative WMD favors vitamin C [Supplementary Table 3].

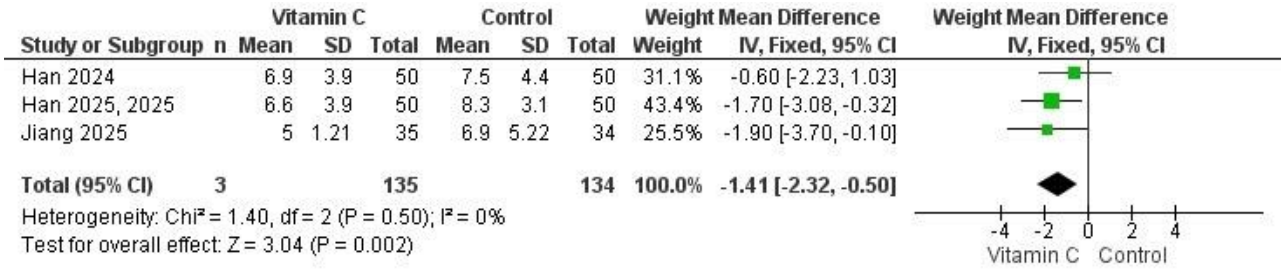

Figure 5. Forest plot of Total Morphine Consumption comparing the vitamin C and control groups. Effect size = Weighted Mean Difference (WMD) with 95% CI; N: number of articles; CI = Confidence Interval; IV = Inverse Variance; SD = Standard Deviation

Inflammatory Response Modulation

Vitamin C supplementation was associated with a significant reduction in postoperative inflammation, with the strongest evidence observed for decreases in C-reactive protein (CRP) and interleukin-6 (IL-6).

•CRP:

The meta-analysis of three studies involving 307 patients undergoing total hip arthroplasty (THA) demonstrated that

vitamin C supplementation significantly reduced C-reactive protein (CRP) levels 24 hours postoperatively (WMD = –11.32 mg/L; 95% CI [–17.90 to –4.74]; P = 0.0007; I^2 = 96%), with evidence of moderate certainty[Figure 6].

No significant effect was observed at 48 hours (P = 0.10) or overall (P = 0.09), both showing high heterogeneity (I^2 > 90%). Han et al. (2024) reported a 40% reduction in CRP at 24 hours (22.33 vs. 37.49 mg/L; P < 0.001), while Han et al. (2025) and Jiang et al. (2025) observed diminishing effects beyond 72 hours.[26,27,30] Supplementary Table 4 presents the GRADE Summary of Findings for CRP, including domain judgments and reasons for downgrading (inconsistency and dose heterogeneity). For continuous outcomes, a negative WMD favors vitamin C [Supplementary Table 4].

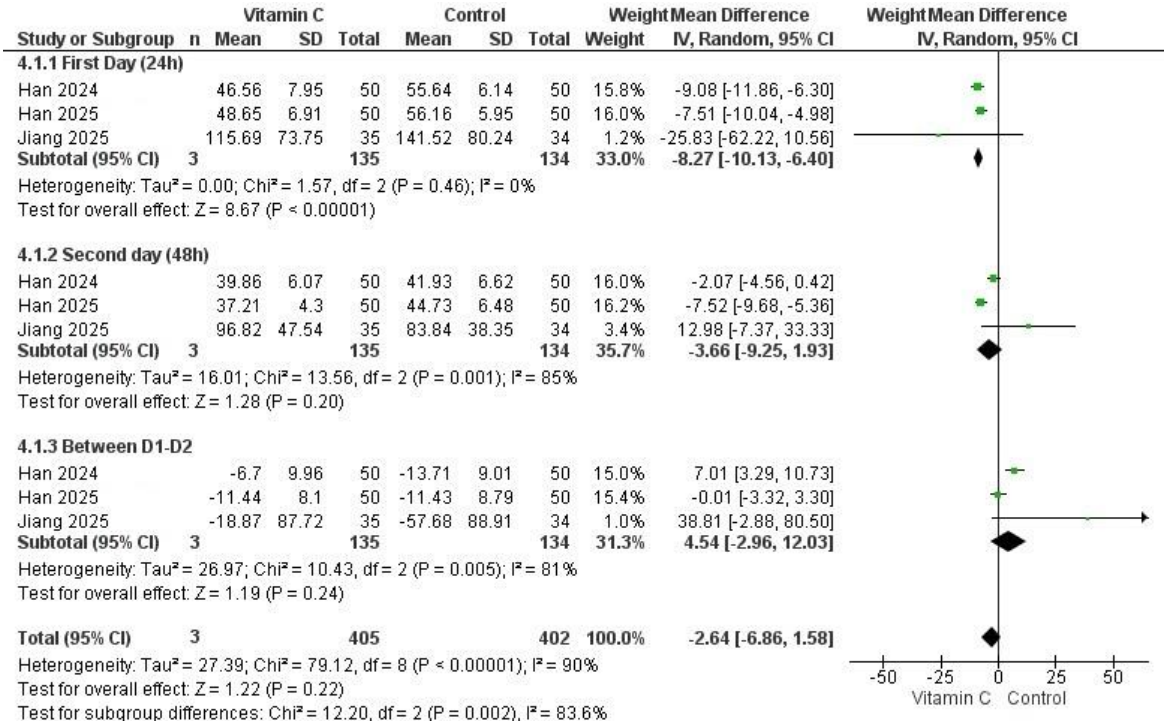

Figure 6. Forest plot of C-reactive protein comparing vitamin C and control groups on postoperative first day (24h), second day (48h), and the change between day 1 and day 2. Effect size = Weighted Mean Difference (WMD) with 95% CI; N: number of articles; CI = Confidence Interval; IV = Inverse Variance; SD = Standard Deviation; D = Day

•IL-6:

The meta-analysis of three studies involving 307 patients undergoing total hip arthroplasty (THA) showed that vitamin C supplementation significantly reduced interleukin-6 (IL-6) levels 24 hours postoperatively (WMD = –8.27 pg/mL; 95% CI [–10.13 to –6.40]; P < 0.0001; I^2 = 0%), with evidence of moderate certainty [Figure 7].

No significant effect was observed at 48 hours or in the overall estimates (P > 0.05), both showing high heterogeneity (I^2 > 90%). Han et al. (2024) reported lower IL-6 levels at 24 hours (51.36 vs. 60.35 pg/mL; P < 0.001), while Han et al. (2025) and Jiang et al. (2025) observed diminishing effects beyond 72 hours.[26,27,30] The certainty of the evidence was rated as moderate. Supplementary Table 5 summarizes the GRADE findings for IL-6 at 24 hours, 48 hours, and between days 1 and 2, with downgrading for heterogeneity and dose variation. For continuous outcomes, a negative WMD favors vitamin C [Supplementary Table 5].

Functional Recovery and Long-Term Outcomes

Evidence for functional improvement, including range of motion (ROM) and mobility, was limited and inconsistent. Behrend et al. (2018) conducted a study in patients undergoing total knee arthroplasty (TKA) and found no significant differences in ROM or in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 12 months (P > 0.05).[22] Han et al. (2024, 2025) observed improved flexion ROM on postoperative day 1 compared with controls following a single dose of vitamin C. [26,27] With multiple doses, flexion improved further; however, no significant differences were detected in extension or abduction during the 72-hour follow-up.

Jacques et al. (2021) investigated total knee arthroplasty (TKA) and reported a lower incidence of complex regional pain syndrome (CRPS) with vitamin C supplementation; however, the study did not provide quantitative data to support this finding.[24] Han et al. (2024, 2025) observed

improved flexion range of motion (ROM) on postoperative day 1 compared with controls following a single dose of vitamin C.[26,27] With multiple doses, flexion improved further; however, no significant differences were detected in extension or abduction during the 72-hour follow-up.

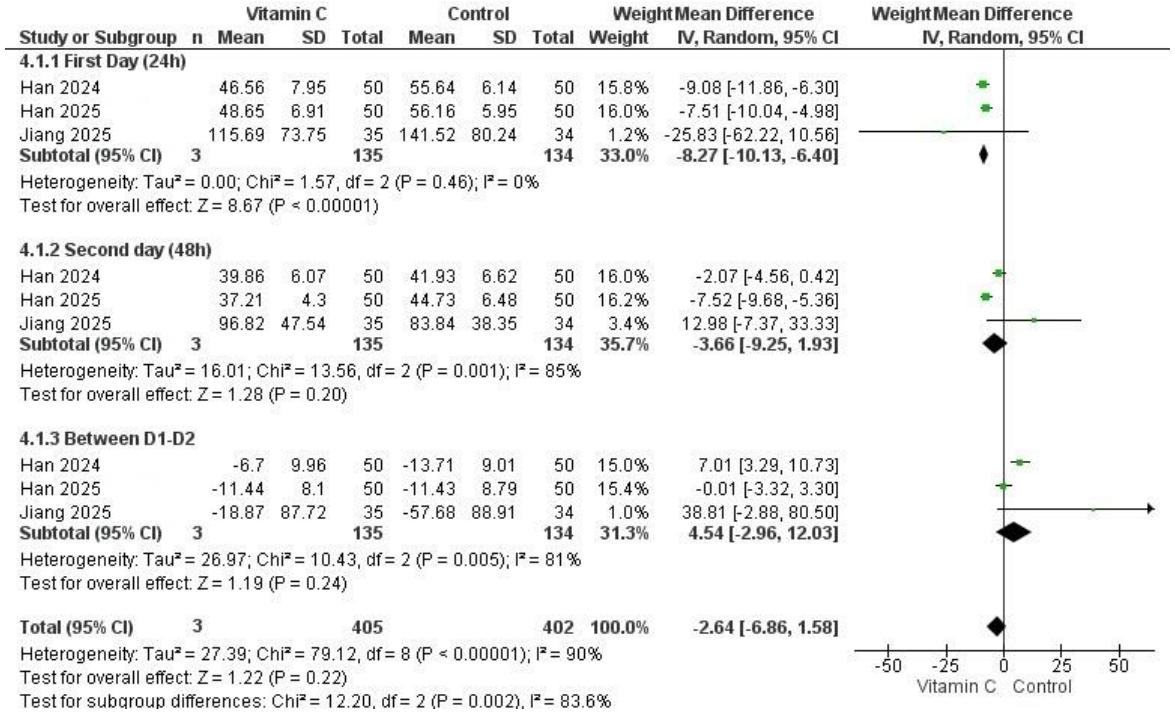

Figure 7. Forest plot of interleukin-6 comparing vitamin C and control groups on the postoperative first day (24h), second day (48h), and the change between day 1 and day 2. Effect size = Weighted Mean Difference (WMD) with 95% CI; N= number of articles; CI = Confidence Interval; IV = Inverse Variance; SD = Standard Deviation; D = Day.

Discussion

This systematic review is the first to comprehensively evaluate the effectiveness of vitamin C supplementation in reducing complications associated with knee and hip surgeries. The findings suggest that vitamin C may help reduce anesthetic requirements, postoperative pain, intraoperative and postoperative complications, opioid consumption, and inflammatory responses, while potentially improving functional outcomes such as range of motion (ROM).

Perioperative Complications

Emerging evidence suggests that vitamin C supplementation may reduce the required dose of propofol during surgery, potentially offering advantages over conventional anesthetic adjuvants. In a clinical trial, Li et al.[25] reported a significant reduction in propofol use among elderly patients who received vitamin C, an important finding given the dose-related adverse effects of propofol, such as hypotension and respiratory depression. Conventional agents such as midazolam, while effective, are associated with risks including cognitive impairment and hemodynamic instability.[32] In contrast, vitamin C is a water-soluble antioxidant with a well-established safety profile and demonstrated neuroprotective properties.[13,33,34] Preclinical studies further support its anesthetic-sparing effects: Guo et al.[35] observed reduced propofol requirements in rodents, and Ochigbo et al. demonstrated enhanced anesthetic depth in goats without cardiovascular complications.

The role of vitamin C in reducing perioperative blood loss during arthroplasty remains inconclusive. Although its antioxidant and endothelial-stabilizing properties provide a theoretical rationale for potential hemostatic benefits, current evidence is limited and inconsistent.[36] In a randomized controlled trial, Hosseini-Monfared et al.[31] reported a 36% reduction in postoperative bleeding 24 hours after intraoperative vitamin C administration in patients undergoing total knee arthroplasty (TKA). In contrast, Jiang et al.[30] found no significant difference in blood loss among patients undergoing total hip arthroplasty (THA). Notably, all participants in both the TKA and THA trials received standardized perioperative tranexamic acid protocols (1 g IV before tourniquet inflation plus 1 g intra-articularly at closure in the TKA study[31]; 2 g IV 15–30 minutes pre-incision and 1 g IV eight hours postoperatively in the THA study).[30] Similarly, Abu-Zaid et al.[18] observed reduced transfusion requirements and shorter operative

times with vitamin C supplementation during myomectomy, but no significant reduction in intraoperative bleeding or postoperative hemoglobin drop.

These mixed findings underscore the need for further high-quality randomized controlled trials in orthopedic populations. Vitamin C shows promise as a propofol-sparing adjunct and appears to be safe in the perioperative setting; however, the current evidence is insufficient to recommend its routine use for hemorrhage prevention in arthroplasty patients.

Postoperative Complications

Postoperative nausea and vomiting (PONV) are common following joint replacement, with reported incidences ranging from 20% to 83%, potentially affecting recovery and patient satisfaction.[37] Jiang et al.[30] observed a lower incidence of PONV in patients receiving intraoperative vitamin C, suggesting a potential antiemetic effect that warrants further investigation.

Effective pain management after joint replacement is critical for optimal recovery. Although intra-articular corticosteroids are frequently administered during arthroplasty to reduce postoperative pain, their use may be limited due to potential side effects.[38] Vitamin C represents a promising adjunct because of its analgesic potential, low cost, and possible role in reducing postoperative opioid consumption and misuse.[39] However, the current evidence remains preliminary; larger, well-designed trials with standardized dosing regimens are needed to confirm the analgesic efficacy of vitamin C and to determine the optimal timing and dosage in perioperative settings. Jiang et al.[30] demonstrated that vitamin C could similarly alleviate pain, reduce analgesic requirements, and attenuate inflammatory markers, comparable to the effects of dexamethasone—a corticosteroid commonly used as an anti-inflammatory agent in patients undergoing total hip arthroplasty (THA).

The analgesic mechanism of vitamin C differs from traditional pathways by scavenging reactive oxygen species (ROS) and protecting tissues and peripheral nerves from oxidative injury and inflammation-mediated pain.[40,41] It also acts as a cofactor in the synthesis of neurotransmitters and neuropeptides, including enkephalins, and may modulate the expression of genes involved in pain pathways.[39,41,42] However, recent clinical studies have shown no significant difference in pain relief between vitamin C and control groups. A single perioperative dose often confers little benefit, likely due to vitamin C's short half-life and the need for frequent replenishment.[27] Conversely, protocols employing repeated dosing have demonstrated significant pain reduction at 48 and 72 hours postoperatively.[26] A recent systematic review by Mędrzycka-Dąbrowska et al.[43] further supports preoperative vitamin C supplementation, reporting reduced opioid requirements and lower incidence of severe pain, suggesting a potential role for vitamin C within multimodal analgesic regimens.

Reducing postoperative pain after joint replacement is essential for minimizing opioid consumption. Meta-analyses indicate that perioperative vitamin C supplementation reduces morphine requirements after hip arthroplasty and decreases overall opioid use, including the need for rescue analgesia, in musculoskeletal surgeries.[41] Similarly, a systematic review by Hung et al.[44] confirmed significant reductions in pain intensity and opioid consumption within 24 hours post-surgery, supporting the potential effectiveness of intraoperative vitamin C administration.

Vitamin C exerts anti-inflammatory effects by downregulating proinflammatory cytokines such as interleukin-6 (IL-6) and by inhibiting nuclear factor kappa-B (NF-κB) activation through its antioxidant activity, which reduces reactive oxygen species (ROS) generation and IκB kinase activity[45-48] It also modulates neutrophil function by suppressing hypoxia-inducible factor-1 (HIF-1) signaling.[49] The present meta-analysis demonstrates that vitamin C supplementation reduces IL-6 and C-reactive protein (CRP) levels within 24 hours after surgery; however, these differences compared with controls did not reach statistical significance, suggesting a biological effect that may not consistently translate into clinical benefit.

Ellulu et al.[45] demonstrated that vitamin C suppresses the acute-phase response and decreases inflammatory cytokines, particularly interleukin-6 (IL-6). Further studies have shown that combined supplementation with vitamins C and E can reduce systemic IL-6 responses by approximately 50% and prevent IL-6 release from contracting skeletal muscle.[48] Consistent with these findings, Han et al. (2024)[27] reported that a single intraoperative dose of vitamin C reduced C-reactive protein (CRP) levels by 40% and significantly decreased IL-6 concentrations within the first 24 hours postoperatively. In a subsequent study, Han et al.[26] demonstrated that multiple doses of vitamin C sustained reductions in CRP and IL-6 levels for up to 72 hours after surgery. Similarly, Roman et al.[29] found that high-dose vitamin C reduced erythrocyte sedimentation rate (ESR) and CRP levels for up to 8 days postoperatively. Collectively, these findings suggest that higher doses or more frequent administration of vitamin C may prolong its anti-inflammatory effects.

Existing studies demonstrate substantial variability in vitamin C administration protocols, including differences in dosage, route of delivery (intravenous, oral, or combined), and timing relative to surgery (pre-, intra-, or postoperative). Repeated dosing appears to provide more consistent analgesic and anti-inflammatory effects, likely because vitamin C has a short plasma half-life. Intravenous administration offers greater bioavailability and more stable plasma concentrations than oral administration. This heterogeneity limits the generalizability of current evidence and underscores the need for standardized, well-designed clinical trials to determine the optimal dosing strategy and route of administration.

Arthrofibrosis is a common complication following total knee arthroplasty (TKA) and total hip arthroplasty (THA).[50,51] Behrend et al. reported that although the mean knee range of motion (ROM) was similar between groups at one year, patients receiving vitamin C experienced significantly lower rates of arthrofibrosis. Moreover, a

greater intraoperative decline in plasma vitamin C levels (exceeding 30 μmol/L) was associated with a higher incidence of arthrofibrosis, suggesting that perioperative vitamin C depletion may be more critical than baseline levels. Han et al.[22] found that a single intraoperative dose of vitamin C improved hip flexion within 24 hours, while multiple doses enhanced ROM for up to 72 hours postoperatively.[26,27] Given vitamin C's short plasma half-life of approximately two hours, administering two to three doses per day may provide more sustained therapeutic benefits.[52]

Limitations and Recommendations

This study has several limitations. The number of eligible trials was limited, primarily due to variations in study design and outcome reporting. High heterogeneity across studies hindered the ability to perform subgroup, sensitivity, and comprehensive risk-of-bias analyses. The follow-up periods were generally short, often restricted to the duration of hospitalization. Furthermore, most studies did not assess preoperative vitamin C levels, making it challenging to determine baseline status or prior supplementation. Considerable variation in vitamin C dosage, frequency, and timing of administration further limits the comparability of findings.

Future studies should adopt high-quality designs with larger sample sizes, longer follow-up durations, and broader variable assessment, including surgical duration, anesthetic requirements, blood loss, hemoglobin levels, wound healing, postoperative complications, and joint arthrofibrosis. Further research is also needed to investigate different vitamin C doses, dosing frequencies, and administration timing, as well as to compare intravenous versus oral delivery to determine the most effective regimen.

Conclusion

This review suggests that vitamin C supplementation may reduce opioid consumption, inflammation, and blood loss in patients undergoing joint surgery. Although several included studies were of high methodological quality, variations in dosage and outcome measures contributed to substantial heterogeneity, thereby limiting the overall strength of the evidence. Given its favorable safety profile and plausible biological mechanisms, vitamin C appears to be a promising perioperative adjunct. However, larger, well-designed randomized controlled trials are warranted to determine the optimal dosage, further elucidate its effects on pain and inflammation, and assess long-term clinical outcomes.

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Authors Contribution:

Authors who conceived and designed the analysis: Shideh Moftakhari Hajimirzaei, Adel Ebrahimpour

Authors who collected the data:
Shideh Moftakhari Hajimirzaei, Masumeh Bagherzadeh Cham, Seyed Morteza Tabatabaee

Authors who contributed data or analysis tools:
Shideh Moftakhari Hajimirzaei, Masumeh Bagherzadeh Cham, Seyed Morteza Tabatabaee

Authors who performed the analysis:
Mohammadreza Dolikhani

Authors who wrote the paper: Shideh Moftakhari Hajimirzaei, Mohammadreza Dolikhani

Other contribution: Mohammadreza Dolikhani, Adel Ebrahimpour

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Shideh Moftakhari Hajimirzaei MD [1,2,3]
Masumeh Bagherzadeh Cham PhD [3]
Mohammadreza Dolikhani MD [1,2]
Seyed Morteza Tabatabaee MD [3]
Adel Ebrahimpour MD [1,2]

1 Department of Orthopedic Surgery,Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Clinical Research Development Unit, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Clinical Biomechanics and Ergonomics Research Center, Department of Physical Medicine and Rehabilitation, AJA University of Medical Sciences, Tehran, Iran

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Supplementary Tables

Supplementary Table 1. Database search strategies and yields.

Database	Search strategy	Number of Studies
Pubmed	("Hip Joint"[MeSH Terms] OR "Knee Joint"[MeSH Terms] OR ("knee"[Text Word] OR "hip"[Text Word])) AND ("vitam*"[Text Word] OR "ascorb*"[Text Word] OR "Ascorbic Acid"[MeSH Terms] OR "vitamin c"[Text Word]) AND ("replacement"[Text Word] OR "surgery"[Text Word] OR ("Arthroplasty"[Text Word] OR "operation"[Text Word]) OR ("surgery"[MeSH Subheading] OR ("Arthroplasty"[MeSH Terms] OR "arthroplasty, replacement, knee"[MeSH Terms] OR "arthroplasty, replacement, hip"[MeSH Terms] OR "arthroplasty, replacement"[MeSH Terms]) OR "surgical procedures, operative"[MeSH Terms]) OR ("replac*"[Text Word] OR "operat*"[Text Word] OR "arthroplast*"[Text Word] OR "surg*"[Text Word]))	1665
Embase	('hip joint'/exp OR 'hip joint' OR 'knee joint'/exp OR 'knee joint' OR 'knee' OR 'hip') AND ('ascorbic acid'/exp OR 'ascorbic acid' OR 'vitamin c') AND ('replacement'/exp OR 'replacement' OR 'surgery'/exp OR 'surgery' OR 'knee arthroplasty'/exp OR 'knee arthroplasty' OR 'hip arthroplasty'/exp OR 'hip arthroplasty' OR 'knee replacement'/exp OR 'knee replacement' OR 'hip replacement'/exp OR 'hip replacement')	615

Supplementary Table 1. Continued		
Scopus	((“Hip Joint" OR "Knee Joint”) AND ("vitam*" OR "ascorb*" OR "Ascorbic Acid" OR "vitamin c") AND ("replacement" OR "surgery" OR "Arthroplasty" OR "operation" OR "replac*" OR "operat*" OR "arthroplast*" OR "surg*"))	237
Web of Sciences	TS= ((("Hip Joint" OR "Knee Joint" OR "knee" OR "hip") AND ("vitam*" OR "ascorb*" OR "Ascorbic Acid" OR "vitamin c") AND ("replacement" OR "surgery" OR "Arthroplasty" OR "operation" OR "replac*" OR "operat*" OR "arthroplast*" OR "surg*")))	1958

Full database-specific strategies and initial yields for the systematic search. Queries combined joint terms (hip/knee arthroplasty), vitamin C terms (vitam*, ascorb*, Ascorbic Acid/MeSH), and surgical/replacement terms using Boolean operators. Field tags: PubMed (MeSH & Text Word), Embase (EMTREE exp), Scopus (Title/Abstract/Keywords), and Web of Science Topic (TS=). Truncation (*) captured word stems; quotation marks indicated exact phrases. No language or date limits were applied at the search stage. Records retrieved: PubMed = 1,665; Embase = 615; Scopus = 237; Web of Science = 1,958(see Methods for deduplication and screening)

Supplementary Table 2. Vitamin C compared to Placebo for Pain after Hip Arthroplasty

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Vitamin C	Relative effect (95% CI)	Risk with Placebo	Risk difference with Vitamin C
pain											
807 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	402	405	-	402	MD **0.01 lower** (0.26 lower to 0.23 higher)
pain - First day (24h)											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	134	135	-	134	MD **0.35 lower** (0.96 lower to 0.26 higher)
pain - Second day (48h)											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	134	135	-	134	MD **0.05 lower** (0.65 lower to 0.54 higher)
pain - Between D1-D2											
269 (3 RCTs)	not serious	not serious	serious[b]	not serious	none	⨁⨁⨁◯ Moderate[b]	134	135	-	134	MD **0.22 higher** (0.11 higher to 0.33 higher)

Supplementary table 2 **CI:** confidence interval; **MD:** mean difference/ **Legend:** GRADE SoF for postoperative pain after hip arthroplasty. Columns show GRADE domains and overall certainty; effect measure is **MD (95% CI). Negative MD favors vitamin C/ Footnotes:** a = downgraded for **inconsistency (I^2>50%)**; b = downgraded for **dose heterogeneity.** “Anticipated absolute effects” do not apply to continuous outcomes.

Supplementary Table 3. Vitamin C compared to Placebo for Morphine consumption after Hip Arthroplasty

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Vitamin C	Relative effect (95% CI)	Risk with Placebo	Risk difference with Vitamin C
Morphine											
269 (3 RCTs)	not serious	not serious	serious[a]	not serious	none	⨁⨁⨁◯ Moderate[a]	134	135	-	134	MD **1.41 lower** (2.32 lower to 0.5 lower)

Supplementary table 3 **CI:** confidence interval; **MD:** mean difference/ **Morphine (GRADE SoF)/ Legend:** GRADE SoF for morphine consumption (morphine equivalents), **MD (95% CI); negative MD favors vitamin C/Footnote:** a = downgraded for **dose heterogeneity.** "Anticipated absolute effects" are not applicable to continuous outcomes

Supplementary Table 4. Vitamin C compared to Placebo for CRP after Hip Arthroplasty

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Vitamin C	Relative effect (95% CI)	Risk with Placebo	Risk difference with Vitamin C
C-reactive protein											
807 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	402	405	-	402	MD **4.33 lower** (4.98 lower to 3.67 lower)
C-reactive protein - First day (24h)											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	134	135	-	134	MD **11.03 lower** (12.07 lower to 9.99 lower)
C-reactive protein - Second day (48h)											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	134	135	-	134	MD **3.54 lower** (4.57 lower to 2.51 lower)
C-reactive protein - Between D1-D2											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⨁⨁◯◯ Low[a,b]	134	135	-	134	MD **7.27 higher** (5.8 higher to 8.73 higher)

GRADE SOF for hemostatic outcomes [specify Hb drop / total blood loss / transfusion]. Effect size is MD (95% CI) for continuous outcomes and OR (95% CI) for binary outcomes. Negative MD or OR < 1 favors vitamin C/ Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; SOF, summary of findings/ **Footnotes:** a = inconsistency (I^2 > 50%); b = dose heterogeneity; c = imprecision (few events/wide CI)/ **Note:** For binary outcomes (e.g., transfusion), 'Anticipated absolute effects' should reflect the observed control-group baseline risk/**CI:** confidence interval; **MD:** mean difference

Supplementary Table5. Vitamin C compared to Placebo for IL-6 after Hip Arthroplasty

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Vitamin C	Relative effect (95% CI)	Risk with Placebo	Risk difference with Vitamin C
IL-6											
807 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⊕⊕◯◯ Low[a,b]	402	405	-	402	MD **2.64 lower** (6.86 lower to 1.58 higher)
IL-6 - First Day (24h)											
269 (3 RCTs)	not serious	not serious	serious[b]	not serious	none	⊕⊕⊕◯ Moderate[b]	134	135	-	134	MD **8.27 lower** (10.13 lower to 6.4 lower)
IL-6 - Second day (48h)											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⊕⊕◯◯ Low[a,b]	134	135	-	134	MD **3.66 lower** (9.25 lower to 1.93 higher)
IL-6 - Between D1-D2											
269 (3 RCTs)	not serious	serious[a]	serious[b]	not serious	none	⊕⊕◯◯ Low[a,b]	134	135	-	134	MD **4.54 higher** (2.96 lower to 12.03 higher)

supplementary table 5 GRADE SoF for IL-6 at 24 h, 48 h, and D1–D2; **MD (95% CI); negative MD favors vitamin C/ Footnotes:** a = **inconsistency (I^2>50%);** b = **dose heterogeneity.** "Anticipated absolute effects" are not applicable to continuous outcomes/**CI:** confidence interval; **MD:** mean difference