SYSTEMATIC REVIEW

The Role of Vitamin C Supplementation in Total Knee Arthroplasty Outcomes: A Systematic Review of Randomized Controlled Trials

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Abstract

Objectives: Oxidative stress, inflammation, and endothelial dysfunction contribute to perioperative morbidity following total knee arthroplasty (TKA). Vitamin C (ascorbic acid), an essential antioxidant cofactor, has been proposed to mitigate these pathways. This systematic review evaluates current evidence on perioperative vitamin C supplementation in TKA and its effects on pain, inflammation, blood loss, and postoperative recovery.

Methods: A systematic search of PubMed, Embase, Scopus, and Web of Science was conducted from database inception through July 2025, following PRISMA 2020 guidelines. Randomized controlled trials (RCTs) assessing perioperative vitamin C use in primary TKA were included. Methodologic quality was appraised using the Cochrane Risk-of-Bias tool (RoB 2). Owing to heterogeneity in dosing, timing, and outcomes, results were synthesized narratively.

Results: Ten RCTs involving 1,364 patients met the inclusion criteria. Vitamin C administration varied substantially in dose, route, and timing. Across studies, findings for postoperative pain, inflammatory markers, blood loss, and functional recovery were inconsistent. Several reported numerical trends favors vitamin C, but most outcomes lacked statistical significance or were supported by a single study. Evidence for reduced complex regional pain syndrome (CRPS) was more consistent but still limited by small sample sizes. No major safety concerns were identified.

Conclusion: Current evidence does not support a definitive benefit of perioperative vitamin C supplementation in TKA. While isolated studies suggest potential reductions in inflammation, blood loss, or pain, these findings are not consistent across trials and often lack statistical significance. Larger, methodologically sound RCTs with standardized dosing protocols are needed before recommending vitamin C as a routine perioperative supplement.

Level of evidence: II

Keywords: Blood loss, CRPS, Immune response, Inflammation, Oxidative stress, Total knee arthroplasty, Vitamin C

Introduction

Total knee arthroplasty (TKA) is one of the most successful and frequently performed orthopedic procedures worldwide, yet postoperative pain, inflammation, and functional recovery remain substantial determinants of patient satisfaction and rehabilitation outcomes.[1,2] The surgical insult associated with TKA induces a cascade of oxidative stress, cytokine release, and endothelial dysfunction, contributing to postoperative pain, swelling, and delayed mobilization.[3,4] These processes not only influence short-term recovery but may also impact long-term joint function and the risk of complications such as complex regional pain syndrome (CRPS).[5,6]

Vitamin C (VC) is a water-soluble antioxidant with well-

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established roles in collagen synthesis, immune modulation, and endothelial protection.[7,8] Beyond its nutritional function, vitamin C acts as an enzymatic cofactor in carnitine biosynthesis and catecholamine regulation, while also neutralizing reactive oxygen species generated during surgical trauma. Experimental and clinical data suggest that adequate vitamin C levels may support tissue repair, mitigate inflammation, and enhance microvascular integrity, which are all relevant to perioperative recovery.[9,10]

In the orthopedic literature, vitamin C has been explored primarily in fracture healing, soft-tissue repair, and prevention of CRPS after limb surgery.[11,12] Its application in the arthroplasty setting, however, has received comparatively limited investigation. Emerging randomized controlled trials (RCTs) have proposed potential benefits of perioperative vitamin C supplementation in TKA, including reduced postoperative pain,[13] decreased blood loss,[4] lower inflammatory markers,[9] and improved early knee function. Nevertheless, dosing strategies, timing, and routes of administration remain heterogeneous, and the overall quality and consistency of evidence have not been critically appraised. Given the growing interest in optimizing perioperative recovery and minimizing opioid consumption through multimodal strategies, vitamin C supplementation represents an appealing, low-cost intervention with plausible biological and clinical rationale. Yet, the evidence base remains fragmented. Therefore, this systematic review aims to synthesize current clinical evidence regarding the perioperative use of vitamin C in total knee arthroplasty, focusing on its effects on pain, inflammation, blood loss, functional recovery, and safety. By critically evaluating the methodological rigor and consistency of reported outcomes, this review seeks to clarify whether vitamin C supplementation confers meaningful clinical advantages in the modern TKA setting.

Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines[14] and followed a predetermined methodology, which was recorded in the Prospective Register of Systematic Reviews under registration ID (CRD420251158711). To ensure the thoroughness of the study, instructions from the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5, 2024) were also followed.[15]

Search Strategy

A complete search up to July 2025 through Medline/PubMed, Scopus, Web of Science, and Embase was conducted. A systematic method combining keywords and Medical Subject Headings (MeSH) terms was used to identify relevant studies. The following terms were used:

("Knee Arthroplast*" OR "Knee Replacement*" OR TKA OR "knee surger*" OR “knee prosthes*”) AND (“Vitamin-C” OR “Vitamin C” OR “L-ascorb*” OR Ascorb* OR Magnorbin)

The complete database-specific search strategy is available in the Supplementary Material.

Eligibility Criteria

English and non-English articles comprising cross-sectional, cohort, case-control, and clinical trials that evaluated supplementation with VC in TKA candidates were considered for inclusion. No restrictions were imposed upon the publication year. Case reports, case series, letters, cadaveric studies, molecular and cellular studies, and review articles were excluded. Studies were included if vitamin C was administered in at least one arm, either as the primary intervention or as part of a comparator group.

Study Selection and Data Extraction

Two independent reviewers (E.N. and M.S.) screened the retrieved articles blindly based on the eligibility criteria. A data extraction Google Sheet was created to extract data from full-text documents. The detailed outlines of data extraction included: First Author, publication year, country, number of TKA candidates, number of supplemented and non-supplemented patients, mean age, number of males and females, mean Body Mass Index (BMI), follow-up duration, and addressed outcomes. The same two authors from the previous team (E.N. and M.S.) independently extracted the data according to the predefined sheet. In case of any discrepancies, reviewers attempted to resolve the issue through discussion. If required, a third reviewer (F.V.) was consulted to facilitate an agreement.

Risk of Bias assessment

To assess the risk of bias in the included studies, the Cochrane Risk of Bias Tool (RoB 2) for RCTs.[16] RoB 2 evaluates bias across five domains: 1) randomization process, 2) deviations from intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported result. Each domain is rated as “low risk”, “some concerns”, or “high risk”. No numerical scoring system is used. Two independent reviewers (I.M.O. and G.N.) performed the assessments, and a senior reviewer (F.V.) was recalled to resolve any disagreements. Results were visualized using RobVis-generated traffic light and summary plots.[17]

Data synthesis

A structured narrative synthesis was created by grouping the results into outcome categories. Quantitative meta-analysis was not feasible due to the heterogeneity in outcomes.

Results

In total, 193 studies were identified through the implementation of the search strategy. After removing the duplicate studies, 119 studies were left for title-abstract screening, of which 93 were excluded. Of the remaining 26 studies, full-text screening identified 10 relevant studies for inclusion in this systematic review. The screening process is summarized in [Figure 1].

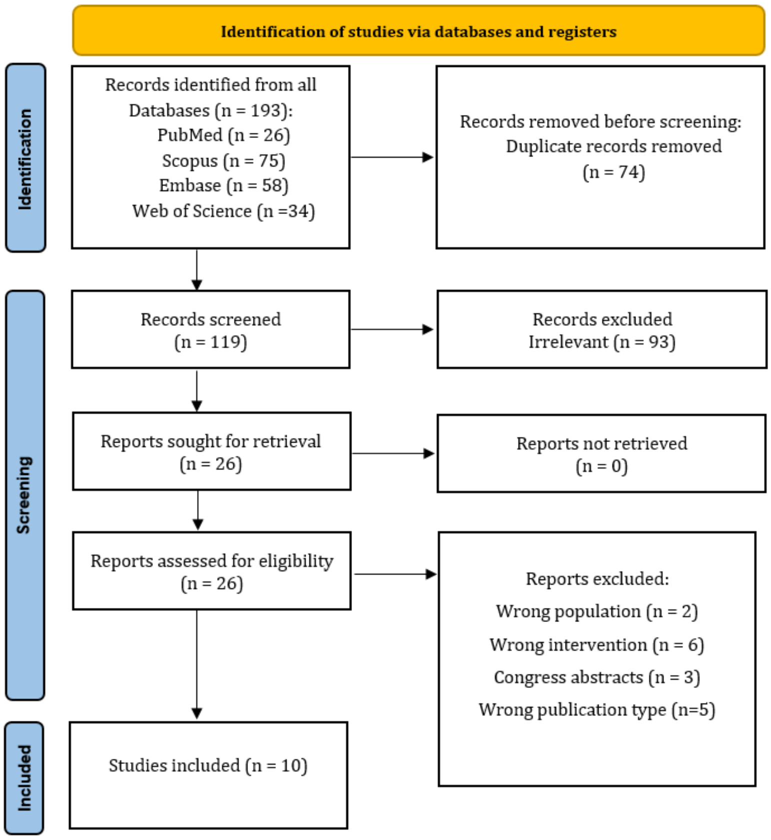

Figure 1. The PRISMA flowchart for inclusion of the studies

All ten included studies were RCTs. [9,13,18-25] Two studies were conducted in the USA.[19,22] Countries including Spain,[25] Belgium,[21] France,[13] Germany,[9] Switzerland,[23] Korea,[26] China,[20] and Iran[18] each contributed one study. A total of 1,364 patients were included in the analysis. The average age across the studies ranged from 43.9 to 71. Nine studies reported gender-specific data, resulting in a male-to-female ratio of 454/844. Key data for each study are summarized in [Table 1]. A detailed summary of vitamin C supplementation protocols is also summarized in [Table 2].

Table 1. Study characteristics of the included studies

Study	Country	No. supplemented patients	No. not supplemented patients	Mean age	SD of age	Mean follow-up (months)	Main outcomes
Hosseini-Monfared et al., 2025 [26]	Iran	59	59	69.43	6.32	6	Postop. Hb, TBL, Hb drop, WOMAC, OKS, FJS, KOOS
LeBrun et al., 2024 [18]	USA	86	86	67.3	8.7	3	PSQI, KOOS-JR, LEAS, VAS, VR-12 PCS, VR-12 MCS, total number of MMEs prescribed
Ramón et al., 2023 [4]	Germany	110	110	66	13.75		CRP, ESR
Jacques et al., 2021 [21]	Belgium	153	139	69.4	8.56		CRPS-1
Li et al., 2021 [25]	China	15	21	68.0	6.45		Total infusion dose of propofol, the average maintenance dose, and induction dose of propofol

Table 1. Continued

Barker et al., 2021 [19]	USA	10	11	N.R		6	serum 25(OH)D, VCc, plasma αT, TNF-α, post-operative IL-6, hsCRP , IL-6/IL-10 ratio
Cazeneuve et al., 2020 [22]	France	44	22	43.9	9.25	12	CRPS
Behrend et al., 2018 [23]	Switzerland	48	47	48.5		12	ROM, AF, WOMAC, FJS-12, VCc
Lee et al., 2010 [24]	Korea	16	16	70.3	4.15	NR	Oxygen free radical production, CPK-MB, serum MDA, MAP, Arterial pressure, $PaCO_2$
Cuenca et al., 2007 [20]	Spain	156	156	70.5	5.5	NR	ABT, Postop Hb

Abbreviations: SD: standard deviation, NR: not reported, Postop Hb: Postoperative Hemoglobin, OKS: Oxford Knee Score, TBL: Total Blood Loss, PSQI: Pittsburgh Sleep Quality Index, KOOS-JR: Knee Injury and Osteoarthritis Outcome Score for Joint Replacement, LEAS: Levels of Emotional Awareness Scale, VAS: Visual Analog Scale, VR-12 PCS and MCS: Veterans Rand 12 Physical Component Score (PCS) and Mental Component Score (MCS), MME: morphine milligram equivalents, CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, 25(OH)D: 25-hydroxy vitamin D, VCc: plasma Vitamin C concentration, αT: α-tocopherol, hs-CRP: high-sensitivity CRP, CRPS: Complex Regional Pain Syndrome, ROM: Range of Motion, AF: Arthrofibrosis:, WOMAC: Western Ontario and McMaster Universities Arthritis Index, FJS-12: Forgotten Joint Score-12, CPK-MB: Creatine phosphokinase-MB, MDA: Malondialdehyde, MAP: Mean Arterial Pressure, ABT: Allogenic Blood Transfusion

Table 2. A summary of the supplementation methods

Study	Supplementation component	VC Dosage	Supplementation protocol
Hosseini-Monfared et al., 2025	Vitamin C	All three: 1 g in 10 mL	First dose: IV at the beginning of the surgery Second dose: IV after tourniquet release Third dose: IV during the first 6 h. after TKA
LeBrun et al., 2024	Vitamin C	125 mg	125 mg VC placebo nightly for 6 weeks following surgery
Ramón et al., 2023	Vitamin C	15g	Parenteral dosage of 15 g of VC after surgery
Jacques et al., 2021	Vitamin C	1g/day	1g per day of oral VC for 40 days after surgery
Li et al., 2021	Vitamin C	0.067 g/kg	0.067 g/kg in a Murphy's dropper, along with anesthesia
Barker et al., 2021	Multivitamin tablet with mineral supplement	N.R	Twice daily starting ~ 6 weeks before and concluding 6 months after surgery. Supplements were not taken the day of surgery and for the first 2 days after surgery while patients were receiving inpatient care.
Cazeneuve et al., 2019	Vitamin c	Group 1: 500 mg Group 2: 500 mg	Group 1: liposomal form, in the morning and evening, for 28 days, starting one week before surgery Group 2: classical VC tablets in the morning and evening for 28 days, starting one week before surgery
Behrend et al., 2018	Vitamin C	1000 mg/day	Oral VC for 50 days
Lee et al., 2010	Vitamin C	Priming bolus: 0.06 g/kg Followed by 0.02g/kg	priming bolus of 0.06 g/kg VC with 100 ml saline followed by 0.02g/kg VC mixed with 30 mL saline, IV
Cuenca et al., 2007	Iron ferrous sulphate, Vitamin C, folic acid	1000mg/day	Iron ferrous sulphate (256 mg/day; 80 mg of Fe2+), VC (1000 mg/day), and folic acid (5 mg/day) during the 30-45 days preceding surgery

Abbreviations: VC: Vitamin C, IV: Intravenous, N.R: Not reported

Risk of Bias Assessment

Among the 10 RCTs, two were assessed to have a high risk of bias,[9,20,23] one was considered to have some concerns,[23,25] and the remaining seven studies were deemed to have a low risk of bias. A higher risk of bias was primarily observed in the first and second domains of the RoB 2 tool, indicating bias arising from the randomization process and bias due to deviations from the intended intervention. The visualized risk-of-bias assessment results for the included studies are shown in [Figures 2A and 2B].

Pain Outcomes

A total of four studies reported pain-related outcomes in TKA patients with VC supplementation.[9,13,19,21] Two studies evaluated CRPS as an outcome in these patients.[13,21] The trial by Cazeneuve compared VC supplementation in liposomal form and classical VC tablets with placebo pills.[13] A one-year follow-up for the liposomal VC group showed no cases of CRPS or any major loco-regional complications, including hematoma, deep infection, dislocation, general thromboembolic events, or cardio-neurovascular complications. In the classical VC supplementation group, three cases of CRPS with one pain syndrome were confirmed by scintigraphy. In the placebo group, five cases of CRPS were confirmed by scintigraphy. This indicates that liposomal encapsulated VC provides protection against CRPS compared with no VC administration. Another study by Jacques et al. assesses the effect of VC on CRPS after TKA.[21] This study shows that the prevalence of CRPS was 3.9% in the VC group, which was significantly lower compared to 12.2% in the control group ($p = 0.008$). The results of the multivariate regression analysis also identified VC as an independent preventive factor for CRPS (relative risk, 0.27; 95% confidence interval, 0.1–0.8; $p = 0.015$). Ramón et al. compared the administration of 15g VC in the postoperative period with a control group. They concluded that patients who received VC experienced reduced pain and required fewer analgesics compared to the control group.[9]

One RCTs administered 125 mg VC as a placebo comparator, with melatonin as the intervention.[19] Although VC was not the primary treatment of interest, outcomes from the VC arm were extracted. The VAS score improved statistically in both the melatonin and VC groups 6 weeks and 90 days postoperatively, but no significant difference was found when comparing the VC and melatonin groups.

Figure 2. (A) Traffic-light plot for risk of bias assessment; (B) Summary plot for risk of bias assessment.

Objective Functional Outcomes

Two studies reported outcomes related to functional recovery after TKA with VC supplementation.[9,23] Ramón et al. reported that patients who received VC experienced improved mobility after TKA surgery.[9] A randomized clinical trial evaluating the range of motion (ROM) in patients receiving VC supplementation and those receiving a placebo showed that the median ROM for both groups was 115° [23]; thus, no significant difference was observed between the two study groups at one year postoperatively. Also, the difference in WOMAC scores and FJS-12 scores between the VC and control groups was not statistically significant.

Patient-Reported Outcome Measures (PROMs)

Three included studies evaluated PROMs. The two studies assessing the Western Ontario and McMaster Osteoarthritis Index (WOMAC) found that although patients who received VC showed slightly better WOMAC scores postoperatively, the difference between the VC and control groups was not significant in either study,[18,23] with one study reporting a p-value of 0.284.[18] This result was also consistent for the Forgotten Joint score-12 (FJS-12) in both of the same studies. Two studies evaluated the Knee Injury and Osteoarthritis Outcome Score (KOOS).[18,19] LeBrun et al. found that KOOS scores showed significant improvements at 6 weeks or 90 days postoperatively in the placebo VC group.[19] This result was also consistent for the Levels of Emotional Awareness Scale (LEAS), Visual Analog Scale (VAS), Veterans Rand 12 Physical Component Score and Mental Component Score (VR-12 PCS and MCS). However, the VR-12 MCS worsened at 6 weeks before returning to the preoperative baseline in the placebo arm only. Hosseini Monfared et al.'s study evaluated the effect of VC supplementation on KOOS score in comparison with the control group and found no significant difference between the two groups.[18] Evaluation of the Oxford Knee Score (OKS) postoperatively also showed no significant difference in these two groups (39.26 ± 4.62 vs. 36.24 ± 7.74; $p = 0.189$).

Inflammatory and Immune Responses

Two studies evaluated the effect of VC supplementation on inflammatory markers and immune responses after TKA.[9,22] Ramón et al. found a statistically significant difference in median CRP values between the two groups ($p < 0.001$).[9] The VC supplementation group had a significantly lower CRP level compared to the control group (21 mg/L [range: 8-42] vs. 42 mg/L [range: 20-79]). Similarly, the ESR values were significantly lower in the VC group compared to the control group (11 mm/h [range: 5-21] vs. 21 mm/h [12-42]; $p < 0.001$). Barker et al. assessed the effect of multivitamin supplementation on various inflammatory markers in TKA patients.[22] Serum TNF-α, IL-8, highly sensitive CRP (hsCRP), IL-6, Systemic Inflammatory Response Index (SIRI), Systemic Immune-Inflammation Index (SII), and Neutrophil-to-Lymphocyte (NLR) were not significantly different between the multivitamin and control groups ($p > 0.05$). However, the increase in serum IL-6/IL-10 at 24 hours and 48 hours was significantly lower in the multivitamin group ($p < 0.05$).

Oxidative stress and antioxidant status

Three studies evaluated plasma ascorbic acid (AA) levels in different groups.[23,26] Behrend et al.'s study demonstrated that preoperative AA concentration did not differ significantly in the two VC and placebo groups.[23] However, AA concentrations were markedly higher in the VC supplementation group 4 and 7 days after surgery ($p < 0.001$).

Barker et al. showed that multivitamin containing vitamins C, D, and E supplementation tended to increase serum 25(OH)D concentrations and plasma AA and αT concentrations prior to surgery. [22] Although serum 25(OH)D levels showed no significant difference from the placebo group after surgery, plasma AA remained notably higher in the multivitamin group, and plasma αT decreased more in the placebo group than in the multivitamin group.

Lee et al. assessed malondialdehyde (MDA) levels after tourniquet application in TKA patients.[26] They understood that MDA levels were significantly lower in the VC group compared to the control group after removing the first and second tourniquets ($p < 0.05$).

Hematological and Blood loss

Two studies assessed the impact of VC supplementation on blood loss after TKA.[18,25] One study by Hosseini-Monfared et al. evaluated blood loss by measuring the Hemoglobin (Hb) drop and found that patients who received VC supplementation experienced a lower Hb drop (1.30 ± 0.72 vs. 1.91 g/dL ± 0.84; p-value < 0.001) and less total blood loss on the first postoperative day (463.60 ± 274.37 vs. 732.11 ± 347.78; p-value < 0.001).[18] In the VC supplementation group, fewer patients reached the minimum clinically significant difference for Hb drop than the control group (15.3% vs 52.5%, p-value < 0.001). Additionally, this study demonstrated that the administration of VC is associated with a decrease in the likelihood of developing postoperative anemia (P = 0.002, Odds Ratio = 8.643; 95%CI = 2.193-34.063).

Cuenca et al. conducted a study to evaluate the requirement for allogenic blood transfusion (ABT) in TKA candidates.[25] One group was given preoperative haematinics, including ferrous sulphate, vitamin C (1000 mg/day), and folic acid. The results showed that compared to the control group, those following the blood-saving protocol and receiving haematinics had a significantly lower transfusion rate (5.8% vs. 32%; $p < 0.01$).

Cardiac and Hemodynamic Outcomes

Lee et al.'s study on free radical production and myocardial enzymes showed that CPK-MB (creatine phosphokinase-MB) levels decreased after surgery in the VC group compared to the control group.[26] However, this difference was not statistically significant ($p > 0.05$). Additionally, postoperatively, Troponin I levels were significantly lower in the VC group than in the control group ($p < 0.05$). The assessment of Mean arterial pressure (MAP) indicated that MAP was significantly lower after the first tourniquet deflation in the control group compared to the VC group ($p < 0.05$). However, no significant differences were observed between the two groups after the second tourniquet deflation. PaO_2 was found to be significantly higher after deflation of the second tourniquet in the VC group compared to the control group ($p < 0.05$).

Behrend et al. assessed the prevalence of arthrofibrosis (AF) at 1-year follow-up in patients who received or did not receive oral VC supplementation.[23] The prevalence of AF was 5 out of 48 patients (10.4%) in the VC group, compared to 11 out of 47 patients (23.4%) in the control group. However, this result was not statistically significant ($p = 0.09$).

A study by Li et al. compared the adverse events of IV vitamin C administration during anesthesia for TKA with the control group.[20] The results of this study showed that no significant difference was seen in the MAP during and after intubation between the VC and control groups. Likewise, there was no significant difference in the incidence of intraoperative hypotension (76.2% vs 60%; $p = 0.465$). This study also showed that VC administration resulted in no significant difference in the time of induction of anesthesia (3 min. (range:2-3) vs. 3 min. (range:2-4); $p = 0.412$), the average induction dose of propofol (1.5 mg vs. 1.4 mg; $p = 0.637$), or the induction dose (100 mg vs. 90 mg; $p = 0.379$). However, the total propofol infusion dose was significantly lower in the VC group (704.3 mg vs. 888.6 mg; $p = 0.016$). This indicates a 20.7% reduction in the total propofol infusion dose with VC administration. Also, the average maintenance dose was found to be lower in the VC group compared to the control group (5.8 ± 1.0 mg/kg/h vs. 6.9 ± 1.6 mg/kg/h; $p = 0.013$).

Discussion

This systematic review suggests that perioperative vitamin C supplementation may attenuate postoperative inflammation, blood loss, and pain in patients undergoing total knee arthroplasty (TKA). Across 10 randomized controlled trials, the signal for benefit was consistent in direction but modest in magnitude. Despite biological plausibility and encouraging early outcomes, the collective evidence remains preliminary and insufficient to support routine clinical implementation. Our study shows that VC supplementation provides clinical benefits across several compelling areas, particularly in CRPS, blood loss mitigation, and systemic inflammation. The most clinically relevant finding of our review is the prophylactic effect of VC of CRPS following TKA. A meta-analysis of eight studies revealed that VC supplementation reduces CRPS-I after limb surgery.[27]

However, this result was not statistically significant. Also, several meta-analyses have concluded that daily vitamin administration may reduce the incidence of CRPS following distal fracture surgery.[28-30] The underlying reason for this pain reduction may be the antioxidant properties of VC, which help reduce inflammation and oxidative stress. Furthermore, ascorbic acid's involvement in the production of various neurotransmitters, including serotonin and dopamine, may be important for pain perception.[8,31] Edema and inflammation are the primary triggers of CRPS following surgery, and VC's anti-inflammatory properties may also underlie this preventive effect.[32] The use of liposomal VC in one of the included studies also warrants further investigation into the clinical efficacy and bioavailability of the supplementation.[13]

Ascorbic acid supplementation was associated with clear improvements in hematological outcomes. The findings of Hosseini-Monfared et al. and Cuenca et al. indicated significant reductions in total blood loss, Hb drop, and ABT requirement.[18,25] VC's involvement in collagen remodeling regulation, vascular endothelium stabilization and maintaining capillary integrity can justify the highlighted results.[24] Moreover, the known anti-inflammatory properties of VC in the perioperative setting led to reduced levels of inflammatory markers, namely CRP and ESR.[9,33]

The interpretability of these findings is constrained by marked heterogeneity in study design, dosing regimens, and outcome definitions. Vitamin C administration varied widely from low-dose oral supplementation to single high-dose intravenous boluses making direct comparisons and pooled quantitative analysis unfeasible. This substantial heterogeneity in vitamin C dosing, timing, routes of administration, and outcome definitions across trials made a narrative synthesis unavoidable. This approach, while appropriate under these conditions, carries inherent interpretive subjectivity and prevents quantitative pooling of effect sizes, limiting the precision of the conclusions. Follow-up durations were short, typically limited to early recovery, and most trials were single-center studies with modest sample sizes. Risk-of-bias assessment identified deficiencies in allocation concealment and blinding in several trials. These methodological limitations temper confidence in the observed effects.

Another limitation of our review is that only ten RCTs met the inclusion criteria. The small number of eligible studies limits overall statistical power, hinders evaluation of consistency across findings, and reduces the generalizability of the review's conclusions. A further limitation of this review is that several included trials did not report p-values, effect sizes, or confidence intervals for key outcomes. This incomplete statistical reporting restricted our ability to evaluate the precision of those findings.

Given its low cost, safety, and mechanistic plausibility, vitamin C represents an appealing adjunctive intervention in perioperative TKA care. However, the existing evidence does not yet justify universal supplementation. At present, clinicians should consider vitamin C use within the context of ongoing research or in high-risk patients where oxidative stress may be pronounced (e.g., diabetics, smokers, or patients with poor nutritional status). Routine use outside of a study protocol is premature. Future research should prioritize multicenter, adequately powered RCTs employing standardized dosing, timing, and administration routes. Comparative studies evaluating intravenous versus oral formulations are particularly needed, as pharmacokinetic differences may influence efficacy. Integration of patient-reported outcome measures and long-term follow-up would help determine whether biochemical benefits translate into durable functional improvements. Finally, dose–response modeling and pharmacodynamic studies could clarify the therapeutic threshold necessary to achieve clinical benefit without unnecessary supplementation.

Conclusion

Perioperative vitamin C supplementation following total knee arthroplasty is biologically plausible and appears safe, with emerging evidence of modest benefit in reducing inflammation, blood loss, and early postoperative pain. However, heterogeneity and limited sample sizes preclude definitive recommendations. Vitamin C should be viewed as a promising but unproven adjunct; further high-quality trials are required to establish optimal dosing strategies and confirm clinical efficacy.

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