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Vitamin C in cardiac surgery: a narrative review

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Abstract

Cardiothoracic surgery, particularly when involving extracorporeal circulation, is associated with a systemic inflammatory response and oxidative stress resulting from the ischemia-reperfusion phenomenon. This phenomenon leads to the release of free radicals, causing cellular damage, activation of pro-inflammatory signaling pathways, and depletion of endogenous antioxidants. These processes contribute to various perioperative complications, including postoperative atrial fibrillation, pulmonary complications and endothelial dysfunction. Due to its antioxidant properties, vitamin C has been proposed to exert a protective effect against these adverse responses and to potentially enhance postoperative recovery.

This narrative review aims to evaluate the role of vitamin C in cardiothoracic surgery and to examine its potential benefits with regard postoperative atrial fibrillation, fatigue, etomidate-induced adrenergic inhibition, cardiac allograft vasculopathy, postoperative pulmonary complications, endothelial function, vasoplegia, acute renal failure, biochemical markers and erythrocytes integrity.

The only outcomes with consistent evidence of benefit from vitamin C supplementation were a reduction in the incidence of postoperative atrial fibrillation, an improvement in endothelial function and a reduction in oxidative stress. Further large-scale, multicenter randomized controlled trials are warranted to establish the optimal dosage, timing of administration and specific patient populations that may derive the greatest benefit from vitamin C administration.

Keywords: **Ascorbic acid, Vitamin C, Thoracic Surgery, Cardiac Surgical Procedures.**

Introduction

Cardiothoracic surgery, particularly when involving extracorporeal circulation, is associated with a systemic inflammatory response and oxidative stress primarily driven by ischemia–reperfusion injury. This process triggers a significant release of free radicals that contribute to postoperative organ dysfunction[1].

Intraoperative oxidative stress damages mitochondrial structures, impairs vascular endothelial function, and disrupts nitric oxide signaling, ultimately leading to cellular apoptosis and clinical manifestations such as myocardial injury, arrhythmias, impaired cardiac output, acute respiratory distress syndrome, pulmonary edema, and renal failure[2].

Moreover, reactive oxygen species (ROS) activate pro-inflammatory pathways and promote cytokine release through various biochemical mechanisms including nitrosylation, carbonylation, disulfide bond formation, and glutathionylation[3]. This widespread oxidative insult results in a marked depletion of endogenous antioxidant reserves, by approximately 70% within the first 24 hours postoperatively, with levels often remaining suppressed for up to two weeks[4].

Vitamin C, or ascorbic acid (AA), is a potent water-soluble antioxidant that serves as an effective free radical scavenger[5], thereby mitigating oxidative cellular injury[6]. Free radicals can be derived from oxygen species (ROS) or from nitrogen and sulfur compounds[3]. Vitamin C

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also contributes to the regeneration of vitamin E (α-tocopherol), reinforcing cellular antioxidant defenses[7].

Humans rely entirely on dietary intake for vitamin C, a dependency resulting from the evolutionary loss of the gene responsible for endogenous synthesis, attributed to the historical abundance of vitamin C-rich plants over 60 million years ago. A daily intake of 100 to 200 mg is generally sufficient to maintain plasma concentrations between 50 and 75 µmol/L[8].

Patients undergoing cardiac surgery frequently exhibit low plasma levels of vitamin C, largely due to increased metabolic consumption driven by oxidative stress. Numerous clinical studies have investigated the role of vitamin C supplementation in this setting. Despite the relevance of this topic, given that approximately 1.5 million cardiac surgeries are performed worldwide each year, there are currently no established clinical guidelines regarding its perioperative use[9]. Key questions remain concerning the optimal dosing regimen, timing of administration, and potential clinical benefits of vitamin C in the context of cardiothoracic surgery.

The aim of this narrative review is to synthesize the current body of evidence regarding the effects of perioperative vitamin C supplementation on postoperative outcomes in cardiothoracic surgery.

Methodology

Although this article is not a systematic review, the literature search and study selection process were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework to promote methodological transparency and reproducibility.
The research question was structured using the PICO format as follows:

- P (Population): Adult patients undergoing cardiothoracic surgery
- I (Intervention): Administration of vitamin C
- C (Comparator): Any other intervention or no intervention
- O (Outcomes): Clinical benefits associated with vitamin C administration.

Literature search

A comprehensive bibliographic search was performed in October 2024 using the MEDLINE database via PubMed, covering the period from January 2000 to October 2024. The search was restricted to studies published in English and involving human subjects. A free-text keyword approach was used to construct the search strategy, with terms applied to the [Title/Abstract] field. Boolean operators OR and AND were employed to ensure both sensitivity and specificity of the query. The full MEDLINE search strategy is detailed in Table I.

Study selection

Only primary studies reporting clinical outcomes in human subjects were considered for inclusion. The following exclusion criteria were applied:

- Articles published in a language other than English
- Animal or in vitro studies
- Studies involving patients under 18 years of age
- Abstracts or articles without full-text availability
- Narrative or systematic reviews and meta-analyses

The initial screening was based on titles and abstracts to exclude clearly irrelevant records. This screening was performed by reviewer Q.L. Full texts of all potentially eligible studies were then retrieved and independently assessed by the same reviewer to determine final inclusion in the narrative review.

Data extraction

For each included study, relevant data were manually extracted and organized into thematic domains. The following data were collected:

- Study characteristics: first author, year of publication, country, and study design
- Population: sample size, type of cardiothoracic procedure, and demographic characteristics
- Intervention: vitamin C dosage, route and timing of administration
- Comparator(s): placebo, standard care, or no treatment
- Reported outcomes: clinical endpoints including atrial fibrillation, vasoplegia, renal function, fatigue, oxidative stress, and other postoperative complications.

Data extraction was conducted by reviewer Q.L. and findings were categorized thematically based on the primary clinical outcome investigated. These domains were subsequently used to structure the presentation of results in the Results and Discussion sections. While not exhaustive, the selected themes reflect the most consistently reported or clinically relevant outcomes identified in the reviewed literature.

Each domain is discussed in terms of the reported findings, proposed mechanisms of action, and potential implications for perioperative care. Given the narrative nature of this review, no quantitative

Table I. — Research strategy.

#	Research terms	# of results
1.	"cardiac surg*"[Title/Abstract]	61,383
2.	"cardiac surgery"[Title/Abstract]	55,786
3.	"thoracic surg*"[Title/Abstract]	24,689
4.	"thoracic surgery"[Title/Abstract]	18,371
5.	"heart valve prothesis implantation"[Title/Abstract]	1
6.	"heart transplantation"[Title/Abstract]	21,865
7.	"heart bypass"[Title/Abstract]	883
8.	"coronary artery bypass"[Title/Abstract]	49,462
9.	"extracorporeal membrane oxygenation"[Title/Abstract]	20,263
10.	"atrial fibrillation"[Title/Abstract]	104,707
11.	"troponin"[Title/Abstract]	35,743
12.	"ascorbic acid"[Title/Abstract]	40,928
13.	"vitamin C"[Title/Abstract]	30,291
14.	"ascorbic acid"[Title/Abstract] OR "vitamin c"[Title/Abstract]	64,782
15.	"troponin"[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR "extracorporeal membrane oxygenation"[Title/Abstract] OR "coronary artery bypass"[Title/Abstract] OR "heart bypass"[Title/Abstract] OR "heart transplantation"[Title/Abstract] OR "heart valve prothesis implantation"[Title/Abstract] OR "thoracic surgery"[Title/Abstract] OR "thoracic surg*"[Title/Abstract] OR "cardiac surgery"[Title/Abstract] OR "cardiac surg*"[Title/Abstract]	296,027
16.	("vitamin c"[Title/Abstract] OR "ascorbic acid"[Title/Abstract]) AND ("troponin"[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR "extracorporeal membrane oxygenation"[Title/Abstract] OR "coronary artery bypass"[Title/Abstract] OR "heart bypass"[Title/Abstract] OR "heart transplantation"[Title/Abstract] OR "heart valve prothesis implantation"[Title/Abstract] OR "thoracic surgery"[Title/Abstract] OR "thoracic surg*"[Title/Abstract] OR "cardiac surgery"[Title/Abstract] OR "cardiac surg*"[Title/Abstract])	240
17.	(("vitamin c"[Title/Abstract] OR "ascorbic acid"[Title/Abstract]) AND ("troponin"[Title/Abstract] OR "atrial fibrillation"[Title/Abstract] OR "extracorporeal membrane oxygenation"[Title/Abstract] OR "coronary artery bypass"[Title/Abstract] OR "heart bypass"[Title/Abstract] OR "heart transplantation"[Title/Abstract] OR "heart valve prothesis implantation"[Title/Abstract] OR "thoracic surgery"[Title/Abstract] OR "thoracic surg*"[Title/Abstract] OR "cardiac surgery"[Title/Abstract] OR "cardiac surg*"[Title/Abstract])) AND ((casereports[Filter] OR clinicaltrial[Filter] OR controlledclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (fft[Filter]) AND (humans[Filter]) AND (2000/1/1:2024/10[pdat]) AND (english[Filter]) AND (alladult[Filter]))	31

data pooling or statistical meta-analysis was performed.

Quality appraisal

Although the present work is a narrative review, its methodological quality was assessed with the Scale for the Assessment of Narrative Review Articles (SANRA)[10]. SANRA examines six domains: (i) justification of the article's importance for the readership, (ii) explicit statement of objectives, (iii) detailed description of the literature search, (iv) completeness and accuracy of referencing, (v) soundness of scientific reasoning, and (vi) appropriate presentation of data.

The finalized manuscript attained a SANRA score of 10 out of 12, indicating a high methodological standard and adherence to recommended best practices for narrative reviews. Residual limitations related to heterogeneity of study designs, potential reporting bias, and the intrinsic constraints of narrative synthesis are addressed in the Discussion section.

Data synthesis

No meta-analysis or quantitative synthesis was conducted. Instead, the findings from included studies were narratively synthesized and grouped according to recurring clinical themes. Within each thematic domain, results were described and interpreted with particular attention to the proposed mechanisms of action of vitamin C, the consistency of reported outcomes, and their potential implications for perioperative management in cardiothoracic surgery.

Results

What does the current date tell us in the following setting?

1. Postoperative atrial fibrillation (POAF)

Postoperative atrial fibrillation (POAF) is the most frequent arrhythmia following cardiac surgery, affecting 20-40% of patients undergoing procedures with cardiopulmonary bypass[11], and up to 62% in those undergoing combined coronary artery bypass grafting (CABG) and valve surgery[12]. POAF is associated with increased 30-day and 6-month mortality, with the highest risk occurring in the immediate postoperative period[13]. The pathophysiology of POAF is multifactorial, with ischemia-reperfusion-induced inflammation and oxidative stress recognized as central contributors[14].

Several studies suggest that both preoperative and postoperative vitamin C supplementation may reduce the incidence of POAF, primarily through its antioxidant effects. In 2007, Eslami et al. demonstrated that the combination of a beta-blocker and vitamin C significantly reduced POAF incidence compared to beta-blocker alone (4% vs. 26%, $p = 0.002$)[15]. This result is consistent with findings from subsequent trials evaluating vitamin C monotherapy[16,17]. However, other studies reported no significant reduction in POAF with vitamin C supplementation[12,18,19].

Of note, Stranger et al. observed a reduction in oxidative stress biomarkers in patients receiving antioxidant supplementation[20].

In 2017, Petersen et al. further investigated the mechanistic role of oxidative stress in POAF pathogenesis[21]. Right atrial biopsies were performed to assess the expression and distribution of connexins (gap junction proteins) in cardiomyocytes. These cells are electrically and mechanically coupled via intercalated discs, forming a synchronized functional syncytium. Intercalated discs consist primarily of connexins Cx40, Cx43, and Cx45. Oxidative stress has been shown to disrupt the expression and localization of connexins, particularly promoting lateralization, a process believed to favor arrhythmogenesis.

In the study, participants received either placebo or a combination of n-3 polyunsaturated fatty acids (n-3 PUFA), vitamin C, and vitamin E. Both placebo/POAF and supplemented/POAF groups showed elevated levels of ROS and nitrotyrosine residues compared to patients who remained in sinus rhythm. Interestingly, in the supplemented/POAF group, lateral expression of Cx40 and Cx43 was reduced. However, no downregulation of Cx40 or upregulation of Cx45 (a connexin associated with slowed conduction and pro-arrhythmic remodeling) was observed. These findings suggest that although exogenous antioxidants may not completely prevent oxidative damage, they could modulate atrial remodeling.

Collectively, the available evidence supports a potential role for vitamin C in the prevention of POAF. However, outcome variability across studies highlights the need for adequately powered randomized controlled trials to confirm its clinical efficacy and to define standardized protocols for its use in cardiac surgery (Table II).

2. Fatigue

Fatigue is a multidimensional construct that encompasses physical and mental exhaustion, diminished activity, and reduced motivation to engage in daily life[22]. Among patients undergoing CABG, the prevalence of fatigue may reach up to 50%, significantly impacting both physical and psychological recovery, and posing barriers to effective postoperative rehabilitation.

The etiology of postoperative fatigue is multifactorial and includes oxidative stress[22], immune dysregulation, and hypothalamic-pituitary axis dysfunction, which may result in reduced cortisol secretion[23]. Given its potent antioxidant properties, vitamin C has been investigated as a potential therapeutic agent for alleviating postoperative fatigue.

In a triple-blind randomized controlled trial, Gholami et al. assessed the effects of vitamin C combined with n-3 PUFA on fatigue levels in patients undergoing CABG with cardiopulmonary bypass (CPB)[22]. Fatigue was measured using the Multidimensional Fatigue Inventory (MFI-20), a validated 20-item questionnaire evaluating five domains: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Assessments were conducted one hour before surgery, six hours after surgery, and on postoperative day five.

The results showed a statistically significant reduction in fatigue scores on postoperative day five ($p < 0.0001$). These findings are clinically relevant, as they suggest that vitamin C supplementation may promote earlier mobilization, enhance postoperative recovery, and support a faster return to functional independence in the home setting (Table III).

3. Etomidate-induced adrenergic inhibition

Etomidate is a short-acting hypnotic agent frequently used for the induction of general anesthesia in cardiac patients due to its favorable hemodynamic profile. However, etomidate is known to cause transient suppression of adrenal function by

Table II. — Use of vitamin C for Postoperative Atrial Fibrillation (POAF).

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Antonic et al., 2017	Prospective, randomized, controlled trial	105 elective on-pump CABG *	Preoperative: 2g AA** one daily and 2h before surgery Postoperative: 1g AA** twice daily for 5 postoperative days	I.V.***	Standard of care
2	Bjordahl et al., 2012	Prospective, randomized, placebo-controlled, triple-blind study	185 CABG *	Preoperative: 2g AA** the evening before surgery Postoperative: 1g AA** twice daily for 5 postoperative days	P.O.°°°	Placebo
3	Colby et al., 2011	Randomized, double-blind, placebo-controlled trial	24 cardiothoracic surgeries with either on-pump or off-pump cardiopulmonary bypass or valve replacement	Preoperative: 2g AA** the night before surgery Postoperative: 500mg AA** twice daily for 4 postoperative days	P.O.°°°	Placebo
4	Dehghani et al., 2014	Prospective, randomized, controlled trial	100 elective, isolated, on-pump CABG*	Preoperative: 2g AA** before surgery Postoperative: 500mg AA** twice daily for 5 postoperative days	P.O.°°°	Standard of care
5	Eslami et al., 2007	Prospective, randomized controlled trial	100 scheduled isolated CABG*	Preoperative: 2g AA** the night before surgery Postoperative: 1g AA** twice daily for 5 postoperative days	P.O.°°°	Standard of care
6	Papoulidis et al., 2011	Prospective, randomized, controlled trial	170 electives, isolated on-pump CABG*	Preoperative: 2g AA ** 3 hours before CPB° Postoperative: 500mg AA** twice days for 5 postoperative days	I.V.***	Standard of care
7	Petersen et al., 2017	Randomized, double-blind, placebo-controlled clinical trial with subsequent analysis of atrial tissue samples	203 cardiac surgeries with CPB°	Preoperative: - 2g n-3 PUFA°° daily for 7 days before surgery - 1g AA and 400 UI Vit E**** daily for 2 days before surgery Postoperative: 2g n-3 PUFA°°, 1g AA** and 400 UI Vit E**** daily until hospital discharge	P.O.°°°	Placebo
8	Stanger et al.,2014	Prospective, randomized, double-blind, controlled clinical trial	75 CABG*	Preoperative vitamin group: - 900 mg Vit E**** daily for 10-14 days preoperatively - 2g AA**, 300mg Vit E**** and 600 mg allopurinol the morning of surgery Preoperative n-3 PUFA group: - 2 preoperative infusions of Omegaven® (0.15g of fish oil per kilo of body weight) Preoperative vitamin and n-3 PUFA°° group: - Combination of vitamin and n-3 PUFA°°	I.V.***	Standard of care

* CABG: Coronary Artery Bypass Graft; **AA: Acid Ascorbic; ***I.V.: intravenously; ****Vit E: Vitamin E; ° CPB: Cardiopulmonary Bypass; °° PUFA: Polyunsaturated fatty acids; °°°P.O.: orally.

Table III. — Use vitamin C for fatigue.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Gholami et al.,2019	Randomized, triple-blind, placebo-controlled trial	160 CABG *	Preoperative: 2g n-3 PUFA** and 1g AA° twice daily the day before surgery Postoperative: 2g n-3 PUFA** and 1g AA° twice daily for 5 postoperative days	P.O.°°	Placebo

* CABG: Coronary Artery Bypass Graft; **PUFA: Polyunsaturated fatty acids; ° AA: Acid Ascorbic°°; P.O.: orally.

Table IV. — Use vitamin C for Etomidate induced adrenergic inhibition.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Das et al.,2016	Randomized, double-blind, placebo-controlled trial	70 elective cardiac surgery with CPB*	Preoperative: 500mg AA° twice daily for 7 days before surgery until the morning of surgery	P.O.**	Placebo

*CPB: cardiopulmonary bypass; **P.O.: orally; °AA: Ascorbic Acid.

reversibly inhibiting the enzyme 11β-hydroxylase, resulting in decreased cortisol synthesis and accumulation of its precursor, 11-deoxycortisol.

Ascorbic acid (vitamin C) has been shown to enhance the activity of 11β-hydroxylase and facilitate cortisol biosynthesis by promoting the conversion of 11-deoxycortisol to cortisol[24]. In this context, Das et al. conducted a double-blind, randomized, placebo-controlled trial to evaluate the effect of vitamin C on etomidate-induced adrenal suppression[25]. The study demonstrated that plasma cortisol levels were significantly lower in the placebo group compared to the vitamin C group during various intraoperative phases and across the first 24 hours following anesthetic induction.

In addition, total plasma adrenaline concentrations were significantly higher in the placebo group ($p = 0.047$), suggesting an enhanced stress response in the absence of vitamin C supplementation. However, the between-group difference in noradrenaline levels did not reach statistical significance ($p = 0.064$).

These findings support a potential protective role for vitamin C in attenuating etomidate-induced inhibition of adrenal steroidogenesis and adrenergic activation during the perioperative period (Table IV).

4. Cardiac allograft vasculopathy (CAV)

Cardiac allograft vasculopathy (CAV) is the principal long-term complication limiting survival in heart transplant recipients, affecting up to 70% of patients within three years post-transplantation. Although its exact pathogenesis remains incompletely understood, CAV is believed to result from complex oxidative-reductive (redox) mechanisms associated with allorecognition, endothelial dysfunction, and fibroproliferative responses[26].

In 2002, Fang et al. conducted a double-blind, randomized, placebo-controlled trial involving 40 heart transplant recipients to evaluate the effects of combined vitamin C and vitamin E supplementation on the progression of coronary arteriosclerosis[27]. Intimal thickening was assessed using an intravascular ultrasound-derived intimal index, calculated as the ratio of plaque area to vessel area. Endothelial function was also evaluated at baseline and after one year of treatment.

The results demonstrated a minimal increase in the intimal index in the vitamin-treated group (+0.8%) compared to the placebo group (+8%), indicating a significantly slower progression of coronary artery thickening in the intervention arm. A 10-year follow-up of this cohort showed that continued vitamin C and E supplementation was associated with a significantly lower incidence of CAV and related adverse outcomes, including percutaneous coronary intervention (PCI), myocardial infarction (MI), and CAV-related mortality ($p = 0.015$). Notably, patients initially in the placebo group who later initiated antioxidant therapy also experienced reduced event rates, supporting the long-term vascular benefits of vitamin supplementation (Table V).

5. Postoperative pulmonary complications (PPCs)

CPB is known to elicit a systemic inflammatory response and oxidative stress through multiple mechanisms, including blood contact activation, hypothermia, and ischemia–reperfusion injury. These factors contribute to multiorgan dysfunction, with pulmonary complications occurring in approximately 10% to 25% of cases[28,29]. PPCs are associated with increased morbidity, mortality, and healthcare resource utilization[29].

In 2020, Wang et al. conducted a small-scale, double-blind, randomized placebo-controlled trial

Table V. — Use vitamin C to protect against cardiac allograft vasculopathy.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Fang et al., 2002	Randomized, double-blind, placebo-controlled trial	40 cardiac transplant recipients	Postoperative: 500mg AA* and 400 UI° Vit E°° twice daily for 1 year	P.O.**	Placebo
2	Ujeyl et al., 2011	Randomized, controlled trial with a 10-year follow-up	40 cardiac transplant recipients	1000mg AA* and 800 UI° Vit E°°	P.O.**	Standard of care
*AA: Acid Ascorbic; **P.O.: orally; °UI: International units; °°Vit E: Vitamin E.						

to assess the impact of vitamin C on pulmonary complications following cardiac surgery with CPB[30]. Respiratory outcomes were evaluated using the Postoperative Pulmonary Complications (PPC) score[31], which ranges from 0 to 5: 0 indicates absence of respiratory symptoms, 1 to 4 correspond to increasing severity of complications, 5 represents in-hospital mortality due to pulmonary causes.

The vitamin C group exhibited significantly lower PPC scores compared to the placebo group. Moreover, the incidence of PPCs was reduced in the vitamin C group (12.1% vs. 32.4%, $p = 0.043$). However, no significant differences were observed in secondary outcomes such as recovery time, ICU length of stay, or total hospital stay.

More recently, in 2022, Karadžić Kocica et al. conducted a prospective, single-blind, randomized trial assessing the effect of a parenteral vitamin C-enriched nutritional regimen initiated within 24 hours after CPB[32]. The incidence of PPCs in the intervention group was 13.3%, compared to 60% in the control group ($p < 0.01$). In addition, the severity of complications was significantly lower in patients receiving vitamin C.

These findings suggest a potential protective effect of vitamin C against postoperative pulmonary complications in cardiac surgery, although larger, multicenter trials are needed to confirm these results and evaluate their impact on broader clinical outcomes (Table VI).

6. Endothelial function

The vascular endothelium, which lines the entirety of the circulatory system, plays a central role in coagulation, regulation of vascular tone, and modulation of immune responses. Endothelial dysfunction is commonly observed in conditions such as arterial hypertension, hypercholesterolemia, diabetes, and tobacco use, and is typically characterized by impaired vasodilation due to reduced nitric oxide (NO) bioavailability. As a water-soluble antioxidant, vitamin C has been shown to inhibit NO degradation, thereby supporting endothelial function[33].

This mechanism was investigated by Angdin et al., who conducted a prospective, randomized, double-blind trial assessing whether a combination of antioxidant agents (vitamin C, vitamin E, allopurinol, and N-acetylcysteine) could preserve endothelium-dependent vasodilation in the pulmonary circulation following CPB[34]. Systemic markers of oxidative stress were measured before and after CPB, and pulmonary vascular resistance index (PVRI) was evaluated via pulmonary artery catheterization during an acetylcholine infusion, both after induction of anesthesia and two hours postoperatively.

Table VI. — Use vitamin C to prevent postoperative pulmonary complications.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Karadžić Kočica et al., 2024	Single-center, prospective, randomized, single-blinded, interventional trial	150 elective cardiac surgery with CPB°	Intraoperative: 50mg AA* divided into 3 doses Postoperative: 50mg/kg AA*/6h for 48h (total daily dose 200 mg/kg). Post-discharge: 2g AA* daily for 1 week	I.V.°° and P.O.**	Placebo
2	Wang et al., 2020	Randomized, double-blind, placebo-controlled trial	70 cardiac surgeries with CPB°	Peroperative: 1g AA* C 10 min after induction, 10 min before cardiac reanimation and sternal closure	I.V.°°	Placebo
° CPB: Cardiopulmonary Bypass; °°I.V.: Intravenously; *AA: Acid Ascorbic; **P.O.: orally.						

The results demonstrated that the pulmonary vasodilatory response to acetylcholine was significantly better preserved in the antioxidant-treated group following CPB ($p = 0.048$). In this group, the PVRI reduction induced by acetylcholine was comparable pre- and postoperatively (-24% vs. -20%, $p = 0.422$), whereas in the placebo group it declined markedly from -21% to -8% ($p = 0.026$), suggesting that antioxidant therapy may preserve endothelial function in the pulmonary vasculature.

During CPB, the pulmonary circulation is largely bypassed, rendering lung tissue susceptible to ischemia-reperfusion injury upon restoration of blood flow[35]. This ischemic insult is accompanied by a surge in reactive oxygen species, which is a key driver of post-ischemic endothelial dysfunction. Although the study employed a combination of four antioxidant agents, precluding the identification of the specific contribution of each, the results support a protective effect of antioxidant therapy.

In addition, several studies have independently demonstrated the beneficial effects of vitamin C on endothelium-dependent vasodilation in peripheral arteries, particularly the radial artery, which is frequently harvested as a graft in CABG surgery[36,37] (Table VII).

7. Vasoplegia

Vasoplegia, in the setting of cardiac surgery, is characterized by profound hypotension despite normal or elevated cardiac output, reduced systemic vascular resistance, and increased requirements for intravenous fluids and vasopressor support during or following CPB. Its reported incidence ranges from 5% to 25%[38]. The underlying pathophysiological mechanisms involve CPB-induced systemic inflammation, ischemia–reperfusion injury, and surgical tissue trauma[39]. These insults trigger the release of pro-inflammatory cytokines and vasoactive mediators, while also promoting oxidative stress through excessive production of ROS, which leads to depletion of endogenous antioxidants and contributes to the maintenance of a vasoplegic state[39].

Given its potent antioxidant properties, vitamin C has been proposed as a potential adjunctive therapy in the management of vasoplegia. In 2020, Yanase et al. conducted a double-blind, randomized controlled trial to evaluate the effect of high-dose intravenous vitamin C in patients with vasoplegia following cardiac surgery[40]. The study found no significant differences between the vitamin C and placebo groups with respect to time to vasoplegia resolution or total norepinephrine requirements over the first 48 hours postoperatively. Similarly, there were no statistically significant differences in secondary outcomes, including ICU length of stay, hospital length of stay, ICU mortality, or overall hospital mortality.

Despite these negative findings, the authors emphasized the importance of further research,

Table VII. — Use of Vitamin C to preserve endothelial function.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Angdin et al., 2003	Prospective, randomized, double-blind, placebo-controlled trial	28 scheduled elective cardiac surgery with CPB°	Preoperative: - 900mg Vit E°° 10-14 days before surgery - 2g AA** and 300mg allopurinol the day before and morning of surgery Peroperative: 150mg/kg acetylcysteine bolus during surgery followed by infusion	P.O. *** and I.V.°°°	Placebo
2	Drossos et al., 2003	Study 1: Case-control study Study 2: Randomized, double-blind, parallel-arm trial	Study 1: 30 healthy subjects (15 smokers, 15 non-smokers) Study 2: 30 patients with coronary artery disease awaiting CABG*	Study 1: 2g AA** 1x Study 2: 2g AA**	P.O.***	Study 2: 180mg Diltiazem
3	Uzun et al., 2013	Randomized controlled trial	93 patients awaiting CABG*	Group 1: 2g AA Group 2: 2g AA + 600 mg Vit E	P.O.***	Placebo

* CABG: Coronary Artery Bypass Graft; **AA: Acid Ascorbic; ***P.O.: orally; ° CPB: Cardiopulmonary Bypass; °°Vit E: Vitamin E; °°°I.V.: intravenously.

particularly in well-defined subpopulations, before drawing definitive conclusions regarding the efficacy of vitamin C in the treatment of vasoplegia after cardiac surgery (Table VIII).

8. Acute renal failure

Acute renal failure, more accurately referred to as acute kidney injury (AKI), is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as any of the following: an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours, an increase to ≥ 1.5 times baseline within the previous 7 days, or a urine output of < 0.5 mL/kg/h for at least 6 hours[41]. AKI is characterized by a rapid decline in renal function, impairing the excretion of metabolic waste products, fluid homeostasis, and acid-base regulation.

Following cardiac surgery, the incidence of AKI may reach up to 40% and is associated with increased perioperative morbidity and mortality, prolonged hospitalization, elevated healthcare costs, and a heightened risk of progression to chronic kidney disease [42]. The pathogenesis of AKI in this context is multifactorial and includes renal hypoperfusion, systemic inflammatory responses, oxidative stress, exposure to nephrotoxic agents, and embolic phenomena[43].

In 2018, Amini et al. conducted a randomized controlled trial evaluating the effects of N-acetylcysteine, vitamin C, and selenium on the prevention of AKI in patients undergoing off-pump CABG[44]. Participants were randomized into four groups: vitamin C, selenium, N-acetylcysteine, and control. The study found no significant differences among groups regarding the incidence, severity, onset, or duration of AKI, nor in related morbidity or mortality.

Similarly, in 2022, Djordjevic et al. performed a prospective, randomized controlled trial to assess the impact of perioperative vitamin C administration on the incidence of AKI during the first five postoperative days in patients undergoing cardiac surgery with CPB[42]. Again, no statistically significant reduction in postoperative AKI was observed in the vitamin C group compared to the control.

Collectively, these findings suggest that vitamin C supplementation does not significantly reduce the incidence of AKI in patients undergoing cardiac surgery. However, given the complexity of AKI pathophysiology, further large-scale trials focusing on well-defined patient subgroups are warranted to clarify the potential renoprotective role of antioxidant therapies (Table IX).

9. Biochemical markers

The generation of free radicals during surgical stress and CPB has deleterious effects on mitochondrial function, sarcoplasmic membrane integrity, endothelial cells, and NO production. These alterations contribute to myocardial injury, cardiomyocyte apoptosis, and the development of postoperative arrhythmias.

In 2019, Emadi et al. conducted a randomized, double-blind clinical trial to evaluate the effect of high-dose vitamin C on biochemical markers of myocardial injury, including creatine kinase-myoglobin binding (CK-MB), troponin I, and lactate dehydrogenase (LDH), in patients undergoing CABG[2]. Blood samples were obtained at four time points: anesthesia induction, end of surgery, and 6 and 24 hours postoperatively.

The analysis revealed no statistically significant differences between the vitamin C and control groups in serum levels of CK-MB, troponin I, or LDH. However, a notable difference in left ventricular ejection fraction (LVEF) was observed at 72 hours postoperatively: LVEF decreased by 4.2% in the control group but increased by 0.8% in the vitamin C group ($p = 0.009$). Additionally, the length of stay in the intensive care unit (ICU) was significantly shorter in the vitamin C group ($p = 0.012$).

These findings suggest that while vitamin C may not significantly influence standard biochemical markers of myocardial injury, it could confer functional cardiac benefits and contribute to enhanced postoperative recovery (Table X).

10. Oxidative stress

In 2017, Safaei et al. conducted a randomized controlled trial to investigate whether vitamin

Table VIII. — Use vitamin C to treat vasoplegia.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Yanase et al., 2020	Prospective, double-blind, randomized, placebo-controlled trial.	50 postoperative vasoplegia after cardiac surgery	1500mg/6h AA* until vasoplegia resolution	I.V.°	Placebo

*AA: Acid Ascorbic; °I.V.: intravenously.

Table IX. — Renal failure and Vitamin C.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Amini et al., 2018	Randomized, controlled clinical trial	291 elective off-pump CABG*	Preoperative: 24h before surgery - Selenium group: 0,5mg twice daily - AA** group: 1500mg twice daily - N-acetylcystein group: 600mg twice daily Continued for 2 postoperative days	P.O.°	Standard of care
2	Djordjevic et al., 2022	Prospective, randomized, controlled trial.	332 scheduled cardiac surgery with CPB°°	Peroperative: - 2g AA** before anesthesia - 2g AA** before aortic cross-clamp removal Postoperative: 1g AA**/8h for 5 postoperative days	I.V.***	Standard of care
*CABG: Coronary Artery Bypass Graft; **AA: Acid Ascorbic; ***I.V.: intravenously; °P.O.: orally; °°CPB: Cardiopulmonary Bypass.						

Table X. — Vitamin C and biochemical markers.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Emadi et al., 2019	Double-blind, randomized controlled trial.	50 CABG*	Peroperative: - 5g AA** before anesthesia induction - 5g AA** in cardioplegic solution	I.V.°	Placebo
* CABG: Coronary Artery Bypass Graft; **AA: Acid Ascorbic; °I.V.: intravenously.						

C and grape seed extract (GSE), a natural antioxidant compound rich in vitamins C and E, could attenuate ischemia-reperfusion injury during cardiac surgery with CPB[45,46].

Patients were randomized into three groups: a control group, a GSE group, and a vitamin C group. Blood samples were collected from the coronary sinus via a retrograde cardioplegia cannula at three intraoperative time points: T1: prior to aortic cross-clamping (baseline), T2: during the ischemic phase, just before clamp release, T3: ten minutes after reperfusion.

The following biomarkers were assessed: hematocrit, urea, total antioxidant capacity (via colorimetric assay), malondialdehyde (MDA, a marker of lipid peroxidation), superoxide dismutase (SOD, an enzyme catalyzing superoxide radical dismutation), and glutathione peroxidase (an enzyme that reduces hydrogen peroxide).

The results demonstrated that total antioxidant capacity was significantly higher in both the GSE and vitamin C groups at T2 and T3 compared to the control group ($p < 0.05$). Similarly, MDA levels were reduced in both treatment arms, although only the GSE group exhibited a statistically significant reduction at T3 ($p = 0.04$); the reduction in the vitamin C group did not reach statistical significance ($p > 0.05$). No significant differences in glutathione peroxidase activity were observed among the three groups.

In summary, perioperative supplementation with GSE and vitamin C increased total antioxidant capacity and reduced oxidative stress markers such as MDA, without affecting glutathione peroxidase activity. These findings suggest that the antioxidant effects of vitamin C and GSE are mediated via alternative enzymatic or non-enzymatic pathways (Table XI).

11. Vitamin C and erythrocytes

Erythrocytes play a central role in redox regulation, cellular metabolism, and tissue oxygen delivery[47]. Their deformability is essential for efficient microcirculatory transit and oxygen transport. Oxidative stress during cardiac surgery may impair erythrocyte flexibility, potentially contributing to hemolysis and impaired microvascular perfusion[48].

Table XI. — Vitamin C and oxidative stress.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Safaei et al., 2017	Randomized controlled trial	87 elective CABG*	Preoperative: 100mg/6h GSE** starting 24 hours preoperatively Perop : 25mg/kg AA° via CPB	P.O.*** and I.V.°°	Standard of care
* CABG: Coronary Artery Bypass Graft; **GSE: Grape seed extract; ***P.O.: orally; °AA: Acid Ascorbic; °°I.V.: intravenously.						

In 2022, Tai Y-H et al. conducted a randomized controlled trial investigating the impact of vitamin C on ROS production and erythrocyte deformability during cardiac surgery involving CPB[48]. Erythrocyte membrane deformability was assessed by measuring the phosphorylation of non-muscle myosin IIA (NMIIA), as well as vasodilator-stimulated phosphoprotein (VASP) and focal adhesion kinase (FAK), two cytoskeletal proteins whose phosphorylation is closely associated with membrane flexibility and structural integrity[49].

Following CPB, systemic vascular resistance was significantly higher in the vitamin C group ($p < 0.001$), and ROS elevation was attenuated, although not reaching statistical significance ($p = 0.1073$). Notably, phosphorylation levels of NMIIA, VASP, and FAK were all significantly increased in the vitamin C group compared to the control ($p = 0.0237$, $p = 0.0069$, and $p = 0.0019$, respectively). In addition, phosphorylation of endothelial nitric oxide synthase (eNOS) was significantly higher in the vitamin C group ($p = 0.03$), suggesting enhanced endothelial function.

This study was the first to demonstrate a potential role for vitamin C in preserving erythrocyte membrane integrity and supporting vascular homeostasis during cardiac surgery. These findings suggest that vitamin C may exert protective effects against hemolysis and microcirculatory impairment in patients undergoing CPB (Table XII).

Discussion

Vitamin C is a potent water-soluble antioxidant that plays a central role in protecting cells against oxidative stress. The aim of this narrative review was to synthesize the evidence from the past two decades regarding the use of vitamin C in the setting of cardiac surgery, with a focus on selected clinical and biochemical outcomes.

The findings across studies are heterogeneous. Several investigations have demonstrated beneficial effects, including a reduction in the incidence of postoperative atrial fibrillation (POAF)[15-17], improved endothelial function and vascular reactivity[27,34,36,37], a lower incidence of postoperative pulmonary complications[30,32], and enhanced total antioxidant capacity[45]. Collectively, these results suggest that vitamin C may help mitigate cardiovascular and pulmonary complications associated with cardiac surgery.

However, other studies have failed to demonstrate significant clinical benefits with vitamin C supplementation[2,12,18,19,40,42,44]. This discrepancy may be attributed to heterogeneity in study design, sample size, patient populations, dosing regimens, and routes or timing of administration. Importantly, pharmacokinetics appear to be a critical consideration: peak plasma concentrations occur approximately two hours after oral ingestion, whereas intravenous administration yields immediate peak levels[50], with a plasma half-life of approximately one hour[51]. Therefore, the timing of administration, ideally in close proximity to ischemia-reperfusion events, may be essential for maximizing antioxidant efficacy.

Notably, Karadžić Kocica et al. reported that high-dose intravenous vitamin C was well tolerated and not associated with any adverse events[32], supporting the safety of perioperative administration in cardiac surgery patients.

Conclusion

Although substantial heterogeneity in study designs, patient populations, and intervention

Table XII. — Vitamin C and erythrocytes.

	Author and Year	Study design	Population	Drug regimen in the intervention group	Route	Control group
1	Tai et al., 2022	Randomized, controlled trial	30 cardiac surgeries with hypothermic CPB*	Perop : 20mg/kg AA** during CPB* rewarming	I.V.°	Placebo
* CPB: Cardiopulmonary Bypass; **AA: Acid Ascorbic; °I.V.: intravenously.						

protocols precludes definitive conclusions, vitamin C appears to be a promising adjunctive therapy for the prevention and management of postoperative complications in cardiothoracic surgery. Current evidence suggests that vitamin C supplementation may provide particular benefit in high-risk patient populations. However, the lack of standardized protocols regarding dosage, route of administration, and timing remains a major barrier to its routine clinical use.

Future research should focus on defining optimal administration strategies (including route, timing, and duration) identifying patient subgroups most likely to benefit and adopting standardized clinical outcome measures to enhance comparability and reproducibility across studies.

Ultimately, large-scale, multicenter randomized controlled trials will be required to confirm the clinical efficacy of vitamin C in cardiac surgery and to establish its potential role within standard perioperative care pathways.

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