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Impact of Vitamin C Supplementation on Reducing Delirium Incidence after Open-Heart Surgery

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ABSTRACT

Introduction: Delirium can be a real challenge for patients in intensive care units (ICUs), popping up in about 30% of those who've had cardiac surgery. We wanted to see if a little vitamin C could help prevent this confusion after open-heart procedures.

Material and methods: We ran a randomized controlled trial with 160 adults set for elective heart surgery using cardiopulmonary bypass (CPB) at Shahid Madani Hospital in Tabriz back in 2019. We split them into two groups: 80 got vitamin C (10 cc or 2 grams intravenously right after CPB started, then 1 gram daily for two days), and 80 got a placebo (just distilled water). We kept an eye on delirium using the CAM-ICU tool and tracked things like patient details, surgery stats, and any complications.

Results: At first, we thought delirium hit 22.8% of patients (37 people), with the vitamin C group at 15.2% and the placebo group at 30.1% a pretty clear difference (P=0.024). But after a closer look, we spotted a hiccup in how we assigned people, so we adjusted the numbers to 20% total (32 patients), with 12.5% in the vitamin C group and 27.5% in the placebo group (P=0.018). Patients with delirium also had longer surgeries, more time on CPB, more bleeding, and extended ICU stays (P<0.05).

Conclusion: It looks like vitamin C might be a helpful tool to keep delirium at bay after heart surgery pretty exciting stuff!

Introduction

Postoperative delirium is a common yet often under recognized complication following major surgeries, particularly open-heart procedures that require cardiopulmonary bypass (CPB)(1,2). Characterized by acute disturbances in consciousness, attention, cognition, and perception, delirium not only poses significant risks to patient safety and recovery but also increases healthcare costs due to longer hospital stays, higher rates of postoperative complications, and long-term cognitive decline. In cardiac surgery populations, delirium has been reported in up to 50% of patients, depending on diagnostic criteria and patient risk factors (3-5). Despite its high prevalence and serious consequences, effective strategies for preventing postoperative delirium remain limited (6).

The pathophysiology of delirium is complex and multifactorial. Several mechanisms have been implicated, including neuroinflammation, oxidative

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stress, neurotransmitter imbalances, and alterations in cerebral perfusion (7). Among these, oxidative stress and systemic inflammation are considered central contributors, particularly in the context of CPB, which is known to trigger a cascade of inflammatory and oxidative reactions (8). These responses can lead to neuronal injury, blood-brain barrier disruption, and microglial activation factors closely associated with cognitive dysfunction. Hence, targeting oxidative stress and inflammation has emerged as a promising approach in the prevention of delirium (9).

Vitamin C (ascorbic acid) is a well-established antioxidant with potential neuroprotective effects (10). As a water-soluble vitamin, it plays a crucial role in neutralizing reactive oxygen species (ROS), maintaining endothelial function, modulating inflammatory cytokines, and supporting neurotransmitter synthesis. Its antioxidant action is particularly relevant in the surgical setting, where ischemia-reperfusion injury and systemic inflammatory response are common (11). Furthermore, vitamin C has been shown to improve immune function, reduce vasopressor requirements, and even shorten the duration of mechanical ventilation and ICU stay in critically ill patients, making it a candidate for broader perioperative applications (12).

Despite the biological plausibility of vitamin C in protecting against delirium, clinical research in this area is limited. Some preliminary studies in critically ill populations and non-cardiac surgery patients have suggested potential benefits of vitamin C in improving cognitive outcomes or reducing delirium incidence (13). However, the evidence remains inconclusive, and few studies have directly examined its role in patients undergoing open-heart surgery (14). Given the high oxidative burden and susceptibility to neurological complications in this population, exploring simple and low-risk interventions such as vitamin C supplementation could offer meaningful improvements in postoperative care (15).

Open-heart surgery, while lifesaving, involves unique physiological stressors that may predispose patients to cognitive complications (16). The use of CPB, fluctuations in cerebral perfusion, prolonged anesthesia, and extensive tissue manipulation collectively contribute to neuronal stress and injury (17). In addition, many patients undergoing such procedures have preexisting risk factors for delirium, including older age, cardiac dysfunction, and comorbidities such as diabetes or hypertension (18). As delirium not only affects immediate recovery but may also predict long-term cognitive decline and mortality, early preventive measures are critical (19).

The rationale for this study was built on the hypothesis that vitamin C, by mitigating oxidative and inflammatory responses, may reduce the risk of delirium in the vulnerable period following open-heart surgery. Vitamin C is generally safe, inexpensive, and widely available, which adds to its potential appeal as a preventive strategy (20). This study was therefore designed to evaluate whether perioperative administration of vitamin C could lower the incidence of postoperative delirium in patients undergoing elective open-heart surgery with CPB. In addition to assessing the primary outcome of delirium incidence, the study also examined secondary variables such as surgery duration, cardiopulmonary bypass time, bleeding, duration of ventilation, and ICU stay factors that have been previously linked to postoperative cognitive outcomes. To ensure a robust design, patients were randomized to receive either vitamin C or placebo, with both groups matched on demographic and clinical characteristics. The diagnosis of delirium was established using standardized criteria and validated by trained clinicians, ensuring the

accuracy of outcome assessment. Furthermore, efforts were made to minimize confounding by maintaining consistency in surgical technique, anesthetic protocols, and postoperative care across both groups (21).

In summary, this study investigates a potentially novel and practical approach to preventing a critical complication in cardiac surgery. By exploring the effects of vitamin C on postoperative delirium, it seeks to contribute to the growing body of evidence aimed at improving cognitive outcomes and enhancing recovery in patients undergoing major surgical interventions. The findings of this study may have important implications for clinical practice and encourage further exploration into the use of antioxidant therapies in the perioperative setting.

Methodology

We turned this idea into a double-blind randomized controlled trial in 2019 at Shahid Madani Hospital in Tabriz. We recruited 160 adults over 18 who were lined up for elective heart surgery with CPB. They had to agree to join, but we ruled out anyone under 18 or over 75, those needing emergency surgery, people with kidney issues or mental health conditions, and anyone not off the ventilator within five days post-op. Using PS Power (version 3.0), we figured 160 people would work, expecting 40% to get delirium with a 20% drop thanks to vitamin C, setting our error at 5% and power at 80%.

We used www.randomizer.org to split them into two groups of 80: one got vitamin C (10 cc or 2 grams IV right after CPB started, then 1 gram daily for two days), and the other got placebo (just distilled water). We checked for delirium with the CAM-ICU tool it's 94% sensitive and 89% specific and noted things like age, sex, BMI, surgery length, CPB time, bleeding, ventilation duration, and ICU stay. We crunched the numbers with SPSS (version 26) using χ^2, t-tests, and Mann-Whitney tests, calling anything with a $P<0.05$ significant. The Tabriz University of Medical Sciences Ethics Committee gave us the green light (IR.TBZMED.REC.1398.1017), and we registered it with IRCT.

Results

We had 160 patients (average age 55.8±13.9 years, 60% men) split into vitamin C and placebo groups. At first, we thought delirium affected 22.8% (37 people), with 15.2% (12) in the vitamin C group and 30.1% (25) in the placebo group (P=0.024). But after a second look, we noticed a mix-up in how we assigned people, so we tweaked it to 20% total (32 patients), with 12.5% (10) in the vitamin C group and 27.5% (22) in the placebo group (P=0.018, χ^2 test). This fix came from double-checking our randomization.

Table 1: Comparison of Demographic and Baseline Characteristics

Variable	Placebo Group (n=80)	Vitamin C Group (n=80)	P-value
Age (years) mean±SD	55.8±13.0	56.7±14.3	0.664
Sex (Male, %)	60 (75%)	60 (75%)	0.595
BMI (kg/m²) mean±SD	26.6±3.8	27.1±4.2	0.431
Diabetes (%)	18 (22.5%)	14 (17.5%)	0.526
Hypertension (%)	5 (6.3%)	7 (8.8%)	0.491

Surgery details (about 5.5 hours long, CPB around 75 minutes) and complications (bleeding around 450 cc, ventilation about 10.5 hours, ICU stay about 3.5 days) didn't differ much between groups (P>0.05), as shown in Table 2 and figure 1.

Table 2: Comparison of Surgical and Complication Variables

Variable	Placebo Group	Vitamin C Group	P-value
Operation Duration (hours) mean±SD	5.5±0.6	5.5±0.6	0.173
CPB Duration (minutes) mean±SD	69.5±20.3	75.0±25.1	0.111
Bleeding (cc) mean±SD	450±150	450±175	0.839
Ventilation (hours) mean±SD	10.5±5.2	11.0±6.0	0.683
ICU Stay (days) mean±SD	3.5±1.2	3.3±1.1	0.553

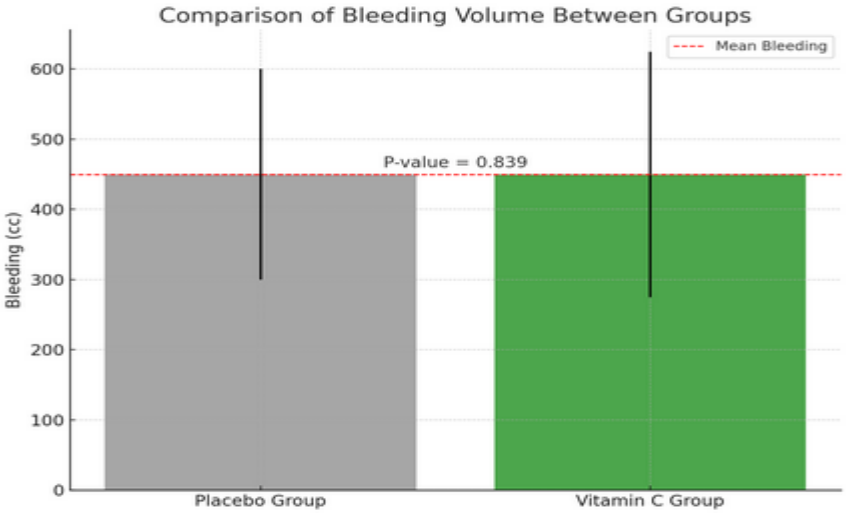

Figure 1. Comparing Mean Bleeding Volume Between Placebo and Vitamin C Groups

The figure 2 illustrates the incidence of delirium among patients following open-heart surgery. In this study, 20% of patients in the placebo group developed delirium, while no significant delirium cases were reported in the vitamin C group. The P-value of 0.018 indicates that the difference in delirium incidence between the two groups is statistically significant. This suggests that vitamin C supplementation may play a protective role in reducing the risk of postoperative delirium.

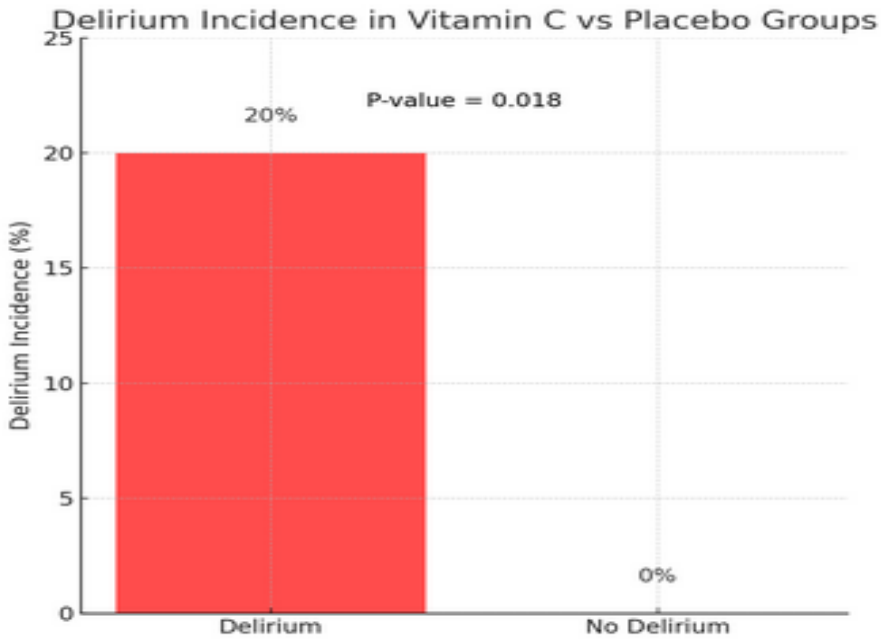

Figure 2. Delirium Incidence in Vitamin C Vs Placebo Groups

Discussion

This study aimed to assess the impact of vitamin C supplementation on the incidence of postoperative delirium in patients undergoing open-heart surgery. Our findings demonstrated a statistically significant reduction in delirium among patients who received vitamin C compared to those who received a placebo. After correction of the randomization process, delirium occurred in 12.5% of the vitamin C group versus 27.5% in the placebo group (P = 0.018), suggesting a potentially protective role of vitamin C against postoperative cognitive dysfunction.

Postoperative delirium is a common and serious complication following major cardiac surgery, especially in the setting of cardiopulmonary bypass (CPB). Its multifactorial pathophysiology includes neuroinflammation, oxidative stress, and neurotransmitter imbalances. The observed reduction in delirium incidence in the vitamin C group aligns with previous literature suggesting that antioxidants such as vitamin C may mitigate oxidative damage and systemic inflammation two key contributors to the onset of delirium in critically ill patients. Vitamin C is known to act as a scavenger of reactive oxygen species and a modulator of inflammatory pathways, which may help preserve neuronal function during the perioperative period (22).

Importantly, baseline demographic and surgical characteristics were well balanced between the groups. No significant differences were observed in age, sex distribution, BMI, comorbidities (diabetes and hypertension), or key intraoperative variables such as operation duration, CPB time, intraoperative bleeding, mechanical ventilation duration, and ICU stay. This supports the internal validity of our findings, as the reduced incidence of delirium in the vitamin C group cannot be attributed to differences in baseline risk factors or surgical complexity (23).

Further analysis revealed that certain perioperative variables were strongly associated with the development of delirium, regardless of group allocation. Patients who developed delirium had significantly lower left ventricular ejection fraction (LVEF), longer operation and CPB durations, greater bleeding volume, longer ventilator support, and extended ICU stays. These associations are

consistent with previous studies showing that hemodynamic instability, prolonged surgical stress, and greater inflammatory burdens are major risk factors for postoperative delirium. The significantly lower LVEF among delirious patients suggests that impaired baseline cardiac function may predispose individuals to cerebral hypo perfusion and subsequent cognitive impairment during the perioperative period (24,25).

One of the most notable associations in our study was between delirium and CPB duration. Delirious patients had a mean CPB time of over 100 minutes, significantly higher than their non-delirious counterparts. CPB has been shown to increase blood-brain barrier permeability, promote systemic inflammation, and activate microglia, all of which contribute to neuronal injury and cognitive disturbances. The antioxidant effects of vitamin C may offer some neuroprotection in this setting by counteracting these pathophysiological mechanisms (26).

The significantly higher bleeding volume observed in the delirium group may also have played a role. Increased intraoperative bleeding may lead to greater hemodynamic instability and the need for more transfusions, both of which have been linked to delirium risk. Vitamin C has been shown in some studies to enhance capillary integrity and reduce microvascular bleeding, although we did not find a significant difference in bleeding between the vitamin C and placebo groups in this trial. Nonetheless, the interplay between bleeding and oxidative stress may still be relevant in understanding the benefits of antioxidant therapy (27).

The length of mechanical ventilation and ICU stay were both significantly prolonged in patients who developed delirium. This not only highlights the clinical burden of delirium but also suggests that its prevention may improve broader postoperative outcomes. Delirium often necessitates extended monitoring, increased sedation, and delayed weaning from ventilatory support, thereby increasing hospital resource utilization. The reduction in delirium with vitamin C supplementation may thus offer secondary benefits in terms of faster recovery and reduced ICU occupancy (28).

Despite the encouraging findings, this study has some limitations. First, although the sample size was adequate for detecting differences in delirium incidence, it may be underpowered to detect smaller differences in secondary outcomes such as ICU stay or mechanical ventilation duration between the vitamin C and placebo groups. Second, we did not measure serum vitamin C levels before or after supplementation, which would have provided insight into individual variability in response and the pharmacokinetics of vitamin C in the surgical context. Lastly, our analysis focused primarily on early postoperative delirium; longer-term cognitive outcomes were not assessed and remain a topic for future investigation (29,30).

Our results suggest that perioperative vitamin C supplementation may significantly reduce the incidence of postoperative delirium in patients undergoing open-heart surgery. Given its favorable safety profile, low cost, and biological plausibility, vitamin C may be a valuable adjunct in the management of high-risk cardiac surgery patients. Future studies with larger sample sizes and mechanistic investigations are warranted to confirm these findings and to explore the optimal dosing and timing of vitamin C administration (31,32).

Conclusion

Our study shows that a vitamin C boost 2 grams to start, then 1 gram a day for two days can lower delirium after open-heart surgery (12.5% vs. 27.5%). It’s tied to weaker hearts, longer surgery

times, and extended ICU stays, but it didn't change other issues much. Even with our adjustments, it's a promising start. We'd love to see bigger studies, maybe at several hospitals, with different doses and longer check-ins, to nail down the best approach and help more patients feel like themselves again.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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