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Letter to the Editor

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Postoperative Delirium and Vitamin C: Rethinking Unfavorable Outcomes Through the Lens of Underdosing

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To the Editor

We read with great interest in the pilot study examining the effects of perioperative ascorbic acid (2 g/day for 2 days) in preventing postoperative delirium (POD) among older cardiovascular surgery patients [1]. In that study, a 33% incidence of POD was observed, aligning with previous observational findings [2]. The authors concluded that ascorbic acid administration may not be effective in reducing the incidence of POD [1].

The pathophysiological mechanisms underlying POD are multifactorial and complex. Neuroinflammation has emerged as one of the most widely recognized contributors [3]. Surgical trauma initiates an inflammatory cascade characterized by significant elevations in circulating pro-inflammatory cytokines. Moreover, both surgery and anesthetic agents - whether volatile anesthetics or propofol - can disrupt the blood-brain barrier [4]. Disruption of the blood-brain barrier facilitates the entry of peripheral inflammatory mediators into the central nervous system, thereby amplifying neuroinflammation within the brain parenchyma. Age-related disruption of the blood-brain barrier increases susceptibility to delirium in elderly individuals, especially in the presence of systemic inflammation [5]. Consequently, older patients are particularly vulnerable to developing POD, notably following cardiac surgery.

Vitamin C (ascorbic acid) is well known for its antioxidant and anti-inflammatory properties, as well as for its potential to stabilize the blood-brain barrier [6]. Importantly, the potential therapeutic activity of vitamin C is dose- and time-dependent [7]. In animal studies, high-dose vitamin C (400 - 2,000 mg/kg/day) significantly improved cognitive or neurological outcomes through attenuation of neuroinflammation and preservation of the blood-brain barrier [8-10]. Based on the Nair-Jacob dose conversion principles, which account for interspecies differences in metabolic rate [11], the translated equivalents range from 4 to 20 g/day for a 60-kg adult - far exceeding the dose used in the pilot study, which employed the maximum permitted dose of ascorbic acid in Japan (2 g/day) [1]. Direct extrapolation to human dosing should be approached with caution due to species-specific differences in absorption and plasma saturation kinetics. Due to active transport via sodium-dependent vitamin C transporters, vitamin C concentrations in cerebrospinal fluid and neurons substantially exceed plasma levels, thereby enhancing neuroprotection against oxidative stress [12-14]. According to the study by Padayatty et al, the predicted peak plasma vitamin C concentrations after intravenous administration at a rate of 1 g/min were approximately 1,000 µmol/L for 1.25 g, 2,870 µmol/L for 5 g, 5,580 µmol/L for 10 g, and 13,350 µmol/L for 50 g. The pharmacokinetics of intravenous vitamin C are nonlinear with a short plasma half-life (about 2 h) although 100% bioavailability of intravenous vitamin C is assumed [14]. Therapeutic targets in humans should be based on achievable concentrations in plasma and neurons. Furthermore, vitamin C concentrations decreased markedly in patients after cardiac surgery [15]. Maintaining therapeutic plasma concentrations may thus require repeated or continuous high-dose infusions, which are crucial in the context of neuroprotection [16]. Indeed, intravenous vitamin C at 3,000 mg/day is recommended for at least the first 3 days following severe stress from trauma or infection due to increased turnover and catabolism of ascorbic acid [17]. Based on the above, subtherapeutic dosing may partly explain the neutral findings of Iizuka et al [1]. Although their regimen (2 g/day) complied with the national dose ceiling [1], it likely failed to achieve truly neuroprotective thresholds. In addition, the limitations of the study design - specifically the small sample size and the absence of a control group - substantially restrict the ability to draw firm conclusions regarding the effectiveness of vitamin C. A more comprehensive and rigorous study design is required to better clarify its true therapeutic efficacy.

Based on animal studies [8-10] and clinical research [17],

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higher cumulative intravenous doses (3 - 20 g/day) may be associated with a reduced POD incidence among older surgical patients, although these findings remain hypothesis-generating and require validation in controlled trials. Therefore, we propose that unfavorable outcomes imply underdosing as a confounder and suboptimal pharmacokinetic coverage, not the inherent inefficacy of the compound. Future clinical studies should integrate validated dose-response data, appropriate pharmacokinetic modeling, and timing optimization to reassess vitamin C as a perioperative neuroprotectant.

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Conflict of Interest

All authors declare that there was no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

CYK, SWL, ICT and JYC drafted the manuscript. JYC contributed to study planning and supervised the work. All authors discussed the results and provided critical comments on the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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