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Original Article

A Pilot, Double-Blind, Randomized, Controlled Trial of High-Dose Intravenous Vitamin C for Vasoplegia After Cardiac Surgery

Fumitaka Yanase, MD[*,†], Laurent Bitker, MD[*,‡], Lara Hessels, MD[*,§], Eduardo Osawa, MD[*], Thummaporn Naorungroj, MD[*,‖], Salvatore L. Cutuli, MD[*], Paul J. Young, MD, PhD[¶], Jay Ritzema, MD[¶], Georgia Hill, MClinlm[¶], Charlotte Latimer-Bell, MClinlm[¶], Anna Hunt, RN, BN, PGDip, HSM[¶], Glenn M. Eastwood, PhD[*], Andrew Hilton, MD[*], Rinaldo Bellomo, MD, PhD[*,†,#,1]

[*]*Department of Intensive Care, Austin Hospital, Melbourne, Australia*
[†]*Australian and New Zealand Intensive Care Research Centre, Monash University School of Public Health and Preventive Medicine, Melbourne, Australia*
[‡]*Service de médecine intensive et réanimation, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France*
[§]*Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[‖]*Department of Intensive Care, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[¶]*Department of Intensive Care, Wellington Hospital, Wellington, New Zealand*
[#]*Centre for Integrated Critical Care, Department of Medicine & Radiology, University of Melbourne, Melbourne, Australia*

Objective: To conduct a pilot feasibility and physiologic efficacy study of high-dose vitamin C in patients with vasoplegia after cardiac surgery.
Design: Prospective, double-blind, randomized, controlled trial.
Setting: Two tertiary intensive care units (ICUs).
Participants: Post-cardiac surgery patients with vasoplegia.
Interventions: The authors randomly assigned the patients to receive either high-dose intravenous vitamin C (1,500 mg every 6 hours) or placebo. The primary outcome was time from randomization to resolution of vasoplegia. Secondary outcomes included total norepinephrine equivalent dose in the first 2 days, ICU length of stay, ICU mortality, and in-hospital mortality.
Measurements and Main Results: The authors studied 50 patients (25 patients in each arms). The mean (standard deviation) time to resolution of vasoplegia was 27.0 (16.5) hours in the vitamin C group versus 34.7 (41.1) hours in the placebo group (mean decrease with vitamin C of 7.7 hours, 95% confidence interval −10.5 to 25.9, p = 0.40). The median (interquartile range) norepinephrine equivalent dose in the first 2 days was 64.9 (23.5-236.5) μg/kg versus 47.4 (21.4-265.9) μg/kg in the vitamin C and placebo group (p = 0.75). The median duration of ICU admission was similar (1.4 [0.5-2.5] days and 1.5 [0.5-3.3] days in the vitamin C and placebo group; p = 0.36). Only 1 patient, in the vitamin C arm, died.

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[1]*Address reprint requests to* Rinaldo Bellomo, MD, PhD, Director, Intensive Care Research, Austin Health, 145 Studley Road, Heidelberg, Melbourne, Victoria, Australia, 3084.

E-mail address: rinaldo.bellomo@austin.org.au (R. Bellomo).

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Conclusion: In patients with post-cardiac surgery vasoplegia, high-dose vitamin C infusion was feasible, appeared safe, and, within the limitations of a pilot study, did not achieve statistically faster resolution of vasoplegia.

Key Words: cardiopulmonary bypass; hypotension; post-cardiac surgery; postoperative care; vasoplegia; vitamin C

Vasoplegia is a recognized complication of cardiac surgery, and its incidence varies from 5% to 25%.[1] It is characterized by a preserved or increased cardiac index, vasodilatation, and hypotension sufficient to warrant vasopressor therapy.[2] Possible triggers for such a vasoplegic state include an inflammatory reaction to the bypass circuit, ischemia-reperfusion injury, and operative tissue trauma.[3] These processes appear to induce the release of cytokines and other inflammatory mediators that lead to the activation of vasodilatory pathways, diminished response to the effect of vasopressor hormones and drugs, and the consumption of endogenous antioxidants in response to increased reactive oxygen species generation.[1]

Vitamin C has potent immunomodulatory and antioxidant properties, acting as scavenger for both reactive oxygen and nitrogen species. High oxidative stress is implicated in the pathogenesis of vasoplegia after cardiac surgery and in sepsis-induced hypotension.[4] Thus, vitamin C is a potential treatment for patients with vasoplegia after cardiac surgery.[3,5] In this regard, a previous study of high-dose intravenous vitamin C (6,000 mg per day) combined with hydrocortisone and high-dose thiamine showed decreased vasopressor requirement and diminished mortality in septic patients with sepsis-associated severe vasoplegia.[6] In cardiac surgery patients, however, corticosteroids and thiamine already have been examined and found to have no effect on vasoplegia.[7,8] In contrast, to date, the hemodynamic effects of high-dose intravenous vitamin C in patients with post-cardiac surgery vasoplegia have not been studied.

Accordingly, the authors conducted a pilot feasibility, safety, and physiologic efficacy trial to investigate the effect of high-dose vitamin C in patients with vasoplegia after cardiac surgery, with the aim of establishing whether larger trials could be conducted successfully and justified by promising preliminary findings. The authors hypothesized that in patients admitted to intensive care unit (ICU) after cardiac surgery, high-dose vitamin C therapy would be associated with earlier resolution of postoperative vasoplegia.

Methods

Trial Design and Ethical Oversight

This study was a randomized, 2-center, double-blind feasibility, safety, and physiological efficacy pilot trial comparing high-dose vitamin C to placebo in the treatment of vasoplegia in patients admitted to the ICU after cardiac surgery.

The study was conducted in 2 tertiary ICUs, 1 in Australia and 1 in New Zealand. The study was approved by the Austin Hospital Human Ethics Committee in Australia (reference number DT 17/162) and Health and Disability Ethics Committees in New Zealand (reference number 17/NTA/212), and written informed consent was obtained from all participants participating in the trial. The trial was registered with the Australian New Zealand Clinical Trial Registry prior to patient enrollment (ACTRN12617000793314). The report of the present study adheres the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.[9]

Informed Consent

Research staff in New Zealand obtained consent before surgery and, if the patient met inclusion criteria in the ICU, they started the intervention. Therefore, when patients met exclusion criteria before surgery, for example by receiving steroid therapy before surgery, they were not enrolled. The research team in Australia enrolled patients after surgery. They obtained written consent after ICU admission when the patient's legally responsible decision maker was in the ICU or the patient was extubated and able to provide such consent. If the patient was intubated and their legally responsible person was not in the hospital, the patient was enrolled in the trial. Delayed written consent to use the data and to continue treatment was obtained later when the patient was extubated and able to provide such consent or when the legally responsible person was available (such approach to consent is permitted for time-sensitive intervention in the state of Victoria, Australia, for Ethics Committee-approved studies)

Patients

The authors included adult patients (≥18 years of age) who underwent on-pump cardiac surgery, were admitted to the ICU, and met the study enrollment criteria for postoperative vasoplegia. The authors included patients only when they met inclusion criteria and could be randomized within 6 hours after ICU admission. As no consensus definition exists, for the purpose of this study and in keeping with key characteristics used to describe this condition in previous literature, the authors defined post-cardiac surgery vasoplegia as hypotension with normal or increased cardiac index and a low systemic vascular resistance.[1] Specifically, for the purpose of inclusion in this trial, the authors operatively defined vasoplegia by the above criteria and the need for any dose of continuous vasopressor (norepinephrine, vasopressin, dopamine, phenylephrine, epinephrine, or metaraminol) infusion to a maintain mean arterial pressure (MAP) >65 mmHg, in the setting of a cardiac index ≥2.2 L min/m and/or of a central venous oxygen saturation >60%.

Exclusion criteria were pregnancy, the use of vasopressor or inotropic drugs in the preoperative period, off-pump cardiac surgery, corticosteroid use prior to or after surgery, a history of oxalate nephropathy, hemochromatosis, and glucose 6 phosphate dehydrogenase deficiency. The authors also excluded patients if the treating clinician believed there was an additional cause for

hypotension other than vasoplegia (bleeding, fluid requirement, pneumothorax, pacemaker issues, heart failure, or infection).

Randomization and Protocol

The authors randomly assigned eligible patients to receive either vitamin C or placebo, with a 1:1 ratio. Randomization was performed by means random number sequences using permuted blocks of variable size, and allocation was concealed using sequentially numbered sealed envelopes. Each envelope contained the patient's study number and the study arm allocation.

Patients received either 1,500 mg of vitamin C (vitamin C, Rotexmedica GmbH Arzneimittelwerk, Trittau, Germany in Australia or Ascor L 500, McGuff Pharmaceuticals, Inc, California, in New Zealand) in normal saline (100-mL bag) administered 6 hourly in the vitamin C group or normal saline (100-mL bag) administered 6 hourly in the placebo group. The study drug was administered over 1 hour.

The ICU research staff members, who were not involved in direct patient care, prepared all study drugs. All 100-mL study solutions were labeled as "vitamin C 1,500 mg or placebo." Thus, patients and clinical staff were kept blinded to treatment allocation. Infusion of the study drug was commenced rapidly after randomization. The study drug was given until the resolution of the vasoplegic state. This was defined as no vasopressor being administered to maintain a MAP >65 mmHg for a consecutive period of 4 hours, or if 96 hours had passed since randomization.

All other perioperative patient treatment, including hemodynamic management and sedation, was based on usual care and ICU protocols and dictated by the attending clinicians, who were blinded to treatment allocation. In the 2 study centers, anesthesia and perfusion techniques were similar (Supplementary Material S1). The surgery plan was dependent on the consultant surgeon.

Data Collection

All patient information was recorded in the electronic charting systems. Vasopressor dose was recorded as hourly dose in the ICU charting system. Vasopressin, dopamine, and epinephrine dose were converted to equivalent dose of norepinephrine to derive a cumulative dose of vasopressors, as previously described (Supplementary Table S3).[10]

Outcomes

The primary physiological efficacy outcome was time to resolution of postoperative vasoplegia. Secondary efficacy outcomes included total norepinephrine equivalent dose given in the first 2 days after randomization, ICU length of stay, ICU mortality, and hospital mortality. Feasibility outcomes included recruitment rate, eligibility rate, randomization to eligibility rate, protocol compliance, follow-up rate, and adverse event rate.

Sample Size

For this pilot study, which was focused on preliminary evidence of physiological effect, feasibility, safety, recruitment, and compliance, the authors aimed to enroll 50 patients over 2 sites. Such a study would provide a greater than 78% power to detect a difference in the duration of vasopressor therapy equal to that reported in a recent study of septic vasopelgia.[6] The authors considered that such sample size also would provide sufficient information to assess feasibility, a point estimate of a possible physiological effect, and sufficient pilot data to estimate an appropriate sample size for such studies.

Statistical Analysis

Analysis was performed on an intention-to-treat basis. A 2-sided p value less than 0.05 was considered statistically significant. Normally distributed continuous variables were compared using Student's *t* test or analysis of variance, and skewed variables were compared with either a Mann-Whitney U test or Kruskall-Wallis test, or log-transformed and compared by parametric tests. Categorical data were compared by Fisher's exact test. Time to shock resolution was compared using the log-rank test. Cox proportional hazard analysis then was performed, to adjust for possible confounders. Baseline variables with a univariate $p < 0.15$ on univariable analysis and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) were included in the Cox regression analysis. All analyses were performed using *R* version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

(https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373018&isReview=true

Results

Patients

The authors screened 456 patients from November 8, 2017 to October 29, 2018, and enrolled 50 patients (25 patients in each group) in the study (Fig 1).

Study patient characteristics are presented in Table 1. The median age was 67.0 years in the vitamin C group and 64.0 years in the placebo group. The median EuroSCORE was 5.0 in both groups, and 96.0% of the patients received norepinephrine (Supplementary Table S1) as the primary vasopressor drug. The median baseline norepinephrine equivalent dose was the same in both groups at 0.06 μg/kg/min of norepinephrine, equivalent to approximately 5 μg/min in an 80-kg patient.

Feasibility Outcomes and Protocol Compliance

Of 456 patients, 52 (11.4%) were eligible and 50 (11.0%) were included. Overall, 23 (46.0%) patients were included in Australia and 27 (54.0%) in New Zealand. All included patients completed the study protocol, and no patient was lost to follow-up or discontinued study treatment. Of the 50 patients, 48 (96.0%) patients stopped the study drug after postoperative vasoplegia resolution. One patient in the vitamin C group stopped the study drug because of death, and 1 patient in the placebo group stopped the study drug after 96 hours from randomization.

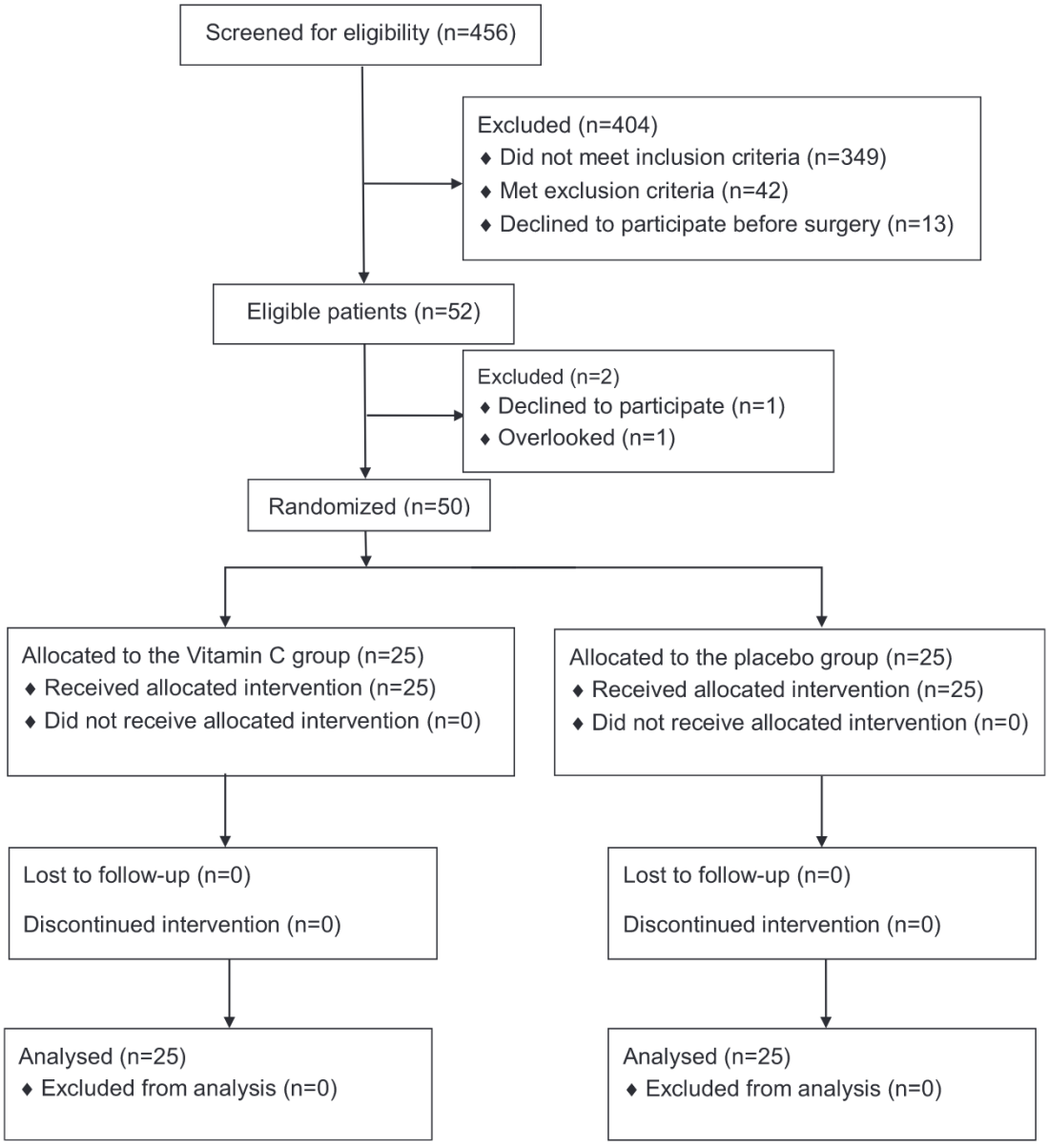

Fig 1. Trial screening and enrollment flowchart.

There were 2 cases (4.0%) of protocol deviation where extra doses of the study drug were given incorrectly after vasoplegia resolution (1 patient in each group).

There was no adverse event related to blood glucose measurements or other possible vitamin C-related events (hemolysis, kidney stones). One patient (4.0%) died of cardiogenic shock in the vitamin C group.

Primary Outcome

The mean (standard deviation) to vasoplegic shock resolution was 27.0 (16.5) hours in the vitamin C group and was 34.7 (41.1) hours in the placebo group (mean difference: 7.7 hours, 95% confidence interval [CI], −10.5 to 25.9 hours) (Table 2). There was no difference between the 2 groups for time to postoperative vasoplegia resolution ($p = 0.51$) (Fig 2). On Cox proportional hazard regression analysis, adjusted for age, sex, left ventricular ejection fraction, New York Heart Association class, and EuroSCORE (Table 3), high-dose vitamin C was not associated with earlier shock resolution (hazard ratio = 1.19; 95% CI, 0.55-2.55; $p = 0.66$).

Secondary Outcomes

There was no statistical difference in the median (interquartile range [IQR]) total norepinephrine equivalent dose administered on the first 2 calendar days after randomization (64.9 [IQR, 23.5-236.5] μg/kg for vitamin C and 47.4 [IQR, 21.4-265.9] μg/kg for placebo, respectively; $p = 0.75$). The median ICU length of stay was similar in the 2 groups (1.4 [IQR, 0.45-2.5] days in the vitamin C group and 1.5 [IQR, 0.5-3.3] days in the placebo group; $p = 0.36$). Other clinical outcomes were also similar in the 2 groups (Table 2). Moreover, MAP, heart rate, cumulative norepinephrine equivalent dose, and fluid administration in the first 3 days showed no difference between the 2 groups (Supplementary Fig S1).

Table 1
Baseline Characteristics of Study Patients

	Vitamin C	Placebo	p Value
Age, y	67.0 (82.0-74.0)	64.0 (59.0-69.0)	0.11
Sex, male	15/25 (60.0%)	23/25 (92.0%)	0.02
BMI,* kg/m^2	29.8 (26.8-32.9)	27.2 (24.4-30.7)	0.38
Admission category, urgent	7/25 (28.0%)	10/25 (40.0%)	0.55
EuroSCORE	5.0 (4.0-8.0)	5.0 (3.0-7.0)	0.51
LVEF†			0.12
<30%	1/22 (4.5%)	1/23 (4.3%)	
30%-49%	5/22 (22.7%)	12/23 (52.2%)	
≥50%	16/22 (72.7%)	10/23 (43.5%)	
NYHA class (%)			0.04
Class I	10/25 (40.0)	13/25 (52.0)	
Class II	6/25 (24.0)	11/25 (44.0)	
Class III	8/25 (32.0)	1/25 (4.0)	
Class IV	1/25 (4.0)	0/25 (0.0)	
Preoperative comorbidities (%)			
Hypertension	15/25 (60.0)	16/25 (64.0)	>0.99
Diabetes	8/25 (32.0)	12/25 (48.0)	0.39
Hyperlipidemia	8/25 (32.0)	9/25 (36.0)	>0.99
Previous myocardial infarction	6/25 (24.0)	9/25 (36.0)	0.54
Cerebrovascular disease	1/25 (4.0)	2/25 (8.0)	>0.99
Peripheral vascular disease	1/25 (4.0)	1/25 (4.0)	>0.99
Previous cardiac surgery	3/25 (12.0)	1/25 (4.0)	0.60
Chronic lung disease	3/25 (12.0)	3/25 (12.0)	>0.99
Atrial fibrillation	6/25 (24.0)	3/25 (12.0)	0.46
Ischemic heart disease	8/25 (32.0)	10/25 (40.0)	0.77
Severe pulmonary hypertension	3/25 (12.0)	1/25 (4.0)	0.60
Preoperative medication (%)			
ACEi/ARB	13/25 (52.0)	17/25 (68.0)	0.39
Beta-blocker	12/25 (48.0)	16/25 (64.0)	0.39
Calcium-channel blocker	5/25 (20.0)	7/25 (28.0)	0.74
Nitrate	4/25 (16.0)	3/25 (12.0)	>0.99
Statin	17/25 (68.0)	14/25 (56.0)	0.56
Serum creatinine, μmol/L	85.0 (75.0-98.0)	92.0 (80.0-100.0)	0.35
Type of surgery (%)			0.62
CABG	13/25 (52.0)	15/25 (60.0)	
Valvular surgery or valve and CABG	11/25 (44.0)	8/25 (32.0)	
Other	1/25 (4.0)	2/25 (8.0)	
Cross-clamp time, min	76.0 (69.0-107.0)	94.0 (78.3-109.3)	0.31
Cardiopulmonary bypass time, min	119.0 (97.0-172.0)	119.5 (104.8-159.3)	0.84
Intraoperative RBC transfusion	3/25 (12.0%)	1/25 (4.0%)	0.61
Baseline vasopressor			
Norepinephrine (μg/kg/min)	0.06 (0.05-0.11)	0.06 (0.04-0.14)	0.87
Norepinephrine equivalent dose‡ (μg/kg/min)	0.06 (0.05-0.11)	0.06 (0.04-0.16)	0.81

NOTE. Categorical data are presented as number/total number (%); continuous data are presented as median (25th-75th percentiles). Age, sex, NYHA, and LVEF had a $p < 0.15$ for the difference between the 2 study groups, and hence were added to the multivariate Cox regression model of time to shock resolution, along with study group allocation.
ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBC, red blood cell.
* BMI is the weight in kilograms divided by the square of the height in meters.
† LVEF value before surgery.
‡ Vasopressin, dopamine, and epinephrine were converted to equivalent dose of norepinephrine.[10]

Table 2
Primary Secondary and Other Outcomes

	Vitamin C	Placebo	p
Primary outcome			
Time to vasoplegia resolution,* h	27.0 (16.5)	34.7 (41.1)	0.40
Secondary outcomes			
Cumulative norepinephrine equivalent dose in the first 2 d,* μg/kg	64.9 (23.5-236.5)	47.4 (21.4-265.9)	0.75
ICU length of stay, d	1.4 (0.5-2.5)	1.5 (0.5-3.3)	0.36
Hospital length of stay, d	13.2 (7.9-20.2)	12.5 (8.1-16.7)	0.92
ICU mortality	1/25 (4.0%)	0/25 (0.0%)	>0.99
Hospital mortality	1/25 (4.0%)	0/25 (0.0%)	>0.99
Other outcomes			
Hospital length of stay, d	13.1 (7.9-20.2)	12.5 (8.1-16.7)	0.91
AKI			0.76
No AKI†	11/25 (44.0%)	13/25 (52.0%)	
Stage 1	3/25 (12.0%)	1/25 (4.0%)	
Stage 2	10/25 (40.0%)	9/25 (36.0%)	
Stage 3	1/25 (4.0%)	2/25 (8.0%)	
Atrial fibrillation‡	11/25 (44.0%)	8/25 (32.0%)	0.56
Time to extubation,§ h	16.1 (7.2-20.0)	10.1 (5.4-18.9)	0.48

NOTE. Categorical data are presented as number/total number (%); continuous data are presented as median (25th-75th percentiles) except for time to shock resolution (mean [standard deviation]), because it is used for sample size calculation.
AKI, acute kidney injury.
* Vasopressin dose was converted to equivalent dose of norepinephrine.[7]
† Acute kidney injury defined as modified Kidney Disease Improving Global Outcomes guideline.
‡ Incidence of newly diagnosed atrial fibrillation in intensive care unit.
§ Time from intensive care unit admission to extubation.

Discussion

Key Findings

In this double-blind, randomized, placebo-controlled pilot feasibility and physiologic efficacy study of high-dose vitamin C for patients with vasoplegia after cardiac surgery, the authors found that resolution of the vasoplegic state occurred relatively rapidly with standard care. In this setting, the administration of high-dose vitamin C did not lead to a faster resolution of postoperative vasoplegia or a decrease in the total norepinephrine equivalent dose administered in the first 2 calendar days after randomization. Finally, the observed 95% CIs were consistent with vitamin C therapy having an effect on duration of shock that ranged from a 25.9-hour reduction to a 10.5-hour increase, an effect size that the authors submit is unlikely to be clinically important in this population.

Relationship to Previous Studies

High-dose vitamin C has a strong biological rationale in post-cardiac surgery vasoplegia. Vitamin C scavenges reactive oxygen species, which likely contribute to vasoplegia after cardiac surgery; stimulates norepinephrine synthesis; and decreases the incidence of atrial fibrillation, cardiac enzyme release, and the level of markers of oxidative stress.[11,12] In addition, cardiac surgery patients have decreased vitamin C levels compared to preoperative values, suggesting increased consumption and/or dilution.[13]

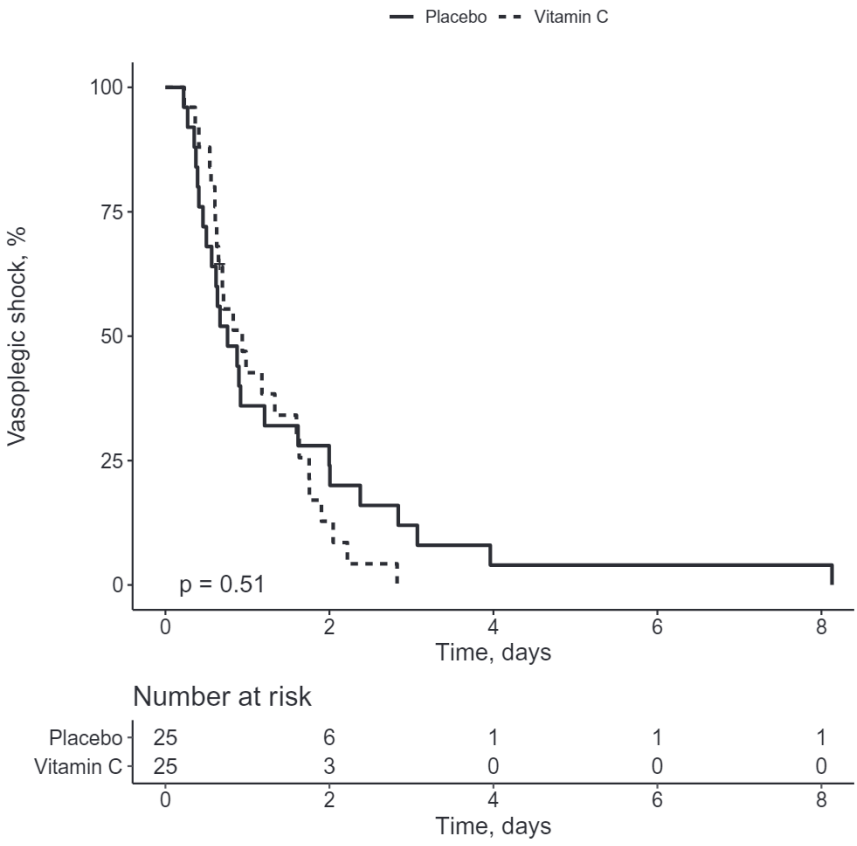

Fig 2. Time to vasoplegia resolution according to treatment.

Previous studies of vitamin C in cardiac surgery patients have not focused on postoperative vasoplegia and on the duration of vasopressor therapy and have not administered high-dose vitamin C.[14-19] Instead, they investigated the use of vitamin C in unselected patients undergoing cardiopulmonary bypass and focused on creatinine kinase and the development of atrial fibrillation. In addition, vitamin C was given enterally in 3 of the 6 studies reported so far.[14-19] This is problematic, because vitamin C absorption after enteral high-dose administration is limited by intestinal transporter (sodium-vitamin C transporter-1) function, and peak plasma vitamin C levels after enteral intake in healthy volunteers are one-sixth of those measured after the same dose given by intravenous infusion.[20] Thus, enteral therapy is unlikely to deliver sufficient amounts of vitamin C to these patients.[6,21,22]

In addition, with the exception of 1 study, vitamin C has been given at a much lower dose, and, in the only high-dose study prior to the authors' investigation, it was given as a single dose prior to cardiopulmonary bypass.[14-19]

Of relevance to this study, high-dose intravenous vitamin C has recently been used to treat vasodilatory septic shock, another type of vasoplegic state.[6,22,23] Such studies used high-dose (6000 mg per day in 4 divided doses) vitamin C in association with thiamine and hydrocortisone and found a decrease in vasopressor therapy duration. However, because corticosteroid or thiamine therapy for cardiac surgery patients has been shown to have no effect on hemodynamic or clinical outcomes, the authors decided to use high-dose intravenous vitamin C monotherapy in this study.[7,8]

Table 3
Cox Proportional Hazard Regression Analysis for Time to Resolution of Post-Cardiac Surgery Vasodilatory Shock With 95% CI

Variables	Hazard Ratio (95% CI)	p
Study group		0.66
Placebo	1	
Vitamin C	1.19 (0.55-2.55)	
NYHA		0.97
Class I or II	1	
Class III or IV	0.98 (0.32-2.97)	
Age, 1 y	1.02 (0.97-1.06)	0.41
Sex		0.62
Female	1	
Male	1.24 (0.53-2.90)	
EuroSCORE	0.95 (0.79-1.14)	0.58
LVEF		0.74
≥50%	1	
<50%	0.88 (0.42-1.86)	

NOTE. LVEF was missing for 5 patients (10.0%).
EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction value before surgery; NYHA, New York Heart Association.

Implications of Study Findings

This study implies that postoperative vasoplegia, as defined in the study, resolves within 1 to 2 days with usual care. It also implies that, in such unselected patients, high-dose intravenous

vitamin C is unlikely to have a clinically important effect on the duration of the vasoplegic state. Moreover, given the point estimate of its effect, hundreds of similar patients would be needed to provide evidence of statistical significance.

Strengths and Limitations

To the authors' knowledge, this is the first double-blind, randomized, controlled study of high-dose intravenous vitamin C study for post-cardiac surgery vasoplegia. The authors enrolled essentially all eligible patients, and the study protocol was delivered successfully in essentially all patients, with complete follow-up and no adverse events related to the study drug. It provided information on the duration of postoperative vasoplegia in an unselected population and evidence that, in such patients, high-dose vitamin C is unlikely to have a clinically important effect. Moreover, these results provide clear evidence of feasibility and an estimate of sample size for a future trial. As such, they suggest that hundreds of patients would be needed to demonstrate an effect of vitamin C equal to the point estimate found in the authors' pilot study on the duration of vasopressor therapy in this setting. The authors acknowledge several limitations. One-third of study patients received milrinone as an inotropic drug, and such treatment may have caused vasodilation and contributed to hypotension. However, the proportion of patients with milrinone was the same in both groups. The authors did not use the cardiac index to defined the resolution of vasoplegia. Instead, the authors chose a practical approach to vasoplegia resolution, because the authors expected that several patients would have their pulmonary artery catheter removed while on low-dose vasopressor therapy. In addition, when measured, the systemic vascular resistance index was the same in the 2 groups. One patient treated with vitamin C died from cardiogenic shock, and this was not considered a drug-related side effect by the treating clinical team. The average EuroSCORE in the study patients was 5. Thus, the expected mortality rate was 5%. Finally, the authors did not investigate very high doses (≥1 g/kg per day) of vitamin C given intravenously as has been done in other conditions. Whether such very high doses may prove more useful remains untested.[24,25]

Conclusion

In conclusion, in a pilot double-blind randomized trial in cardiac surgery patients with postoperative vasoplegia, the authors found that resolution of the vasoplegic state occurred on average within 1.5 days. The authors also found that high-dose intravenous vitamin C did not decrease the duration of vasopressor therapy significantly and appeared unlikely to have a clinically important impact on this outcome. Investigation of patients with much a higher intensity of postoperative vasoplegia may be warranted.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2019.08.034.

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