Journal of Cardiothoracic Surgery

RESEARCH

Open Access

Ascorbic acid and microcirculation in cardiothoracic surgery: a pilot feasibility trial and matched cohort study

Patrick M. Wieruszewski[1,2*], Misty A. Radosevich[2], Scott D. Nei[1], Kianoush B. Kashani[3,4], Sarah E. Normand[5], Hartzell V. Schaff[6] and Erica D. Wittwer[2]

Abstract

Background Ascorbic acid is an essential cofactor of catecholamine synthesis that increases capillary bed density and improves microcirculation perfusion. We hypothesized early ascorbic acid administration in cardiothoracic surgery would preserve the microcirculatory integrity and minimize postoperative vasoplegia.

Methods This was a single-arm pilot feasibility study of adults undergoing septal myectomy combined with valve intervention or alone using cardiopulmonary bypass. Intravenous ascorbic acid 1,500 mg was administered before and immediately following cardiopulmonary bypass and every 6 h after for 12 doses. Three historical controls were identified and matched to each trial participant on age, gender, body mass index, preoperative ejection fraction, surgery performed, and time on cardiopulmonary bypass. The feasibility endpoint was a composite of successful and timely 1) ascorbic acid administration, 2) laboratory assessment, and 3) microcirculation measurements across the perioperative phases of care. Clinical endpoints included vasoplegia incidence, acute kidney injury, and lengths of stay compared to controls.

Results Fifteen patients were enrolled and compared to 45 historically matched controls. Participants' median baseline plasma ascorbic acid concentration was 0.5 (0.3, 0.9) mg/dL. Four (27%) patients had suboptimal concentrations. Eleven participants (75%) did not meet the feasibility composite endpoint due to the inability of microcirculation measurement. Incidence of vasoplegia and acute kidney injury, vasopressor duration, and lengths of stay were similar between participants and historical controls. No drug-related adverse events were noted.

Conclusions Timely microcirculation measurements were challenging in the complex cardiothoracic surgery environment. Compared to historical controls, no meaningful differences in clinical endpoints were noted with ascorbic acid treatment. The utility of ascorbic acid on post-cardiopulmonary bypass vasoplegia remains unclear.

Trial registration ClinicalTrials.gov (NCT03744702, registered on November 14, 2018).

Keywords Vasoplegia, Vasodilation, Shock, Vitamin C, Cardiopulmonary bypass, Microcirculation

*Correspondence:
Patrick M. Wieruszewski
wieruszewski.patrick@mayo.edu
Full list of author information is available at the end of the article

Introduction

Vasoplegia is a syndrome characterized by non-cardiogenic, non-hypovolemic, vasodilatory hypotension occurring in up to 5 to 50% of cardiopulmonary bypass patients [1]. Many non-modifiable risk factors have been identified, including preoperative antihypertensive use, lower ejection fraction, and longer bypass and aortic cross-clamp times [2, 3]. Therefore, the primary management of vasoplegia is focused on treatment with vasopressors [1, 4, 5]. However, these agents have side effects of digital and mesenteric ischemia and cardiac arrhythmias, especially when deployed in excessively high dosages [6]. Despite treatment, vasoplegia remains a major contributor to poor outcomes following cardiothoracic surgery, including higher rates of kidney failure, longer lengths of stay, and post-surgical death [2].

Ascorbic acid (vitamin C) is an essential micronutrient cofactor for endogenous catecholamine synthesis and has potent antioxidant and anti-inflammatory effects [7]. The use of ascorbic acid in septic shock in initial studies suggested lower rates of kidney failure, more rapid separation from vasopressors, and a profound death-sparing effect [8]. Subsequent studies failed to demonstrate similar benefits [9, 10]. Although it is unclear what degree of ascorbate deficiency patients with septic shock have, patients who undergo cardiac surgery have been shown to have nearly 50% reduction in total plasma ascorbic acid concentrations following cardiopulmonary bypass without any recovery up to one week after surgery [11]. In a randomized, double-blind trial of patients with vasoplegia requiring norepinephrine after cardiothoracic surgery, ascorbic acid did not reduce the time to vasoplegia resolution [12]. However, ascorbic acid is not a vasopressor, limiting the biological rationale for its use in settings where the shock is already present. Given the known effects of cardiopulmonary bypass, it remains unclear whether preventing deficiency by prophylactic early ascorbic acid administration would be beneficial in these patients.

Amongst its pleiotropic effects, ascorbic acid plays a vital role in vascular endothelial function. Ascorbic acid decreases oxidative stress, prevents vascular leakage, and improves microcirculatory flow by inhibiting intracellular adhesion of leukocytes and microthrombi generation [13]. The effects of cardiothoracic surgery and cardiopulmonary bypass on the microcirculation are well known and include reductions in perfused capillary density and decreased proportion and density of perfused small vessels [14, 15]. Alterations in the microcirculation, despite achieving macrocirculatory targets (i.e., mean arterial pressure, heart rate, cardiac output), have been associated with organ failure, perioperative complications, and death [14, 16]. Despite this, little information is available to inform clinicians how to prevent or treat microcirculatory dysfunction in significant physiologic stress. Mechanistically, the administration of ascorbic acid around the time of cardiopulmonary bypass can potentially impact essential pathways involved in microcirculatory dysfunction and subsequently limit the insult of oxidative processes on the vascular endothelium, maintain vascular responsiveness to catecholamines, and prevent endothelial barrier breakdown [13, 17]. Such potential prompted microcirculatory evaluation in the current investigation. This study aimed to assess the feasibility of a multifaceted intervention across the perioperative phases of care, including ascorbic acid administration, laboratory assessment, and microcirculation measurements in the context of complex cardiothoracic surgery to inform the potential for more extensive studies. We also sought to compare clinical endpoints to matched historical controls.

Methods

Participants and setting

The first phase of this study was a single-arm pilot feasibility trial in adults undergoing cardiothoracic surgery between July 1, 2019 and March 1, 2021. Adults (≥ 18 years old) were approached for consent during their preoperative clinic visit if they were planning to undergo open valve intervention or myectomy using median sternotomy and cardiopulmonary bypass. Patients were excluded if they underwent emergency surgery, were scheduled for isolated coronary artery bypass grafting surgery or cases requiring circulatory arrest, had active infection or sepsis, severe liver disease or ascites, preoperative kidney dysfunction requiring dialysis, preoperative need for midodrine, preoperative use of oral or intravenous steroids, were pregnant or had known glucose-6-phosphate dehydrogenase deficiency.

The second phase of this study was a matched cohort study using historical controls. We evaluated the records of all adult patients who underwent cardiothoracic surgery during the timeframe of the pilot trial. We applied the same inclusion and exclusion criteria used in the pilot trial. We then evaluated for potential suitable matches to pilot trial participants using the following criteria: age (± 10 years), gender (exact), body mass index (± 5 kg/m^2), preoperative ejection fraction (± 10%), surgical procedure performed (exact), and time on cardiopulmonary bypass (± 15 min). We aimed to obtain three suitable historical controls for every trial participant. Historical controls were then matched to trial participants using a standard method based on these criteria. Only pairs that exactly matched on all the specified criteria were included.

The local Institutional Review Board approved the study, and we registered the trial in clinicaltrials.gov. The

trial was carried out ethically following the Helsinki Declaration 1975, revised in 2000.

Interventions and definitions

Trial participants were evaluated for inclusion during the preoperative clinic appointment, where written informed consent was obtained. Following induction of anesthesia, 1,500 mg intravenous ascorbic acid (Ascor®, McGuff Pharmaceuticals Inc., Santa Ana, CA) was administered. Cardiopulmonary bypass, the surgical procedure, and all other aspects of patient care, including placement of pulmonary artery catheters for hemodynamic management, were carried out per routine, including fluid resuscitation and administering inotropes or vasopressors as needed at the discretion of the attending anesthesiologist and cardiac surgical team. At our institution, there is no specific protocol for vasoplegia, however, at the discretion of the attending anesthesiologist, norepinephrine or vasopressin infusion is used first to maintain mean arterial pressure (MAP) of at least 65 mmHg, only after demonstration of adequate cardiac function, appropriate fluid resuscitation, and exclusion of hemorrhage. A second dose of 1,500 mg intravenous ascorbic acid was administered after separation from cardiopulmonary bypass following protamine administration. Subsequent doses of 1,500 mg intravenous ascorbic acid were administered every 6 h after that for 12 doses. This dosing schema was extrapolated from initial studies in shock suggesting benefit and on the basis that 6 g per day of ascorbic acid is suggested to sufficiently replete stores in critical illness [8, 10, 12].

Postoperative vasoplegia was defined by the need for any dose of a continuous intravenous vasopressor (norepinephrine, epinephrine, phenylephrine, dopamine, or angiotensin II) for a minimum of 6 h to maintain a mean arterial pressure (MAP) $\geq$65 mmHg in the setting of cardiac index $\geq$2.2 L/min/m^2. Systematic vascular resistance was not used in addition to these criteria. Using previously described formulae, cumulative vasopressor dosage was calculated in norepinephrine equivalents (mcg/kg/min) [18]. All norepinephrine dosages are presented as base norepinephrine [19]. The sublingual microcirculation was evaluated using a sidestream dark field video microscope (Microscan by Microvision Medical; Amsterdam, Netherlands) at specific time points, including baseline (before administration of ascorbic acid), after the first ascorbic acid dose, on cardiopulmonary bypass, immediately after cardiopulmonary bypass, and postoperatively in the intensive care unit (within 24 h). We obtained at least three images at each time point as recommended by the 2018 ESICM Consensus on the Assessment of Sublingual Microcirculation [20]. We recorded the computer-generated measurements of DeBacker Density (DD, also referred to as small vessel density) and percentage/proportion of perfused vessels (PPV). Patients were not receiving any vasodilatory medications through the entire follow-up period in which microcirculation was assessed. Acute kidney injury was assessed using the Kidney Disease: Improving Global Outcomes staging schema using only the serum creatinine criteria [21].

Outcomes

The feasibility endpoint was a composite of successful and timely multifaceted interventions at the pre-specified timepoints across the preoperative, intraoperative, and postoperative phases of care, including 1) administration of ascorbic acid, 2) collection of laboratory specimens, and 3) performance of microcirculation measurements. Clinical endpoints included maximum vasopressor exposure and duration, incidence of acute kidney injury, length of stay, and death. Adverse events related to ascorbic acid, including allergic reactions, hyperglycemia, hemolytic anemia, formation of kidney stones, and acute kidney injury, were monitored daily for all trial participants.

Data analysis

Categorical data were summarized as counts with percentages and compared using the chi-square test or Fisher exact test, as appropriate. Continuous data were summarized by medians with interquartile ranges (25 th and 75 th quantiles) and compared using the Wilcoxon rank sum test. All data were handled using R version 4.3.2 (R Core Team, The R Foundation for Statistical Computing, Vienna, Austria, 2023).

Results

Participant characteristics

Fifteen patients were enrolled in the pilot feasibility trial, and 45 suitable historical controls (3 matched controls per every trial participant) were successfully identified (Fig. 1). The details regarding patient characteristics, demographics, and surgical information are summarized in Tables 1 and 2. The baseline characteristics and surgical specifics were similar between the pilot participants and the historical controls following the matching procedure. In trial participants, the median baseline plasma ascorbic acid concentration was 0.5 (0.3, 0.9) mg/dL, and 4 (27%) patients had suboptimal concentrations (< 0.4 mg/dL), one of which was below the lower limit of assay detection (< 0.1 mg/dL).

Feasibility endpoint

Only four enrolled patients (25%) achieved the feasibility composite endpoint of successful and timely 1) administration of ascorbic acid, 2) laboratory assessment, and

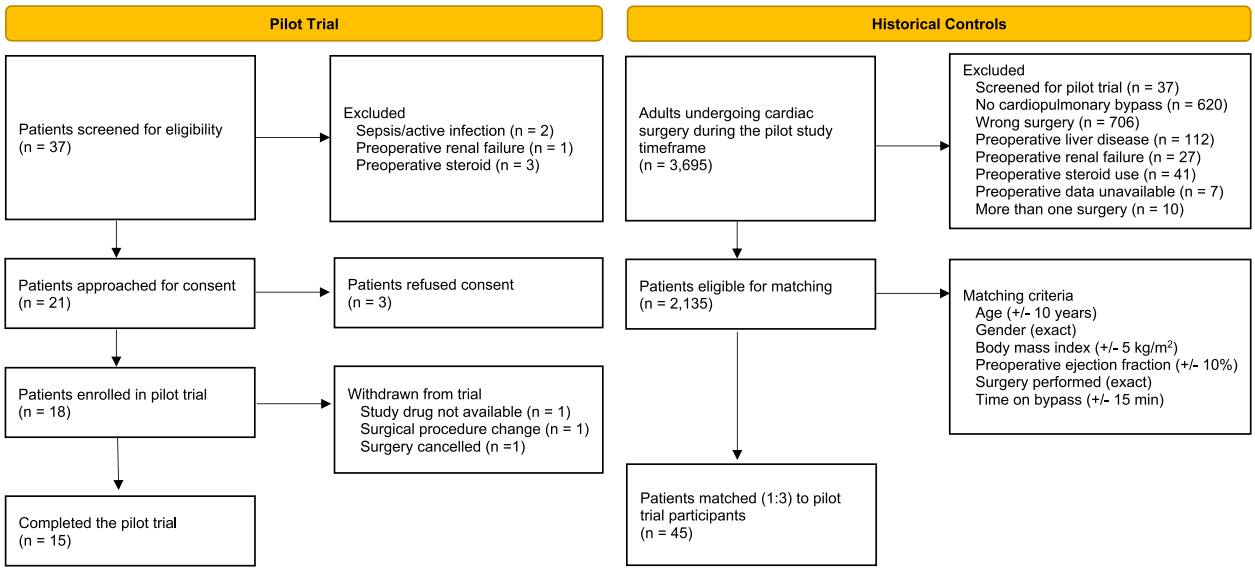

Fig. 1 CONSORT flow diagram

Table 1 Patient characteristics

	Pilot Participants (*N* = 15)	Historical Controls (*N* = 45)	*p*-value
Age, y	60 (54, 67)	60 (56, 67)	0.66
Male sex	9 (60%)	27 (60%)	1
BMI, kg/m^2	31.8 (28.6, 35.2)	31.4 (27.4, 34.3)	0.74
LVEF, %	66 (61, 72)	67 (62, 70)	0.76
Chronic kidney disease	3 (20%)	11 (24%)	0.72
Arrhythmia	4 (27%)	18 (40%)	0.35
History of ablation	1 (7%)	3 (7%)	1
Preoperative antihypertensive therapy			
β-blocker	7 (47%)	33 (73%)	0.06
ACE inhibitor	1 (7%)	5 (11%)	0.62
Angiotensin receptor antagonist	3 (20%)	5 (11%)	0.38
Calcium channel blocker	4 (27%)	11 (24%)	0.86
Baseline laboratory data			
Ascorbic acid, mg/dL	0.5 (0.3, 0.9)	–	–
< 0.4	4 (27%)		
0.4–1.0	10 (67%)		
> 1.0	1 (7%)		
Creatinine, mg/dL	1.05 (0.86, 1.22)	1.02 (0.87, 1.17)	0.41
Cystatin C, mg/L	0.97 (0.82, 1.06)	–	–

Data are presented as median (IQR) or *n* (%)

ACE Angiotensin-converting enzyme, *BMI* Body mass index, *LVEF* Left ventricular ejection fraction

3) microcirculation measurement at the pre-specified time points across the preoperative, intraoperative, and postoperative phases of care (Table 3). This low achievement of the feasibility composite endpoint was driven by the inability to perform microcirculation measurement. All 15 enrolled patients (100%) received all dosages of ascorbic acid and laboratory assessment at all the specified time points.

Microcirculation measurements

Evaluation of the microcirculation was performed in only 6 (40%) patients, as our study coincided with the

Table 2 Surgical operation details

	Pilot Participants (*N* = 15)	Historical Controls (*N* = 45)	*p*-value
Surgical procedure			
Myectomy	11 (73%)	33 (73%)	1
Valve replacement	6 (40%)	18 (40%)	1
Valve repair	1 (7%)	3 (7%)	1
Repeat sternotomy	2 (13%)	2 (4%)	0.23
Total cardiopulmonary bypass time, m	53 (45, 90)	51 (43, 91)	1
Total aortic cross-clamp time, m	41 (25, 74)	41 (31, 72)	0.67
Intraoperative pre-bypass LVEF, %	65 (60, 70)	65 (60, 70)	0.94
Intraoperative post-bypass LVEF, %	65 (60, 70)	65 (60, 70)	0.66
Post-procedure fluid balance, mL	3178 (1524, 3495)	2312 (1061, 3540)	0.33

Data are presented as median (IQR) or *n* (%)

LVEF Left ventricular ejection fraction

Table 3 Patient outcomes

	Pilot Participants (*N* = 15)	Historical Controls (*N* = 45)	*p*-value
Composite primary endpoint	4 (25%)	–	–
Ascorbic acid administration	15 (100%)		
Laboratory assessment	15 (100%)		
Microcirculation measurements	4 (25%)		
Postoperative vasoplegia	9 (60%)	17 (38%)	0.13
Max vasopressor dosage at any time, mcg/kg/min	0.09 (0.04, 0.13)	0.04 (0.02, 0.05)	0.03
Cardiac index at max vasopressor dosage, L/min/m^2	3.04 (2.49, 3.65)	2.39 (2.10, 3.05)	0.05
Vasopressor duration, h	11 (5.5, 17.8)	5.8 (3.5, 17.5)	0.20
Acute kidney injury			0.89
Stage 1	2 (13%)	8 (18%)	
Stage 2	1 (7%)	2 (4%)	
Stage 3	0 (0%)	1 (2%)	
ICU length of stay, h	25 (22, 45)	23 (21, 27)	0.11
Hospital length of stay, d	6 (5, 7)	5 (5, 7)	0.36
Death	0 (0%)	1 (2%)	0.56

Data are presented as median (IQR) or *n* (%)

beginning of the COVID-19 pandemic, and non-essential intraoral manipulations were avoided. The remaining 9 (60%) patients received ascorbic acid as protocolized above but did not undergo microcirculation evaluation. Of the six patients who underwent microcirculation imaging, only 5 (33%) had measurements at each planned time point. Post-ascorbic acid (first dose) administration images were not collected in one patient due to a short incision-to-bypass time. Only one image could be collected during cardiopulmonary bypass due to a short bypass run. No postoperative patient images were obtained in the same patient due to a software malfunction preventing image collection and analysis. In another patient, only one image could be collected and analyzed before administering ascorbic acid (rapid progression from incision to initiation of bypass). Only two images could be obtained and analyzed on cardiopulmonary bypass with a very short bypass time. We elected to discontinue intraoperative image collection in the third patient due to the development of visible mucosal irritation of the sublingual tissue. Postoperatively, the patient denied any discomfort in this area, and no visible injury was apparent. Like the second patient, only one pre-ascorbic acid and no post-ascorbic acid, pre-bypass images could be collected in the fourth patient due to a short incision-to-bypass time. All images were collected in the fifth and sixth patients. An example series of images are presented in Fig. 2. Despite dedicated efforts and significant time investment, images were frequently of suboptimal quality regarding stability, absence

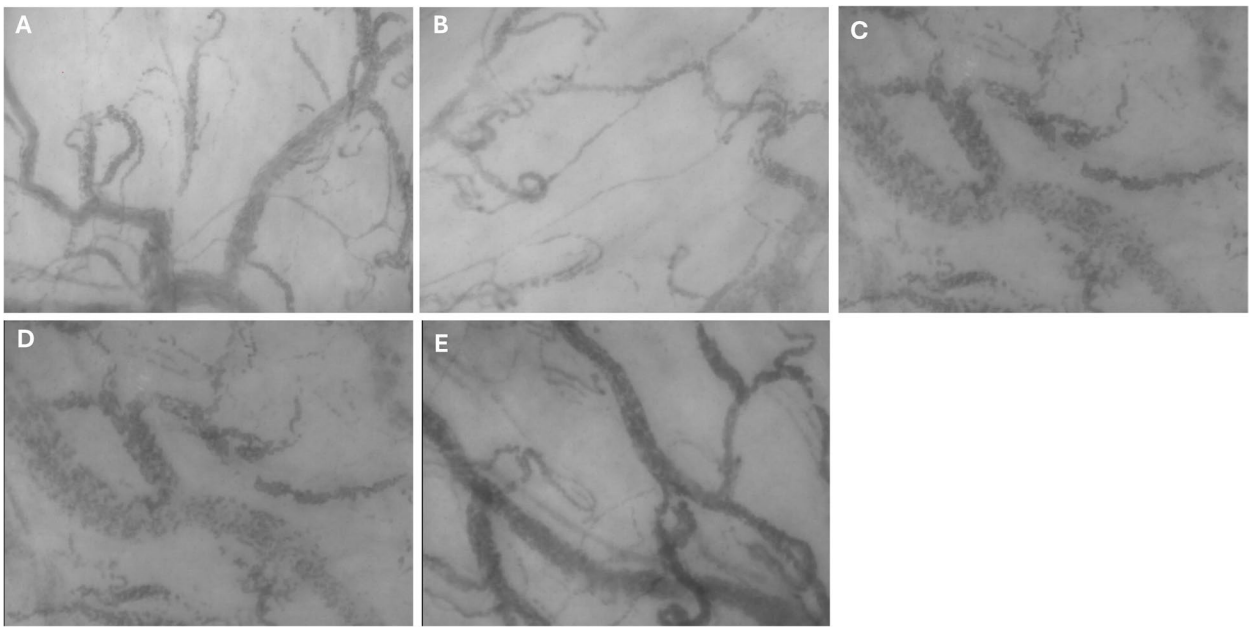

Fig. 2 Example series of dark field microscopy images (still snapshots of video) from patient 6 collected pre-ascorbic acid (**A**), post-ascorbic acid (**B**), on cardiopulmonary bypass (**C**), post-cardiopulmonary bypass (**D**), and postoperative in the intensive care unit (**E**)

of bubbles, vessel loops, and focus. We present the DeBacker Density and PPV in Table 4.

Clinical endpoints

Postoperative vasoplegia was identified in 9 (60%) of the trial participants compared to 17 (38%) of the historical controls ($p = 0.13$). The maximum postoperative vasopressor dosage at any time was greater in trial participants (0.09 mcg/kg/min) than in historical controls (0.04 mcg/kg/min), $p = 0.03$. No patients in either group received any other vasoplegia treatments (e.g., steroids, methylene blue, or hydroxocobalamin). The groups were similar in the overall vasopressor duration, occurrence of acute kidney injury, and intensive care unit and hospital lengths of stay. One historical control died on postoperative day zero due to hemorrhagic shock. No ascorbic acid-related adverse events were noted in any of the trial participants.

Table 4 Microcirculation variables

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
PPV						
Before AA	94%	84%	79%	63%	78%	87%
After AA	NA	88%	NA	78%	81%	92%
On CPB	78%	74%	NA	84%	92%	80%
Post-CPB	90%	90%	NA	88%	60%	82%
Post-op in ICU	NA	85%	79%	89%	87%	88%
DeBacker Density						
Before AA	7.44	10.6	8.93	8.08	8.9	8.70
After AA	NA	10	NA	7.44	8.43	6.70
On CPB	7.87	7.4	NA	8.29	10.1	9.6
Post-CPB	8.86	10.1	NA	9.47	9.1	8.86
Post-op in ICU	NA	7.12	8.14	7.07	8.2	9.9

Data is presented as the average value obtained

AA Ascorbic acid, *CPB* Cardiopulmonary bypass, *ICU* Intensive care unit, *PPV* Proportion/percentage of perfused vessels

Discussion

In this single-arm pilot study, providing a multifaceted intervention, including ascorbic acid administration, laboratory assessment, and microcirculation assessment, was not feasible in the totality of the complex environment of cardiothoracic surgery. Although no adverse drug events were noted with the use of ascorbic acid, no clinically meaningful improvements were identified in the trial participants. Trial participants required higher doses of vasopressors.

Ascorbic acid (vitamin C) is a water-soluble, essential antioxidant and anti-inflammatory micronutrient and a cofactor to tyrosine hydroxylase and dopamine-β-hydroxylase in the endogenous biosynthesis of catecholamines [13]. Because of this, there has been recent interest in applying ascorbic acid to sepsis and septic shock. However, studies have found mixed results, leaving no straightforward utility of this agent in that population [8–10]. We previously reported a catecholamine-sparing effect with ascorbic acid administration in three vasoplegic patients following cardiopulmonary bypass, while two of them were liberated from vasopressors within 24 h [22]. A subsequent randomized trial of ascorbic acid failed to demonstrate a reduction in the time to vasoplegia resolution in patients requiring norepinephrine after cardiopulmonary bypass [12]. However, because ascorbic acid is not a vasopressor, we hypothesize that earlier administration, around the time of insults leading to hypotension, would maximize its benefit in patients with shock. Accordingly, in animal models, ascorbic acid has been shown to increase capillary bed density, improve microcirculation perfusion, and protect against the vasodilatory effects of nitric oxide production from inducible nitric oxide synthetase [23–25]. However, the direct impact of ascorbic acid on the endothelial glycocalyx surface components in humans has not been studied.

Cardiopulmonary bypass is an ideal scenario to test this hypothesis, as the precise timing of the insults leading to vasoplegia is well-known. In addition, cardiopulmonary bypass surgeries are known to be associated with significantly reduced plasma ascorbate concentrations [11]. Indeed, the endothelial glycocalyx is prone to injury when exposed to cardiopulmonary bypass, leading to dysregulation of the vascular endothelium function [26]. Endocan, a vascular endothelial surface glycan with increased expression during states of inflammation, is significantly upregulated following cardiopulmonary bypass [27, 28]. One study found increased endocan concentrations associated with a greater duration of catecholamine use in patients with post-cardiopulmonary bypass vasoplegia [27]. Similarly, syndecan-1, an endothelial surface proteoglycan involved in flow-mediated nitric oxide production and vascular endothelial homeostasis, has been negatively associated with vasopressor requirements in vasoplegia after cardiopulmonary bypass [29]. Interestingly, another study found that while cardiopulmonary bypass did not affect soluble P-selectin concentrations, those with higher preoperative soluble P-selectin were more likely to develop vasoplegia [30]. Targeting these endothelial insults and microvascular injuries may serve as a mechanism for preventing or reducing the severity of postoperative vasomotor function and vasoplegia. However, it is important to note that the pathogenesis of vasoplegia is multifactorial and assessing any one specific intervention may not be entirely feasible.

Our intent in microcirculatory measurements in this study was to inform the feasibility of obtaining measurements intraoperatively to guide larger investigations. However, we noted the feasibility of physically fitting the microscope tip into the patient's mouth and the sublingual area was challenging given the presence of an endotracheal tube, tracheal tube tie, and a transesophageal echocardiography probe. It was difficult to adequately suction the submucosal area and wipe away oral secretions to optimize image quality for similar reasons. Furthermore, a protective horseshoe-shaped bar is secured over the supine patient's head at our institution, and sterile drapes are placed atop the device. This added physical limitation increased the complexity of optimally placing the video microscope in the correct sublingual position and holding a stable image. For the above reasons, acquiring the guideline-recommended three images of any quality at each pre-determined endpoint was time-intensive. Due to the nature of the video microscope analysis software (AVA4, Microvision Medical; Amsterdam, Netherlands), the analysis of images automatically began once an image was captured and required approximately 5 min for each image. Considering the time for acquiring satisfactory images and the time for image analysis, it was often not feasible to collect three images for pre-bypass or on-bypass time points in short incision-to-bypass times or short bypass runs. Lastly, the suboptimal image quality limits the DeBacker Density and PPV interpretation.

Limitations

The benefits of any prophylactic treatment should outweigh the potential risks to justify its empiric use. Patients undergoing cardiopulmonary bypass are at high risk of acute kidney injury. Ascorbic acid is metabolized and degraded to several byproducts, including oxalate. Hyperoxaluria, especially in the setting of high ascorbic acid dosages, leads to the deposition of oxalate crystals in the renal tubules and may result in acute kidney injury and acute or chronic kidney diseases [31]. We were unable to measure plasma or urine oxalate concentrations

and thus cannot exclude the potential for calcium oxalate precipitation and longer-term adverse kidney effects with use of ascorbic acid. The dosage of ascorbic acid used in our study is consistent with other studies evaluating its utility in shock. It is on the basis that 6 g per day is sufficient to restore adequate concentrations in those deficient due to critical illness [8, 10, 12, 22], however the dose necessary to replete ascorbate loss during cardiopulmonary bypass is unknown. Despite this relatively large dose, meta-analyses of 1) 74 studies in which 2,801 subjects received 6 g per day or more of ascorbic acid and 2) 15 studies in which 2,490 subjects received less than or greater than 10 g per day of ascorbic acid, did not conclude any increased harm with the administration of ascorbic acid compared to placebo [32, 33]. Five patients in our study presented for cardiac surgery with already low baseline ascorbic acid concentrations, though were unable to assess the reasons for these deficiencies, or whether these patients had a different response to ascorbic acid treatment. No unified definition for vasoplegia exists, and the definition used in our study may overestimate the true incidence. We sought to include patients undergoing valve or myectomy surgery due to our center's experience and internal data demonstrating such elective cases to have a higher likelihood of vasoplegia, and exclusion of isolated coronary revascularization surgeries as these have been shown to provide a protective effect against vasoplegia [34]. Because of this, the findings should not be extrapolated to all types of cardiac surgeries. Additionally, the patients included in our study had relatively short cardiopulmonary bypass runs whereas longer durations have been associated with increased risk of vasoplegia [34], and thus, our findings may not reflect those at highest risk. Because of our small sample size, the comparison of clinical outcomes may be unreliable. The reasons for higher vasopressor dosages in the treatment group are unclear and unable to be determined. Additionally, because we only performed microscopy on patients in the pilot trial and not on the historical controls, we cannot draw any conclusions on the effects of ascorbic acid on microcirculation.

Conclusions

A multifaceted intervention of ascorbic acid administration, laboratory assessment, and microcirculation measurement in preoperative, intraoperative, and postoperative phases of care in patients undergoing cardiopulmonary bypass was not feasible in this single-arm pilot study. Evaluation of the microcirculation in the setting of cardiac surgery and cardiopulmonary bypass was challenging. Due to limited patient numbers and data points and suboptimal quality images obtained, our ability to comment on the impact of ascorbic acid on the microvasculature is limited. Advances in video microscopy and software improvements that enhance image acquisition and analysis that are now available, and devices that assess other vascular beds such as other mucosal membranes or nail beds could improve the feasibility of studying the microvasculature in this context. The utility of ascorbic acid on post-cardiopulmonary bypass vasoplegia remains unclear.

Abbreviations

DD DeBacker density
MAP Mean arterial pressure
PPV Proportion perfused vessels

Acknowledgements

The authors would like to thank Laurie Meade, RN and the Anesthesia Clinical Research Unit for their assistance with this study.

Meeting presentation

A portion of the data from this study have been presented in abstract form at the *International Anesthesia Research Society Annual Meeting 2021*, May 16, 2021.

Authors' contributions

PMW, SDN, and EDW conceived and designed the study. PMW, MAR, SEN, and EDW were responsible for acquisition of the data. PMW performed the analysis. All authors interpreted the data. PMW drafted the manuscript. All authors read and substantially modified subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Mayo Clinic Department of Anesthesiology Small Grants Program and the Mayo Clinic Department of Pharmacy Small Grants Program.

Data availability

The data generated and analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Mayo Clinic Institutional Review Board (no. 18–003358 and no. 22–009270) and registered in the ClinicalTrials.gov repository on November 14, 2018 (NCT03744702). The trial was carried out ethically following the Helsinki Declaration 1975, revised in 2000. Each trial participant provided written informed consent for enrollment and publication of the study data.

Consent for publication

Not applicable.

Competing interests

PMW serves as a consultant for Wolters Kluwer/UpToDate and has previously served as a consultant for Viatris. EDW serves as a consultant for Pacira Biosciences, Inc. All other authors declare no conflict of interest.

Author details

[1]Department of Pharmacy, Mayo Clinic, 200 First Street SW, RO_MB_GR_722PH, Rochester, MN 55905, USA. [2]Department of Anesthesiology, Mayo Clinic, 200 First Street SW, RO_MB_GR_722PH, Rochester, MN, USA. [3]Department of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA. [4]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA. [5]Department of Pharmacy, Mayo Clinic, Eau Claire, WI, USA. [6]Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, USA.

Received: 27 November 2024 Accepted: 18 May 2025
Published online: 22 May 2025

References

1. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery—review of pathophysiology and update of treatment options. Crit Care. 2020;24:36.
2. Weis F, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, et al. Association between vasopressor dependence and early outcome in patients after cardiac surgery. Anaesthesia. 2006;61:938–42.
3. Levin MA, Lin H-M, Castillo JG, Adams DH, Reich DL, Fischer GW. Early On–Cardiopulmonary Bypass Hypotension and Other Factors Associated With Vasoplegic Syndrome. Circulation. 2009;120:1664–71.
4. Levy B, Fritz C, Tahon E, Jacquot A, Auchet T, Kimmoun A. Vasoplegia treatments: the past, the present, and the future. Crit Care. 2018;22:52.
5. Suero OR, Park Y, Wieruszewski PM, Chatterjee S. Management of Vasoplegic Shock in the Cardiovascular Intensive Care Unit after Cardiac Surgery. Crit Care Clin. 2024;40:73–88.
6. Wieruszewski PM, Khanna AK. Vasopressor Choice and Timing in Vasodilatory Shock. Crit Care. 2022;26:76.
7. Hill A, Wendt S, Benstoem C, Neubauer C, Meybohm P, Langlois P, et al. Vitamin C to Improve Organ Dysfunction in Cardiac Surgery Patients—Review and Pragmatic Approach. Nutrients. 2018;10:974.
8. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock. Chest. 2017;151:1229–38.
9. Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. JAMA. 2021;325:742.
10. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. JAMA. 2020;323:423.
11. Rodemeister S, Duquesne M, Adolph M, Nohr D, Biesalski HK, Unertl K. Massive and long-lasting decrease in vitamin C plasma levels as a consequence of extracorporeal circulation. Nutrition. 2014;30:673–8.
12. Yanase F, Bitker L, Hessels L, Osawa E, Naorungroj T, Cutuli SL, et al. A Pilot, Double-Blind, Randomized, Controlled Trial of High-Dose Intravenous Vitamin C for Vasoplegia After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020;34:409–16.
13. Oudemans-van Straaten HM, Man AMS, De Waard MC. Vitamin C revisited. Crit Care. 2014;18:460.
14. Flick M, Duranteau J, Scheeren TWL, Saugel B. Monitoring of the Sublingual Microcirculation During Cardiac Surgery: Current Knowledge and Future Directions. J Cardiothorac Vasc Anesth. 2020;34:2754–65.
15. Koning NJ, Atasever B, Vonk ABA, Boer C. Changes in Microcirculatory Perfusion and Oxygenation During Cardiac Surgery With or Without Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 2014;28:1331–40.
16. Sakr Y, Dubois M-J, De Backer D, Creteur J, Vincent J-L. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock*. Crit Care Med. 2004;32:1825–31.
17. Biesalski HK, McGregor GP. Antioxidant therapy in critical care—Is the microcirculation the primary target? Crit Care Med. 2007;35 Suppl:S577–83.
18. Jentzer JC, Vallabhajosyula S, Khanna AK, Chawla LS, Busse LW, Kashani KB. Management of Refractory Vasodilatory Shock. Chest. 2018;154:416–26.
19. Wieruszewski PM, Leone M, Kaas-Hansen BS, Dugar S, Legrand M, McKenzie CA, et al. Position Paper on the Reporting of Norepinephrine Formulations in Critical Care from the Society of Critical Care Medicine and European Society of Intensive Care Medicine Joint Task Force. Crit Care Med. 2024;52:521–30.
20. On behalf of the Cardiovascular Dynamics Section of the ESICM, Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, et al. Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2018;44:281–99.
21. Section 2: AKI Definition. Kidney International Supplements. 2012;2:19–36.
22. Wieruszewski PM, Nei SD, Maltais S, Schaff HV, Wittwer ED. Vitamin C for Vasoplegia After Cardiopulmonary Bypass: A Case Series. A&A Practice. 2018;11:96–9.
23. Tyml K. Vitamin C and Microvascular Dysfunction in Systemic Inflammation. Antioxidants. 2017;6:49.
24. Ashor AW, Lara J, Mathers JC, Siervo M. Effect of vitamin C on endothelial function in health and disease: A systematic review and meta-analysis of randomised controlled trials. Atherosclerosis. 2014;235:9–20.
25. Tyml K, Li F, Wilson JX. Septic impairment of capillary blood flow requires nicotinamide adenine dinucleotide phosphate oxidase but not nitric oxide synthase and is rapidly reversed by ascorbate through an endothelial nitric oxide synthase-dependent mechanism*. Crit Care Med. 2008;36:2355–62.
26. Myers GJ, Wegner J. Endothelial Glycocalyx and Cardiopulmonary Bypass. J Extra Corpor Technol. 2017;49:174–81.
27. Bouglé A, Allain P-A, Favard S, Ait Hamou N, Carillion A, Leprince P, et al. Postoperative serum levels of Endocan are associated with the duration of norepinephrine support after coronary artery bypass surgery. Anaesth Crit Care Pain Med. 2018;37:565–70.
28. Madhivathanan PR, Fletcher N, Gaze D, Thomson R, Chandrasekaran V, Al-Subaie N, et al. Perioperative kinetics of endocan in patients undergoing cardiac surgery with and without cardiopulmonary bypass. Cytokine. 2016;83:8–12.
29. Abou-Arab O, Kamel S, Beyls C, Huette P, Bar S, Lorne E, et al. Vasoplegia After Cardiac Surgery Is Associated With Endothelial Glycocalyx Alterations. J Cardiothorac Vasc Anesth. 2020;34:900–5.
30. Kortekaas KA, Lindeman JHN, Reinders MEJ, Palmen M, Klautz RJM, De Groot PG, et al. Pre-existing endothelial cell activation predicts vasoplegia after mitral valve surgery†. Interact Cardiovasc Thorac Surg. 2013;17:523–30.
31. Juncos LA, Wieruszewski PM, Kashani K. Pathophysiology of Acute Kidney Injury in Critical Illness: A Narrative Review. In: Prakash YS, editor. Comprehensive Physiology. 1st ed. Wiley; 2022. p. 3767–80.
32. Zayed Y, Alzghoul BN, Banifadel M, Venigandla H, Hyde R, Sutchu S, et al. Vitamin C, Thiamine, and Hydrocortisone in the Treatment of Sepsis: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. J Intensive Care Med. 2022;37:327–36.
33. Patel JJ, Ortiz-Reyes A, Dhaliwal R, Clarke J, Hill A, Stoppe C, et al. IV Vitamin C in Critically Ill Patients: A Systematic Review and Meta-Analysis. Crit Care Med. 2022;50:e304–12.
34. Dayan V, Cal R, Giangrossi F. Risk factors for vasoplegia after cardiac surgery: a meta-analysis. Interact Cardiovasc Thorac Surg. 2019;28:838–44.

Publisher's Note