ISRCTN29876186 https://doi.org/10.1186/ISRCTN29876186

Vitamin C to prevent pulmonary complications in cardiac surgery

Submission date	Recruitment status	[ ] Prospectively registered
30/01/2024	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
02/02/2024	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
18/03/2025	Respiratory	

Plain English summary of protocol

Background and study aims
This study investigates the influence of high parenteral (200mg/kg/24h) perioperative (48h) doses of vitamin C, on the incidence and severity of postoperative pulmonary complications (PPC) in patients submitted to cardiac surgery (CS) with extracorporeal circulation (ECC). The rationale for this therapeutic regimen relies on the fact that oxidative stress and systemic inflammation are most intense within the first 48 hours after CS, and so is the peak consumption of vitamin C.

Who can participate?
Patients aged ≥18 years undergoing an elective CS procedure with ECC, regardless of the type of planned operation

What does the study involve?
Participants are randomly assigned to control group A (n=75) and interventional group B (n=75). Group B will intraoperatively receive 1/4 of the planned daily vitamin C dose (200mg/kg/24h), diluted in 10 ml of normal saline, divided into three parts, while Group A will receive an equal volume of normal saline at the same time frames. After 6 h from the first intraoperative dose, the following regimen will be applied: Group B: 200 mg/kg/24h - 30 min i.v. infusion of vitamin C in 50 ml of normal saline, every 6h, for the next 48h, and Group A: 30 min i.v. infusion of an equal volume of normal saline every 6 hours, for the next 48h. A scoring tool will be used to determine the incidence and severity of PPC.

What are the possible benefits and risks of participating?
If applied doses of vitamin C significantly reduce the incidence and severity of PPC in CS patients, this would be of great benefit in terms of overall outcome and healthcare costs. Potential risks of high doses of vitamin C are minimized by excluding the patients at risk before the study and by careful monitoring of the renal function.

Where is the study run from?
UC Clinical Centre of Serbia, Clinic for Cardiac Surgery (Serbia)

When is the study starting and how long is it expected to run for?
May 2022 to January 2023

Who is funding the study?
Primary: Sponsoring organization, UC Clinical Centre of Serbia, as a clinical branch of the Medical Faculty, University of Belgrade, is covering medical expenses for all in-hospital patients, including the study patients, following the national health-care policy. The study has not received any external funding nor any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Secondary: All other incidental costs will be covered by the study researchers, declaring no conflict of interest in the protocol and the funding statement of the study.

Who is the main contact?
Mladen J. Kočica, M.D., Ph.D., kocica@sbb.rs (Serbia)

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Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title

The influence of high dose parenteral vitamin C supplementation on incidence and severity of postoperative pulmonary complications after cardiac surgery with extracorporeal circulation: a prospective, randomized, single-blinded, interventional study

Study objectives
High daily doses of parenterally administered vitamin C will reduce the severity of postoperative pulmonary complications after cardiac surgery with extracorporeal circulation.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 07/07/2022, Ethics Committee of Medical Faculty UC Belgrade (8th Dr Subotić St, Belgrade, 11000, Serbia; +381 (11) 3636300; mf.bg@med.bg.ac.rs), ref: 1322/VII-24

Study design
Prospective randomized single-blinded interventional study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment, Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Prevention of postoperative pulmonary complications after cardiac surgery with extracorporeal circulation

Interventions
Randomization will be conducted by assigning each consecutive respondent in a 1:1 manner to either the control (A) or intervention (B) groups. The order of this allocation will be determined through manual random selection.

During the intraoperative phase, patients in the intervention group (B) will receive 1/4 of the planned daily dose of Vitamin C (200mg/kg/24h). This dosage will be divided into three parts, diluted in 10 ml of normal saline, and administered via a central venous catheter. This administration will occur 10 minutes after the induction of anesthesia, 10 minutes before the removal of the aortic cross-clamp (reperfusion), and at the beginning of sternal closure. The control group (A) will receive an equivalent volume of normal saline at the specified times. Postoperatively (beginning 6 hours after the first intraoperative dose), Vitamin C will be administered as follows:

Intervention group (B): 200 mg/kg/24h - 48h - 30 min intravenous infusion of Vitamin C in 50 ml of normal saline every 6 hours, under UV protection.

Control group (A): 30 min intravenous infusion of an equal volume of normal saline every 6 hours, under UV protection.

Patients from group B will continue to receive enteral supplementation of Vitamin C (2g/24h) until discharge and will be advised to continue this supplementation for a week thereafter.

The outcome measures comprise investigating the severity of postoperative pulmonary complications (PPC) using a modified Kroenke's scoring tool where the severity of PPC was graded on an ordinal scale of 0 (no PPC) to 5 (death before discharge) and the values from 1 to 4 depict the increasing severity of the PPC, and the worst registered postoperative value (i.e. the highest score grade) is used for the analyses. The incidence of PPC is also measured using a modified Kroenke's scoring tool to identify the patients with postoperative values ≥ 3 (overall incidence, N, %), and to make further comparisons of PPC incidence between the groups (control-A and intervention-B). Score values are determined and recorded by a blinded assistant.

Intervention Type
Supplement

Primary outcome measure
1. The severity of postoperative pulmonary complications (PPC) measured using the modified Kroenke's scoring tool daily at baseline, and during the first 7 postoperative days
2. The incidence of PPC measured using the modified Kroenke's scoring tool daily, at baseline and during the first 7 postoperative days

Secondary outcome measures
The secondary outcome measures are grouped as follows:

1. Pulmonary Oxygenation and Ventilation:
1.1. Horowitz Index: PaO_2/FiO_2 – is calculated by using PaO_2 values from the ABG analysis and FiO_2 from the oxygen delivery device, 48 hours after the surgery
1.2. Alveolar–arterial Gradient: A-aDO_2 – is directly recorded from the ABG analyzer, 48 hours after the surgery
1.3. Time Spent on Mechanical Ventilation – is calculated for each patient before the transfer from the ICU as the total number of hours spent on mechanical ventilation, from the time of intubation (or initiation of non-invasive ventilation) to the time of extubation (or discontinuation of non-invasive ventilation).

2. Inflammatory Markers: (Procalcitonin, C-reactive Protein, Leucocytes, Neutrophils, Lymphocytes, Sedimentation Rate, Fibrinogen, Albumin, D-dimer, and Ferritin) all measured from blood samples processed in the clinical hematological and biochemical laboratory following standard hospital laboratory protocols and recorded at baseline, 0, 24, 48, 72 and 96 hours after the surgery

3. Renal Function: (Glomerular Filtration Rate (GFR) < 60mL/min, Creatinine, Urea) all measured from blood samples processed in the clinical hematological and biochemical laboratory following standard hospital laboratory protocols and recorded at baseline, 0, 24, 48, 72 and 96 hours after the surgery

4. Non-pulmonary Postoperative Complications: (Postoperative nausea and vomiting -PONV, delirium, transfusion, acute renal failure, wound infection, cardio-pulmonary-resuscitation – CPR) all assessed as an episode (event) after being assessed and documented by the blinded attending practitioner and recorded using the medical documentation tool before the discharge from the hospital

5. Postoperative Organ Dysfunction:
1. SOFA Score - Sequential Organ Failure Assessment (SOFA) score calculated and recorded by a blinded assistant 48 hours after the surgery
2. ASA/SOFA Ratio - The American Society of Anesthesiologists (ASA) score is calculated and recorded by a blinded assistant at baseline and ASA/SOFA ratio is calculated upon discharge from the ICU

6. Intensive Care Unit (ICU) Parameters:
6.1. Re-admission – recorded at the time of occurrence and counted before the hospital discharge, as any new episode (event) of ICU admission after the initial ICU discharge, regardless of medical reason and time spent in the ICU after re-admission.
6.2. Length of Stay - calculated as the total number of hours spent in ICU for each patient upon discharge from the ICU, measured from any (initial and subsequent) admission to ICU to discharge from the ICU

7. Hospital Parameters:
7.1. Length of Stay - calculated as the total number of days spent in the hospital and recorded upon discharge from the hospital measured as the number of days from admission to discharge from the hospital
7.2. Hospital Mortality – defined as death from any cause during the hospital stay and recorded upon discharge from the hospital

Overall study start date
15/05/2022

Completion date
31/01/2023

Eligibility

Key inclusion criteria
1. Aged ≥18 years old
2. Undergoing an elective cardiac surgery (CS) procedure with extracorporeal circulation (ECC), regardless of the type of planned operation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Both

Target number of participants
140

Total final enrolment
150

Key exclusion criteria
1. Previous CS operation
2. Emergency patients
3. Clinically and/or radiographically active lung disease
4. The systolic pressure in the pulmonary artery >60 mm Hg
5. Allergy to ascorbic acid
6. Gout
7. Hemodialysis
8. Significant oxaluria
9. Uric nephrolithiasis
10. Glu-cose-6-phosphate dehydrogenase enzyme deficiency
11. Hemochromatosis
12. Sickle cell anemia
13. Sideropenic anemia
14. Thalassemia
15. Operations with an ECC time ≥6h
16. Death during hospitalization caused by non-pulmonary reasons
17. Withdrawal of previously given consent to participate in the study

Date of first enrolment
15/07/2022

Date of final enrolment
30/11/2022

Locations

Countries of recruitment
Serbia

Study participating centre
UC Clinical Centre of Serbia
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Funder(s)

Funder type
University/education

Funder Name
University of Belgrade

Alternative Name(s)
Univerzitet u Beogradu

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Serbia

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
15/02/2024

Individual participant data (IPD) sharing plan
The dataset generated during and/or analysed during the current study will be available upon request from Mladen J. Kočica, M.D., Ph.D., kocica@sbb.rs

The deidentified participant data and data dictionaries from this trial will be available upon request to researchers who provide a methodologically sound proposal for analyses that are in line with the original study objectives. The data will be available from 6 months after publication until 3 years following the publication of the study. To gain access, data requestors will need to sign a data access agreement and agree to report their findings in a peer-reviewed journal. Data will be shared through a secure online platform. The study protocol, statistical analysis plan, informed consent form, and clinical study report will be available on the trial website.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/03/2024	18/03/2025	Yes	No