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BMJ Open Early intravenous high-dose vitamin C in postcardiac arrest shock (VICEPAC): study protocol for a randomised, single-blind, open-label, multicentre, controlled trial

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ABSTRACT

Introduction The high incidence of morbidity and mortality associated with the post-cardiac arrest (CA) period highlights the need for novel therapeutic interventions to improve the outcome of out-of-hospital cardiac arrest (OHCA) patients admitted to the intensive care unit (ICU). The aim of this study is to assess the ability of high-dose intravenous vitamin C (Vit-C) to improve post-CA shock.

Methods and analysis This is a single-blind, open-label, multicentre, randomised controlled trial, involving 234 OHCA patients with post-CA shock planned to be enrolled in 10 French ICUs. Patients will be randomised to receive standard-of-care (SOC) or SOC with early high-dose intravenous Vit-C administration (200 mg/kg per day, within 6 hours after return of spontaneous circulation, for 3 days). The primary endpoint is the cumulative incidence of vasopressor withdrawal at 72 hours after enrolment, with death considered as a competing event. The main secondary endpoints are neurological outcome, mortality due to refractory shock, vasopressor-free days and organ failure monitored by the sequential organ failure assessment score.

Ethics and dissemination The study protocol was approved by a French Ethics Committee (EC) on 21 February 2023 (*Comit   de Protection des Personnes Ile de France 1*, Paris, France). Due to the short enrolment period to avoid any delay in treatment, the EC approved the study inclusion before informed consent was obtained. As soon as possible, patient and their relative will be asked for their deferred informed consent. The data from the study will be disseminated through conference presentations and peer-reviewed publications.

Trial registration number NCT05817851.

INTRODUCTION

The management of the post-cardiac arrest (CA) period remains a challenging issue among patients admitted to the intensive care unit (ICU) following an out-of-hospital

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A weight-adjusted dose of intravenous vitamin C will be compared with standard-of-care in out-of-hospital cardiac arrest patients requiring vasopressors.
- ⇒ Comprehensive data collection will allow the analysis of vasopressor withdrawal and clinical outcomes, such as organ dysfunction or neurological outcome.
- ⇒ The single-blind design without a placebo in the control group may introduce bias.
- ⇒ Haemodynamic management will be standardised in both arms to avoid variability on the primary endpoint.

cardiac arrest (OHCA), despite advancements in postresuscitation care.¹ Indeed, approximately two-thirds of OHCA patients will develop a post-CA syndrome during the initial hours of their management, which can lead to hypotension and shock in up to 70% of cases.^{2,3} This post-CA shock, potentially reversible within 72 hours, is characterised by cardiac and haemodynamic failure, which frequently leads to multiorgan failure (MOF). In the absence of rapid and appropriate therapies, early death occurs in 20–55% of patients.^{2–6} The current post-CA care strategies are focused on optimising the patient's haemodynamic condition, ensuring adequate organ oxygenation and perfusion, and attempting to reduce the brain injury.⁷ However, the high incidence of morbidity and mortality associated with this post-CA period^{2–6} highlights the necessity for the development of novel therapeutic interventions to improve such patients' outcome.^{1,8}

The overproduction of reactive oxygen species (ROS) during the reperfusion period induces oxidative stress, which is a key component of the post-CA syndrome.^{4 5 9} This oxidative stress contributes to cellular damage, myocardial dysfunction and systemic inflammatory responses. Antioxidants are ROS neutralisers and considered as potential therapeutic agents in managing post-CA syndrome.^{10–12} Ascorbic acid or vitamin C (Vit-C) has been previously described, as an ROS neutraliser and an immune response modulator. Vit-C has been demonstrated to improve endogenous catecholamines and vasopressin synthesis, and to reduce endothelial dysfunction.^{13 14} These multifaceted effects have suggested that Vit-C was a promising agent in mitigating the complex pathophysiology of post-CA shock.¹⁵ Preclinical and clinical studies have suggested the beneficial effect of intravenous high-dose Vit-C to improve shock and organ failures of septic, postoperative or inflammatory origins.^{16–22} Recent meta-analyses have highlighted the potential role of Vit-C to reduce the duration of vasopressor use in patients with septic shock.^{23 24} They also provided safety data on such treatment, with no notable side effects reported in all human studies conducted using high-dose intravenous Vit-C (>200 mg/kg per day). Furthermore, Vit-C seems relevant in animal models of CA, with benefits observed in myocardial function, postresuscitation shock, neuroprotection and survival.^{25 26}

Our aim is to assess the ability of a high-dose intravenous Vit-C administered early following resuscitation to improve the post-CA shock in OHCA. We hypothesise that Vit-C can reduce the severity of post-CA shock, thereby improving organ function, survival and neurological recovery.

METHODS AND ANALYSIS

Study setting

The early intravenous high-dose Vit-C efficacy on post-cardiac arrest shock (VICEPAC) trial is an open-label, multicentre (10 French ICUs), randomised controlled trial (RCT), comparing two arms. The trial is sponsored by the Centre Hospitalier de Béthune-Beuvry – Hôpitaux Publics de l'Artois, a non-university tertiary care centre, without any external funding. The initial study protocol was approved by a French Ethics Committee (EC) on 21 February 2023 (*Comité de Protection des Personnes Ile de France 1*, Paris, France) and will be performed in accordance with the Declaration of Helsinki. The study was prospectively registered at ClinicalTrials.gov on 23 March 2023 (NCT05817851) and at the EudraCT database (EudraCT 2022-500717-64-00). Inclusions have commenced in September 2023. An amended version, to clarify inclusion criteria, was finally approved by the same EC on 4 March 2024. This trial follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines

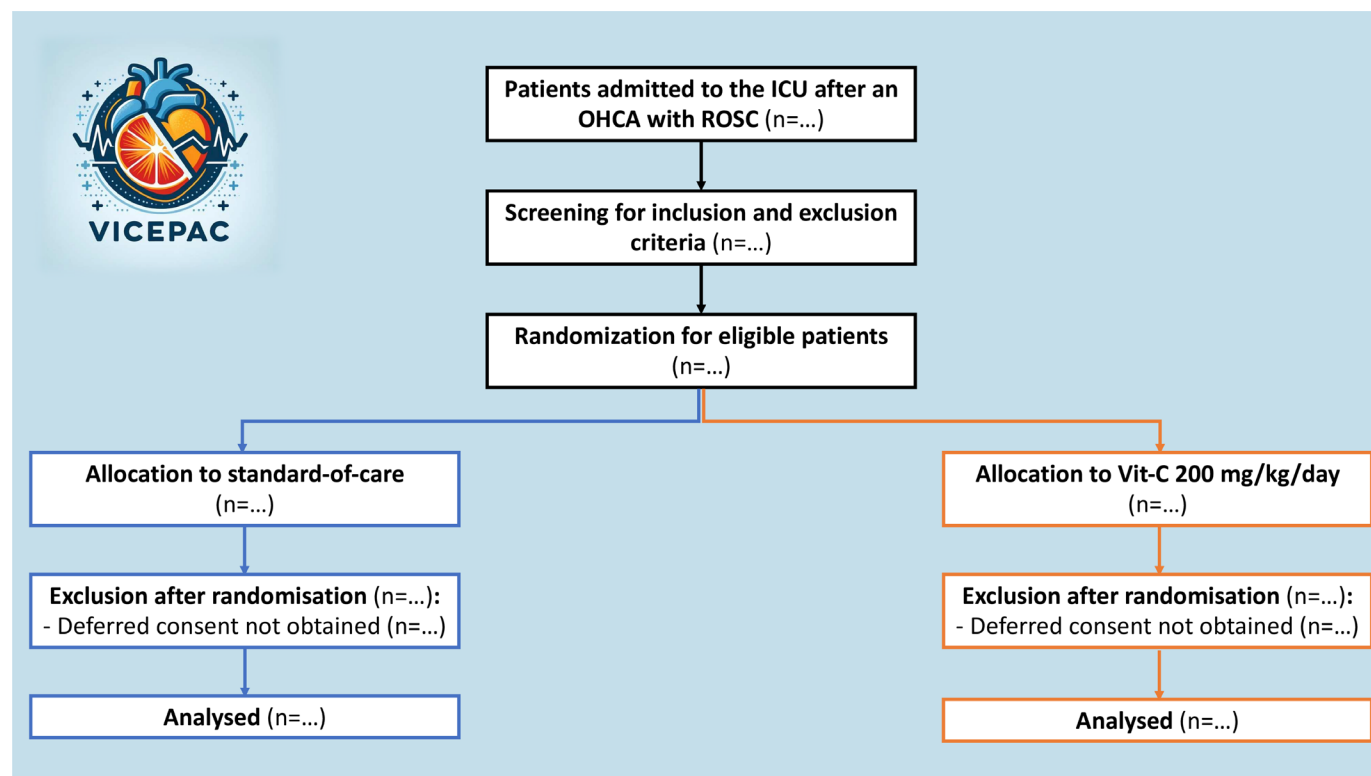


Figure 1 Flow chart of the vitamin C efficacy on postcardiac arrest shock study protocol. ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; Vit-C, vitamin C.

Table 1 Inclusion and exclusion criteria of the vitamin C efficacy on postcardiac arrest shock trial

| Inclusion criteria | Exclusion criteria |
|---|---|
| An adult admitted to ICU for an OHCA with ROSC without obvious extracardiac aetiology, with GCS < 8, and with an early post-CA shock (defined as requirement for epinephrine or norepinephrine continuous infusion, initiated in the first 6 hours after ROSC for at least 30 min to maintain MAP \geq 65 mm Hg). | Pregnancy or No flow+lowflow > 60 min or OHCA to randomisation interval > 6 hours or ECMO requirement in the first 4 hours after ROSC or Known chronic kidney disease with GFR < 30mL per min or Known glucose 6-phosphate dehydrogenase deficiency, or haemochromatosis or History of urolithiasis, oxalate nephropathy or Treatment limitations |

Low flow, interval between basic life support and ROSC; No flow, interval between OHCA occurrence and basic life support. ECMO, extracorporeal membrane of oxygenation; GCS, Glasgow coma scale; GFR, glomerular filtration rate; ICU, intensive care unit; MAP, mean arterial pressure; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

(see online supplemental material for the SPIRIT checklist).²⁷

Patients and public involvement

Patients or the public were not involved in any aspect of the design, conduct, reporting or dissemination of the study protocol.

Population and study protocol

Patients assessed for eligibility will be all the comatose adults admitted alive to a participating ICU after an OHCA. Following screening by the attending physician (see figure 1 for the study flow chart), patients will be included if they meet all the inclusion criteria, including the occurrence of post-CA shock (defined as the requirement for epinephrine or norepinephrine continuous infusion for at least 30 min to maintain mean arterial pressure (MAP) \geq 65 mm Hg) within the first 6 hours after the return of spontaneous circulation (ROSC), and none of the exclusion criteria (table 1). Following their ICU admission, patients will be randomised as soon as possible, within the first 6 hours after ROSC, and allocated to one of two arms (figure 2). The ‘standard-of-care’ (SOC or control) group will be managed according to the current recommendations.¹ Intravenous Vit-C supplementation for up to 1000 mg per day after day 3 and intravenous thiamine supplementation from ICU admission are allowed in the SOC group. In the ‘Vit-C’ group, in addition to SOC, patients will receive 200 mg/kg per day of intravenous Vit-C (Laroscorbine, ascorbic acid ampoules 200 mg/mL, from Bayer Healthcare, France) for 3 days, divided into four boluses of 50 mg/kg every 6 hours, infused for 30 min each (using 100 mL of a 5% dextrose solution). Investigators will be sensibilized to administer the first dose of Vit-C as soon as possible, within 1 hour

following the randomisation. The time of each dose of Vit-C will be recorded. Additionally, patients of the ‘Vit-C’ group will receive intravenous thiamine supplementation (200 mg for 30 min, every 12 hours) for 3 days to prevent the oxalate production and urinary excretion.²⁸

For both groups, post-CA care will be managed in accordance with the local procedures of each participating centre and the current European guidelines¹, including targeted temperature management. Fluid resuscitation and the vasopressor used to restore MAP will be selected by the attending physician, and a decision algorithm will be proposed to adjust the vasopressor continuous infusion level according to MAP (figure 3). Inotrope agents, such as dobutamine, will also be permitted and managed by the attending physician. The prediction of neurological outcome and the decision regarding the withdrawal of life-sustaining therapies will be based on routine practices at each centre in accordance with the current neuroprognostication guidelines.¹

Randomisation and treatment allocation

The randomisation list will be generated by a statistical software programme (SAS, SAS Institute, Cary, North Carolina, USA), according to a balanced parallel design (1:1), stratified by site in the randomised blocks of various sizes. Patients will be randomised in each site by local investigators. Patients and their next of kin will be blinded to the allocated treatment throughout the study period.

Data collection and outcome variables

In each site, all data will be pseudoanonymised and collected using an electronic centralised case report form (eCRF) according to Utstein recommendations²⁹ (see online supplemental table 1 for data collection time

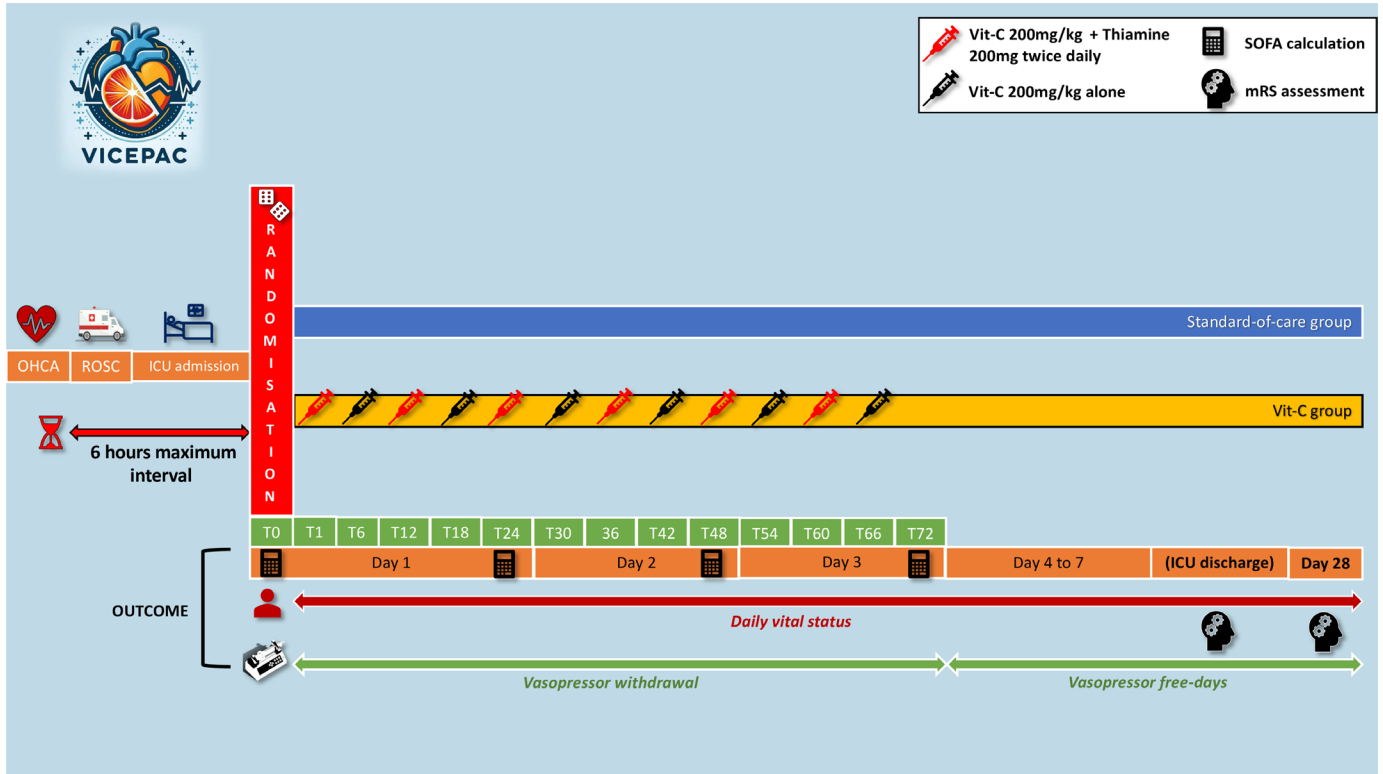


Figure 2 Experimental plan of the vitamin C efficacy on postcardiac arrest shock study protocol. ICU, intensive care unit; mRS, modified Rankin Scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment score; Vit-C, vitamin C.

points). Patient’s characteristics, including age, gender, body mass index and comorbidities, will be collected. The investigator will estimate the patient’s neurofunctional

condition prior to OHCA, using the modified Rankin Scale (mRS). Prehospital data collected will be as follows: OHCA history, CA location and circumstances, bystander

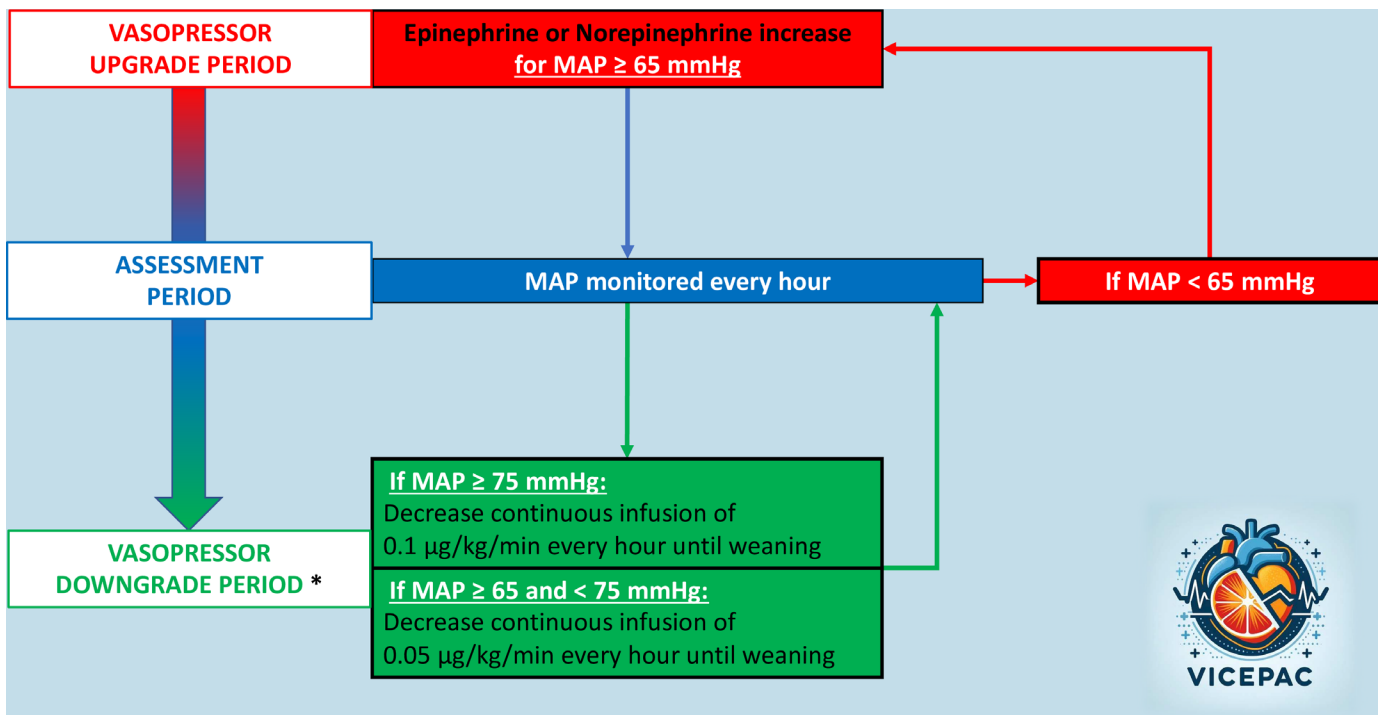


Figure 3 Decision algorithm for haemodynamic management. MAP, mean arterial pressure; *for patients under epinephrine and norepinephrine simultaneously, it is suggested to wean epinephrine first.

cardiopulmonary resuscitation, interval from CA to rescue team arrival, no flow and low flow intervals, initial cardiac rhythm and prehospital management (number of external electric shock delivered and epinephrine boluses, volume of fluid resuscitation and vasopressor dose). The main cause of OHCA (either suspected or confirmed) will be recorded. The sequential organ failure assessment score (SOFA) will be calculated at inclusion ($\text{SOFA}_{\text{baseline}}$), using the worst clinical and biological parameters available between ICU admission and inclusion. Creatinine blood level will be the only considered parameter for the renal $\text{SOFA}_{\text{baseline}}$ subscore, and the neurological $\text{SOFA}_{\text{baseline}}$ subscore will be based on the last Glasgow outcome scale assessed prior to the start of sedation. Daily SOFA from day 1 to 3 after inclusion will be calculated as previously published (patients who die within this interval will be assigned the maximum score of 24 points).³⁰

Primary endpoint

The primary endpoint is the cumulative incidence of vasopressor withdrawal at 72 hours after inclusion. Death during this interval will be considered as a competing event.

Secondary endpoints

The remaining endpoints are as follows: the cumulative incidence of death by refractory shock at day 7 after inclusion, with another mode of death considered as a competing event; the rate of patients with a favourable neurological outcome at day 28 after inclusion (defined as mRS between 0 and 3); the maximal vasopressor level among patients alive during the first 3 days after inclusion; the vasopressor-free days (VFD) at day 28; the difference between SOFA at day 3 (SOFA_{72}) and $\text{SOFA}_{\text{baseline}}$ and the lowest arterial lactate level measured among alive patients up to 72 hours after inclusion.

Statistical method

All statistical analyses will be performed in accordance with the intention-to-treat principle, and the missing data will be considered using the multiple imputation methods.

The primary endpoint will be described in each arm by using the Kalbfleisch and Prentice method, with death considered as a competing event. A comparison will be performed between both groups using the Fine and Grey model, as proposed by Zhou *et al.*³¹, which allows for an adjustment by centre with a marginal model. Furthermore, a sensitivity analysis will be conducted on the per-protocol population, and a subgroup analysis will be performed according to the vasopressor level at inclusion.

The cumulative incidence of death by refractory shock at day 7 will be compared between both groups with the same methodology as described for the primary endpoint. The proportion of surviving patients with a favourable neurological outcome at day 28 will be compared between both groups by a generalised linear model using the generalised estimating equation (GEE) method (with

binomial distribution and log-link function) to account for the centre effect. In case of non-convergence, the Poisson distribution will be used instead of the binomial distribution. The maximal vasopressor level during the first 3 days, the difference between SOFA_{72} and $\text{SOFA}_{\text{baseline}}$ and the lowest arterial lactate level at day 3 will be compared between both groups using a linear mixed model, including centre as a random effect. In case of a non-normal distribution in the residual model, a Mann-Whitney test will be used. A generalised linear model will be used to compare the VFD at day 28 between both groups, with a GEE method (Poisson or negative log-binomial distribution and log-link function) employed to account for the centre effect.

Sample size calculation

In accordance with the findings of the HYPERDIA study³², we have estimated a 28% cumulative incidence of vasopressor withdrawal at day 3 in the SOC group, taking into account of 39% mortality rate in the same interval. A relative increase in the vasopressor withdrawal rate at day 3 of 50% in the Vit-C group (resulting in a 42% cumulative incidence of the primary endpoint) will require the inclusion of 117 patients per group, with a two-sided alpha risk of 5% (log-rank test considering death as a competing event, PASS-12 software), and a power of 80%.

Safety, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR)

A single trial, including 872 ICU patients with septic shock who were randomly assigned to receive either placebo or 200 mg/kg per day of intravenous Vit-C for up to 96 hours, has reported a higher risk of a composite criteria, including death or persistent organ dysfunction at day 28 in the Vit-C group compared with the placebo group. However, all the individual primary and secondary endpoints were comparable between the two groups, and the secondary analysis (such as tissue dysoxia, inflammation or endothelial injury biomarkers) did not identify a potential mechanism for harm associated with Vit-C.³³

The theoretical risks associated with high-dose intravenous Vit-C include a paradoxical pro-oxidative effect among patients with iron overload, haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and the formation of oxalate kidney stones.¹⁴ However, these risks are limited to susceptible patients, who were excluded from the study, such as haemochromatosis, G6PD deficiency or a history of urolithiasis and oxalate nephropathy (table 1). Furthermore, the thiamine supplementation in the Vit-C group will mitigate the risk of oxalate precipitation. Nevertheless, a factitious hyperglycaemia has previously been described among patients treated with high-dose intravenous Vit-C, but only with some capillary blood glycaemia measuring devices.^{33 34} Consequently, each participating centre was advised to measure glycaemia using blood gas analysis or their central laboratory from inclusion to day 7 for patients of the Vit-C group. Several RCTs using similar

high-dose intravenous Vit-C and meta-analyses in critically ill patients have not documented any notable additional AEs or SAEs.^{19 35–37} However, as required by French legislation regarding RCT on medications, all AEs will be reported in the eCRF, and all SAEs and SUSARs will be promptly notified to the study pharmacological vigilance committee. Furthermore, all other treatments administered from the inclusion until day 28 or ICU discharge will also be recorded.

Monitoring

No interim analysis is planned. As requested by French legislation, a safety report will be submitted annually to the French EC and the French national drugs safety agency (*Agence Nationale de Sécurité du Médicament*, St Denis, France).

ETHICS AND DISSEMINATION

The initial study protocol was approved by a French EC on 21 February 2023 (*Comité de Protection des Personnes Ile de France I*, Paris, France). Due to the short enrolment period and the necessity to avoid any delay in treatment, the EC has approved an emergency inclusion procedure, including the deferred informed consent of the patient and his next of kin. In the absence of a relative who could be informed before the maximal delay of inclusion, and given the initial comatose state of such patients, investigators are permitted to include and randomise the patient to start the allocated treatment without delay. As soon as possible, the patient and his relative will be asked for their deferred informed consent. The EC has not established a specific timeframe for obtaining deferred informed consent from both the patient and his relative. Patient or his relative may choose to withdraw their consent to participate at any time in the study. In accordance with French legislation regarding RCT and deferred consent, the data collected prior to their withdrawal may be retained for analysis. The results of the trial will be disseminated via conference presentations and peer-reviewed publications, in accordance with the Consolidated Standards of Reporting Trials statement.³⁸

DISCUSSION

The VICEPAC trial is the first randomised trial to assess the impact of a high-dose intravenous Vit-C, in comparison with SOC, in OHCA patients with post-CA shock requiring vasopressors.

To date, only two recent studies have described the effect of supplemental intravenous Vit-C in such patients. Kim *et al* conducted a retrospective analysis of 234 OHCA patients treated with or without intravenous Vit-C using at a fixed dose of 6 g per day for 3 days. The main result was the absence of a beneficial of Vit-C on neurological outcome at 1 month after ICU admission.³⁹ However, the authors could have underestimated the benefit of Vit-C on patients' outcome for several parameters, including

the lower dose of Vit-C used in comparison with previous studies on sepsis, the various causes of CA in their cohort and a potential selection bias due to the retrospective design.⁴⁰ Privšek *et al* have recently published the results of an RCT, comparing a low-dose intravenous Vit-C (3 g per day for 4 days) to placebo, in a small cohort of 30 OHCA patients. The authors demonstrated no difference in neuron-specific enolase levels between the two groups.⁴¹ The only similar study to ours concluded its enrolment phase recently (NCT03509662). The VITaCCA RCT was designed to include 270 OHCA patients with shockable rhythms, regardless of the occurrence of post-CA shock, to compare two different intravenous Vit-C dosing regimens (3 or 10 g daily for 96 hours) to placebo, on organ dysfunction using SOFA as a primary outcome.⁴²

Limitation

Several limitations must be highlighted. First, we designed a single-blind trial without placebo in the SOC group. Indeed, we consider our study as pragmatic and exploratory, mainly focused on the haemodynamic impact of Vit-C on post-CA shock. However, our study could provide complementary results to the VITaCCA (early high-dose vitamin C in post-cardiac arrest syndrome) trial⁴², and both studies could warrant further investigation regarding Vit-C supplementation in CA. Although the single-blind design may introduce bias regarding our primary endpoints, we believe this will be mitigated by the implementation of the decision algorithm (figure 3) for both groups, which will guide ICU nurses and physicians in vasopressor management during the study period. Second, while two studies have previously demonstrated a significant reduction in vasopressor duration (>50%) using a bundle of hydrocortisone, Vit-C and thiamine supplementation in patients with severe sepsis and septic shock^{18 43}, our primary hypothesis for the sample size calculation remains empirical, given the lack of published preclinical or clinical data on Vit-C in CA. Nevertheless, the VITaCCA trial, as mentioned above, has a similar sample size to assess the ability of Vit-C to improve organ failure in OHCA patients.⁴² Third, we decided that a minimum dose of vasopressor would not be included in the inclusion criteria, even if they are introduced at low levels. Indeed, there is currently no consensus regarding the minimum dose of vasopressor to define post-CA shock. Moreover, we have considered that awaiting a significant increase in vasopressor level might delay the initiation of Vit-C, and we planned a subgroup analysis on the primary endpoint according to the level of vasopressors at inclusion. Fourth, the study does not include any blood measurement of Vit-C levels. OHCA patients were previously described as at high risk of Vit-C deficiency at ICU admission, similar to septic patients. This progressive decline in Vit-C levels over time is mainly due to a significant oxidative stress, with an increasing metabolic demand and an excessive Vit-C consumption.⁴⁴ But the high dose of Vit-C selected in our study is similar to the

previous works on septic shock and allows to reach supra-normal Vit-C blood levels as previously demonstrated.⁴⁵

In conclusion, this trial addresses a significant gap in current postresuscitation care practices by focusing on a novel therapeutic approach. The results of our study could provide valuable insights into the role of Vit-C regarding post-CA care.

Trial status

The first patient was enrolled on 27 December 2023. The current version of the study protocol is V.3.0, dated 22 January 2024. The estimated date of study completion is December 2025.

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Contributors As the study guarantor, JC is responsible for the overall content. JC, HB, and CV conceived, designed, and supervised the study protocol and wrote the first draft of the manuscript. NP, GS, JM, MB, ON, SP, LVPV, FT, FL, ND, TB, and LD are investigators of the participating ICU and reviewed the manuscript for important intellectual content and approved the final submitted version.

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Competing interests None declared.

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