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Sodium bicarbonate for the treatment of severe metabolic acidosis with moderate or severe acute kidney injury in the critically ill: protocol for a randomised clinical trial (BICARICU-2)

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ABSTRACT

Introduction When both severe metabolic acidemia (pH equal or less than 7.20; PaCO2 equal or less than 45 mm Hg and bicarbonate concentration equal or less than of 20 mmol/L) and moderate-to-severe acute kidney injury are observed, day 28 mortality is approximately 55%–60%. A multiple centre randomised clinical trial (BICARICU-1) has suggested that sodium bicarbonate infusion titrated to maintain the pH equal or more than 7.30 is associated with a higher survival rate (secondary endpoint) in a prespecified stratum of patients with both severe metabolic acidemia and acute kidney injury patients. Whether sodium bicarbonate infusion may improve survival at day 90 (primary outcome) in these severe acute kidney injury patients is currently unknown.

Methods and analysis The sodium bicarbonate for the treatment of severe metabolic acidosis with moderate or severe acute kidney injury in the critically ill: a randomised clinical trial (BICARICU-2) trial is an investigator-initiated, multiple centre, stratified, parallel-group, unblinded trial with a computer-generated allocation sequence and an electronic system-based randomisation. After randomisation, the intervention group will receive 4.2% sodium bicarbonate infusion to target a plasma pH equal or more than 7.30 while the control group will not receive sodium bicarbonate. The primary outcome is the day 90 mortality. Main secondary outcomes are organ support dependences.

Ethics and dissemination The trial has been approved by the appropriate ethics committee (CPP Nord Ouest, Rouen, France, 25 April 2019, number: 19.03.15.72446). Informed consent is required. If sodium bicarbonate improves day 90 mortality, it will become part of the routine care.

Trial registration number NCT04010630.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Trial design: multiple centre randomised trial powered to conclude on the usefulness of sodium bicarbonate in critically ill patients with severe metabolic acidemia and acute kidney injury.
⇒ Sample size: largest trial ever conducted on sodium bicarbonate and metabolic acidemia in the critically ill population.
⇒ Trial pragmatism: population enriched trial comparing sodium bicarbonate (without the use of formula to calculate the amount of bicarbonate given) versus no sodium bicarbonate as per routine clinical use.
⇒ A double-blinded trial was not considered feasible because it would have necessitated masking the acid–base balance to clinicians in a population with severe acidemia on enrolment.

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[1] Severe metabolic acidemia is defined by the combination of pH ≤7.20, bicarbonataemia ≤25 mmol/L and PaCO2 ≤45 mm Hg. It is associated with a high rate of intensive care unit (ICU) mortality (up to 60%) in the critically ill population.[2 3] It accompanies a various spectrum of diseases and is secondary to different mechanisms.[4] Aside specific causes of metabolic acidosis such as ketoacidosis, exogenous acid poisoning etc, 50% of the critically ill patients who develop severe metabolic acidosis do present a combination of hyperlactataemia, and moderate-to-severe kidney injury.[3] Although the extensive review of the association between severe acidemia and organ injuries is beyond the scope of the present manuscript, severe metabolic acidemia has been associated decreased cardiac contractility and cardiac output, predisposition to cardiac arrhythmias, peripheral vasodilatation, hypotension, pulmonary hypertension.[4] Other deleterious effects such as impairment of the immune response and stimulation of inflammatory mediators have also been suggested.[4] On the other hand, increased tissue oxygen delivery

and increased blood flow to tissues secondary to vasodilation have also been reported.[4]

The treatment of metabolic acidemia using sodium bicarbonate is a matter of controversy. Experimental data and (most often single centre) observational studies have not suggested a benefit of sodium bicarbonate infusion in critically ill patients with acidemia while surveys did suggest that physicians largely prescribe sodium bicarbonate in their daily practice.[2 5–8] In a previous multiple centre randomised clinical trial, we found that in critically ill patients with severe metabolic acidemia (pH≤7.20) the infusion of sodium bicarbonate to target a pH equal or higher than 7.30 was not associated with a statistically significant difference in outcome (no difference in the primary endpoint which was the combination of organ failure at day 7 and mortality as well as the estimate of the probability of survival at day 28 between the control group and bicarbonate group: (46% (95% CI 40% to 54%) vs 55% (95% CI 49% to 63%); p=0.09 using the log rank test). However, in a prespecified stratum of patients with moderate-to-severe kidney injury, the infusion of sodium bicarbonate in comparison with no sodium bicarbonate infusion was associated with reduced rate of mortality from enrolment to day 28 between the control group and bicarbonate group: 63% (95% CI 52% to 72%) vs 46% (95% CI 35% to 55%); p=0.0283[3] as well as less renal replacement therapy requirement ((66/90 (73%) vs 47/92 (51%), absolute difference: −22.2 (95% CI −36 to −8.5), p=0.002). Although the BICARICU trial suggested a room for sodium bicarbonate in a subgroup of patients, this indication remains controversial and highly debated in the literature especially about the potential side effects of sodium bicarbonate infusion on homeostasis and the potential benefit of acidemia on cells metabolism and oxygenation.[9–12] Recognising the equipoise between sodium bicarbonate and no sodium bicarbonate in this subpopulation, we have chosen to conduct a further investigation into the use of sodium bicarbonate infusion in critically ill patients presenting with both severe acidemia and moderate-to-severe acute kidney injury (AKI).

Objectives

Primary objective

The main objective is to determine whether sodium bicarbonate infusion mitigates all causes day 90 mortality in critically ill patients with severe metabolic acidemia and moderate-to-severe acute kidney injury in comparison with no sodium bicarbonate infusion.

Secondary objectives

The secondary objectives will be the comparison between the two groups (sodium bicarbonate group vs no sodium bicarbonate group) of the organ failure score (Sequential Organ Failure Assessment (SOFA) score at days 1, 2 and 7) and other secondary outcomes.

The main hypothesis is that sodium bicarbonate infusion will be associated with a decrease in day 90 mortality.

Trial design

The BICARICU-2 trial is an investigator-initiated, multiple centre, stratified, parallel-group unblinded trial with a computer-generated allocation sequence and an electronic system-based randomisation. The intervention group will receive intravenous 4.2% sodium bicarbonate to target a plasma pH equal or greater than 7.30 while the control group will not receive intravenous sodium bicarbonate. We will randomly assigned patients by stratified randomisation with minimisation using a computer generated allocation sequence accessible from each centre through a secured dedicated website with stratification according to trial site, age with a cut-off of 65 years and enrolment pH (≤7.10 vs >7.10). This current study protocol has not been modified.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the BICARICU-2 trial.

Eligibility criteria

Inclusion criteria

An individual must fulfil all of the following criteria at the time of trial enrolment in order to be eligible:

- Aged from 18 years old.
- Admitted in the ICU where the BICARICU-2 trial takes place.
- Within 6 hours before enrolment, the patient MUST present on the same arterial blood gas (the last available before enrolment) the three following criteria
  - pH≤7.20.
  - Bicarbonataemia≤20 mmol/L
  - AND $PaCO_2$≤45 mm Hg.
- Moderate-to-severe acute kidney injury ('Kidney Disease Improving Global Outcome', group of 2 or 3).[13]
- Within 48 hours of ICU admission, a total SOFA≥4 or an arterial lactate concentration ≥2 mmol/L.
- Signed informed consent form. According to the French law, considering the severity of the illness, the fact that most of these patients would be unable to consent (need for sedation or potential delirium) and that their proxies might not be contactable at the time of inclusion, a deferred consent process for emergency situations was enabled. When deferred consent was used, written permission to pursue the research was obtained from the patient or proxy as soon as possible. If this consent was not obtained, the patient's data will not be used and they will be withdrawn from the trial.
- Subjects must be covered by public health insurance by the French law.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included

- Pure respiratory acidosis (defined by pH≤7.20, $PaCO_2$≥50 mm Hg, bicarbonataemia equal or greater

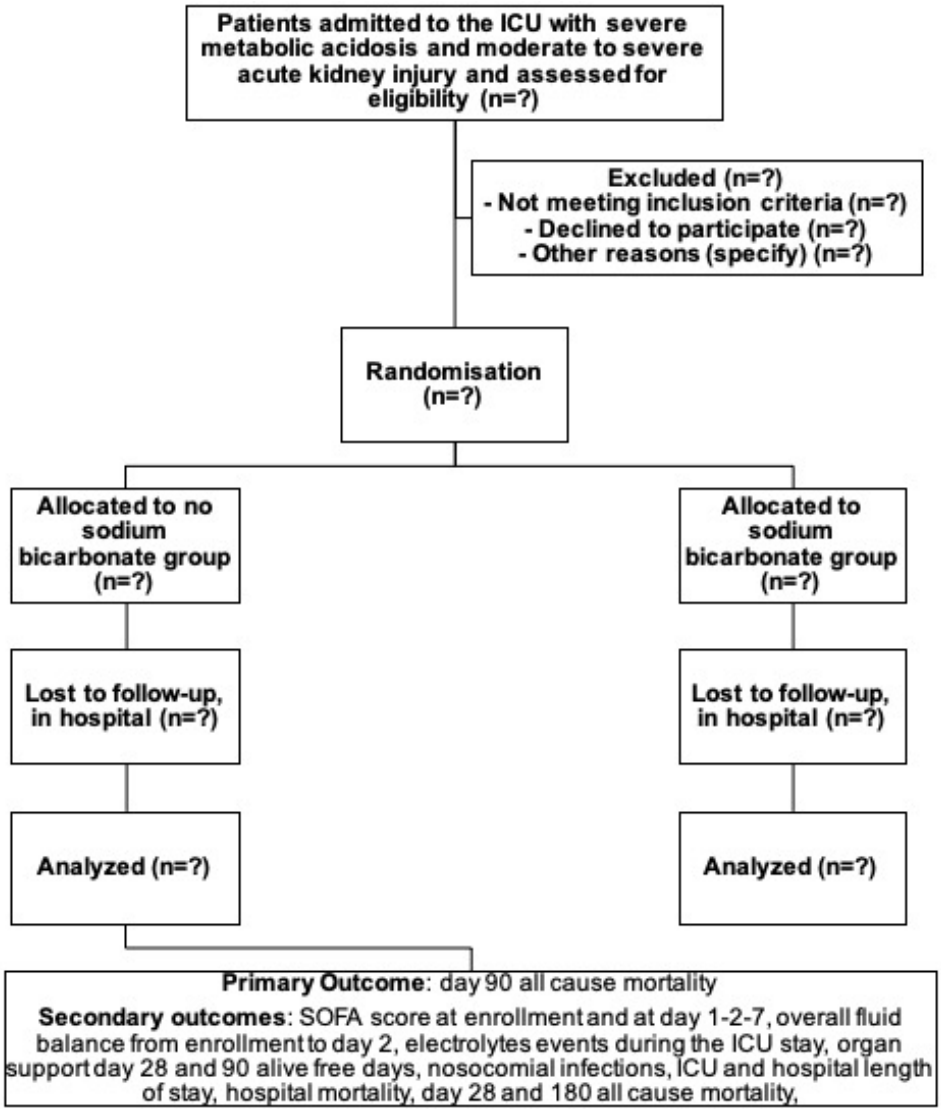

Figure 1 CONSORT diagram of the BICARICU-2 trial. ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; CONSORT, Consolidated Standards of Reporting Trials.

than ($PaCO_2$−40)/10+24), digestive or urinary tract proven loss of fluid (equal or greater than 1500 mL/24 hours) with concomitant loss of sodium bicarbonate, stage IV or V chronic kidney disease, proven tubular acidosis, ketoacidosis, exogenous acids poisoning (aspirin, methanol,), $PaCO_2$≥45 mm Hg and spontaneous breathing, sodium bicarbonate infusion or renal replacement therapy within 24 hours prior to screening prior to screening or imminent in the next 6 hours.

- Pregnant or breastfeeding patient.
- Patient who is in a dependency or employment with the sponsor or the investigator.
- Patient who was enrolled in another study and who is in the exclusion period for any enrolment in the present trial
- Life expectancy less than 48 hours.
- Patients protected by law (Art.L 1121–5, 1121–6, 1121–8 of the French Health Code law register).

Outcomes

Primary outcome

The primary outcome is the day 90 all-cause mortality.

Main secondary outcomes

The main secondary outcomes will be the following

1. Organ Failure assessed by the SOFA score (Time Frame: up to 7 days after enrolment).
2. Overall fluid balance (time frame: day 2).
3. Electrolytes adverse events during the ICU stay (time frame: ICU discharge or day 28).
4. Organ support (renal replacement therapy and mechanical ventilation) day 90 alive free days (time frame: day 90).
5. Hospital-acquired infections (time frame: ICU discharge or day 28).
6. Hospital length of stay (time frame: up to day 180).
7. ICU length of stay (time frame: up to day 90).
8. Day 28 all-cause mortality (time frame: day 28).

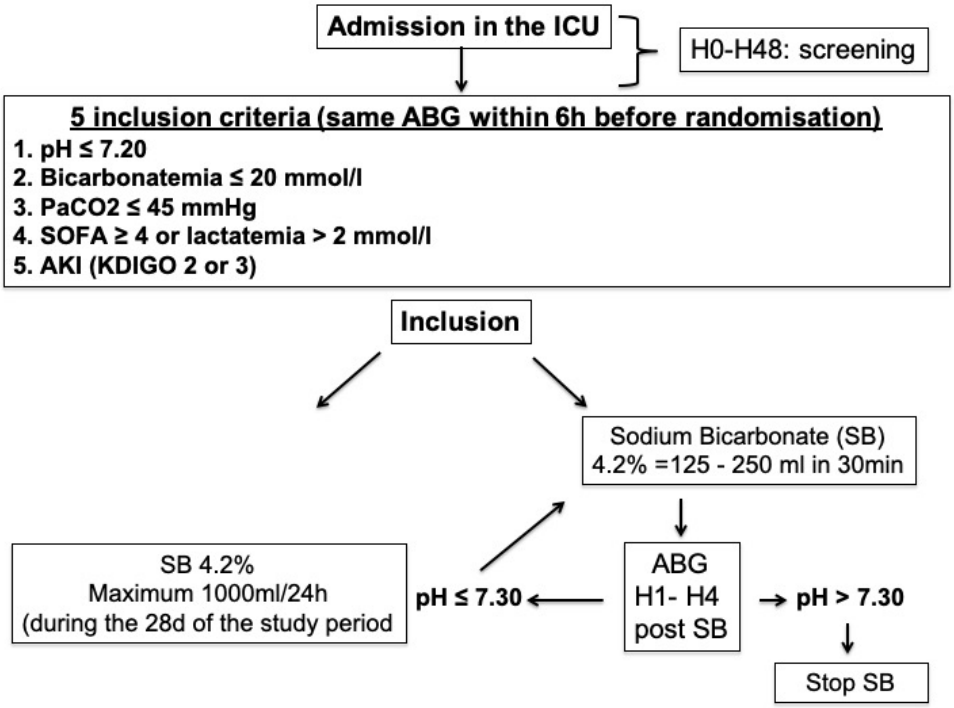

Figure 2 Experimental design of the BICARICU-2 trial. The present trial design was similar than the previously published BICARICU-1 trial except for the inclusion criteria. ABG, arterial blood gas; AKI, acute kidney injury; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SOFA, Sequential Organ Failure Assessment score.

9. Day 180 all-cause mortality (time frame: day 180).
10. Quality of Life of participant (time frame: up to day 180) only in the Montpellier Nimes centres with the centralised post-ICU outpatient clinic.
11. Functional autonomy of patient (time frame: up to day 180) only in the Montpellier Nimes centres with the centralised post-ICU outpatient clinic.

Main safety outcomes

The main safety outcomes will be the incidence, relatedness and severity of treatment-emergent adverse events evaluated at each visit until the end of the trial. According to the BICARICU-2 trial,[3] adverse events will be defined as

- Non-serious: hypernatraemia ≥145 mmol/L without associated neurological disorders, hypokalaemia <3.2 mmol/L without ECG signs, ionised hypocalcaemia <0.9 mmol/L without ECG signs, alkalaemia (pH≥7.45).
- Serious: acute oedema of the lung, severe hypokalaemia with repolarisation disorders and/or cardiac arrhythmias, severe hypocalcaemia with repolarisation disorders and/or cardiac arrhythmias and/or ECG signs of intolerance and cardiopulmonary oedema.

Interventions

Patients eligible for inclusion will be randomly assigned to the experimental group (bicarbonate group) or to the control group (no bicarbonate) (figure 2).

Experimental (sodium bicarbonate) group

Patients randomly assigned to bicarbonate group (sodium bicarbonate 4.2%) will received trial dedicated intravenous 4.2% sodium bicarbonate titrated from 125 mL to 250 mL in 30 min at physician's discretion to target a pH equal or above 7.30. Bicarbonate infusion will be repeated at a maximal volume of 1000 mL per 24 hours. Arterial blood gases will be repeated from 3 to 6 times during the first 24 hours at physician's discretion.

Bicarbonate infusion recommendations will be as follow: a central line is strongly recommended, infusion flow should be performed at 125–250 mL in 30 min with no intravenous push, careful surveillance of metabolic alkalosis, cardiogenic pulmonary oedema, kalaemia, natraemia and calcaemia. Repeated arterial blood gases will be suggested to monitor these critically ill patients and physicians will be informed of the potential side effects of sodium bicarbonate infusion (hypokalaemia, hypocalcaemia, alkalaemia, hypernatraemia, fluid overload).

Control group (no sodium bicarbonate group)

In the control group, patients will not receive any sodium bicarbonate infusion.

There is currently no fluid solution that is associated with no impact of acid–base equilibrium and we can not blind the clinicians for the pH and bicarbonataemia trend over the ICU course of these critically ill patients. We have, therefore, as in the BICARICU-1 trial[3] chose to compare sodium bicarbonate versus no sodium bicarbonate infusion.

Both experimental and control groups

In both groups of patients, criteria will be applied to suggest the need of invasive mechanical ventilation and the renal replacement therapy as follow:

- Invasive mechanical ventilation: respiratory failure with one of the following criteria: respiratory arrest, circulatory arrest, gasps, coma with Glasgow Coma Scale of 8 or below, copious secretions with incapacity to clear the secretions, bradycardia below 50/min with loss of consciousness, circulatory shock needing high dose of vasopressors. Invasive mechanical ventilation will also be suggested in case of respiratory failure with at least two of the following criteria: respiratory acidosis (arterial pH≤7.35 together with PaCO2≥45 mm Hg); arterial O2 saturation by pulse oximetry of less than 90% or PaO2 lower than 60 mm Hg at FiO2 of 0.5 or more; respiratory frequency greater than 35 breaths per min; diminished consciousness, agitation or diaphoresis and clinical signs suggestive of respiratory muscle fatigue, increased work of breathing or both such as use of respiratory accessory muscles, paradoxical motion of the abdomen or retraction of intercostal spaces. Invasive mechanical ventilation will be analysed as a secondary endpoint.
- Renal replacement therapy: on ICU admission and at any time after enrolment, renal-replacement therapy will be strongly recommended when facing kalaemia above 6.5 mmol/L with ECG signs and/or cardiogenic pulmonary oedema with no urine output and PaO2/FiO2<200 with FiO2>50% and PEEP>5 cmH2O. Renal-replacement therapy will be suggested when facing at least two criteria among the following and after 24 hours of enrolment: urine output less than 0.3 mL/kg/24 hours, a pH≤7.20 despite resuscitation or kalaemia above 6.5 mmol/L. Renal replacement therapy will be analysed as a secondary endpoint. Although pH was one of the criteria used in the recent trials[3 14 15] to trigger the initiation of renal replacement therapy, the BICARICU-1 trial suggests that sodium bicarbonate may delay or even avoid in some patients the need for renal replacement therapy. Furthermore, even if acidemia is one of the reason to start renal replacement therapy in the critically ill according to a recent survey,[16] the threshold and the timing to start the therapy is currently unknown. This is the reason why we will recommend in the BICARICU-2 trial, as for BICARICU-1 trial, to start the therapy in case of a persistent acidemia despite 24 hours of resuscitation.

Participant timeline

The participant timeline is described in table 1.

Sample size

Based on the BICARICU-1 trial where day 90 mortality was 81% in the control group and 64% in the bicarbonate group (post hoc analysis of BICARICU-1 trial,[17]) in the population of interest for the BICARICU-2 trial (severe metabolic acidosis and severe acute kidney injury in the critically ill patients), we calculated that a total of 588 patients would be needed for 80% power to show an absolute between-groups difference of 10% in the primary outcome (day 90 all-cause mortality) at a two-sided alpha level of 0.05 (overall p value for the trial), assuming that the administration of bicarbonate would be associated with a day 90 mortality of 70% vs 80% in the control group. Assuming less than 8% non-analyzable patients (lost to follow-up or consent withdrawal; the same rate as in the BICARICU-1 trial), we plan to enrol 640 patients. Two interim analyses are planned. Assuming the overall p value for the trial is 0.05, p value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

Recruitment

Patients are expected to be included during a 3-year inclusion period starting November 2019. Among the 35 participants centre, each one would include one patient per month during the 36 months trial period.

March 2019–October 2019: Protocol, approvals from ethics committee and trial tools development (case report form, randomisation system).

March 12 2020: Ethics committee authorisation to enrol more centres in the trial.

June 9 2021: Ethics committee authorisation to enrol more centres in the trial due to an unexpected decrease in enrolment rates during the pandemic.

November 2019 to ongoing: Inclusion of patients.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Randomisation will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clinical, randomisation module). The randomisation will be centralised and available online. It will be stratified on centre, age and pH balanced with a 1:1 ratio and blocks of variable sizes.

Blinding

Given the nature of the solutions and their impact on acid–base equilibrium, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

- Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Sociodemographic data (age, sex, weight, height, reason for ICU admission, medical history, main cause of acute kidney injury, SAPSII score) will be collected on enrolment.

Table 1 Participant timeline

	Screening/baseline		Final visit
Item	V 1	V 2	V 3
Date	Day 0	Days 190	Day 180
Clinical evaluation	X		
Informed consent	X	X*	
Randomisation	X		
Medical history	X		
Demography	X		
Physical examination	X	X	
Vital signs†	X	X	
Routine laboratory testing‡	X	X	
Experimental treatment	x	x	
Endpoints evaluation§		x	X
AE recording		X¶	

*Informed consent: consent from the patient can be obtained at enrolment but might be confirmed (after or emergency enrolment if the patient cannot consent because of sedation) later during the ICU course and up to the ICU discharge day.
†Vital signs include temperature, heart rate and arterial blood pressure.
‡Routine laboratory testing (blood): haemoglobin, haematocrit, RCC, WCC, PC; INR, PTT, electrolytes, creatinine, ALT, AST, AP, LDH, CRP, arterial blood gases, lactate, albumin.
§Status (alive vs dead) will be collected daily from enrolment to day 90 (main outcome) and at day 180. SOFA score will be collected at enrolment at day 1, day 2 and day 7; electrolytes and fluid balance will be collected at enrolment, day 1, day 2. Electrolytes AEs and nosocomial infections will be collected during the ICU stay with a censored date at day 28. Organ support and ICU and Hospital length of stay will be collected during the ICU stay with a censored date at day 90. Quality of Llife (EQ5D) and autonomy score (Functional Independence Measure score) will be collected at Dday 90 and Dday 180 solely at the Montpellier - Nimes site.
¶Until day 28.
**
AE, adverse event; ALT, Alanine transaminase; AP, Alkaline Phosphatase; AST, Aspartate transaminase; CRP, C reactive protein; EQ5D, European Quality of Life Five Dimension; ICU, intensive care unit; INR, International Normalised Ratio; LDH, Lactate Deshydrogenase; PC, Platelets Count; PTT, Partial thromboplastin time; RCC, red cell count; SOFA, Sequential Organ Failure Assessment; WCC, white cell count.

The primary outcome (day 90 all-causes mortality) will be collected at each trial site. The following secondary outcomes will be collected

- SOFA score[18] at enrolment and at 1 day, 2 days and 7 days after enrolment.
- Overall fluid balance and solutions intake from enrolment to day 2.
- Electrolytes and acid–base status from enrolment to H48.
- Organ support therapies (renal replacement therapy, mechanical ventilation, vasopressors) day 28 alive free days.
- Day 90 renal replacement therapy dependency.
- Nosocomial infections (pneumonia, bacteraemia, urinary tract infection, central line associated blood stream infections) during the ICU stay.
- ICU and hospital length of stay.
- Hospital mortality, day 28 and day 180 all-cause mortality.

Day 90 and day 180 quality of life and autonomy score (ancillary study only in Montpellier Nimes teaching centres with the centralised post-ICU outpatient clinic).

- Presence of treatment limitations during the ICU stay.

Patients and the public involvement

Patients and the public were not involved in any way.

Data and safety monitoring board and interim analysis

An independent data and safety monitoring board (DSMB) will be appointed to oversee the conduct of the trial and review one interim analysis. The DSMB will be composed of two academic intensivists experienced in the conduct of clinical trials. The DSMB will conduct a double interim analysis for efficacy and safety, after enrolment of 200 patients and 400 patients. The DSMB will be blinded to the treatment arm. The interim analysis will be planned for early stopping of the trial owning to safety or efficiency on the primary outcome after the first 200 and 400 patients included assuming the overall p value for the trial is 0.05, p value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary). Although no prespecified rules was implemented in the first version of the protocol, we implemented at the DSMB request the following stopping rules for futility after the first interim analysis (6 October 2021, MSA CPP No 03: the futility is defined as an absolute between-groups difference of 4% or less in the primary outcome (this

threshold for the between-groups difference of 4% is associated with a final statistical power arrowed 20%).

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for pharmacological interventions. Statistical analysis will be performed in an intention to treat population, including all the randomised patients except patients who withdraw their consent or do not meet the inclusion criteria. A per-protocol analysis will be performed among the patients included in the intention-to-reat analysis. The per-protocol analysis will take into account if sodium bicarbonate was eventually administered or not in enrolled patients.

All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.3; SAS Institute and R, V.3.5.0). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using frequencies and percentage for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables according to their distribution.

Primary analysis

An adjusted χ^2 test will be done to compare day 90 mortality proportion between groups. We will perform a multiple logistic regression for the primary outcome. The survival time will be described by means of Kaplan-Meier method and compared with a log-rank test. A Cox proportional-hazards model will be used to calculate HRs for death. For this analysis, data from all patients will be censored at the time of death or at day 90. Logistic and Cox regression models will be adjusted on relevant baseline covariates. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected in a backward selection procedure if $p<0.15$ in the univariate analysis and then presented as adjusted ORs or HRs with 95% CIs. For multiple comparisons in each prespecified stratum, a Holm-Bonferroni method will be done to compute an adjusted p value. A mixed regression model will be used to model repeated measures. Interactions between variables and time will be tested. We will also perform all the analyses described above among prespecified strata of the randomisation. Tests for all outcomes will be two sided.

Secondary analyses

We will conduct the following prespecified secondary analyses:

Secondary and exploratory outcomes

We will perform unadjusted, intention-to-treat analyses comparing patients in the sodium bicarbonate group to patients in the no sodium bicarbonate group with regard to each of the prespecified secondary and exploratory outcomes.

Continuous outcomes will be compared with the Mann-Whitney rank-sum test and categorical variables with the χ^2 test. For repeated data, a mixed linear model will be used, including the subject as a random variable.

Per-protocol analysis

The per-protocol analysis will exclude patients with major protocol violations and will compare patients that did receive sodium bicarbonate group with patients that did not receive sodium bicarbonate group (regardless of group assignment).

Effect modification (subgroup analyses)

We will examine whether prespecified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect modification by fitting a logistic regression model for the primary outcome. Independent variables will include study group assignment. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analysed using restricted cubic splines with 3–5 knots and preferentially displayed as continuous variables using a locally weighted regression or partial effects plots. If the presentation of data requires it, dichotomisation of continuous variables for inclusion in a forest plot will be performed. Prespecified subgroups that may modify the effect of infusing sodium bicarbonate include: pH≤7.10, pH (as a continuous variable), age <65 yo, presence of sepsis, SOFA score on enrolment (median score).

Missing data

Based on the prior trial performed in similar settings, we anticipate less than 5% missing data for the primary outcome. Missing data will not be imputed. Analyses will be performed on the complete cases. We will indicate in each table the number of observed data.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the trial protocol and collecting the trial data, with blinded assessment.

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in

case of major serious adverse events suspected to be associated with the technique of intubation used.

Auditing

An independent DSMB, composed of three experts will monitor the safety of the trial.

Ethics and dissemination

Research ethics approval

This research involving humans will be conducted in compliance with the French law 'Loi no 2012–300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé'), 'Loi No 78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés'). This trial will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation. The trial has been approved by the ethics committee 'Comité de Protection des Personnes Nord Ouest 1 (ref 19.03.15.72446)'. The BICARICU-2 trial is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrials.gov (NCT04010630) 8 July 2019. The first patient was enrolled on 6 October 2019.

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki (online supplemental appendix 1). If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or a vital emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled according to the French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

Declaration of interest

The trial is an investigator-initiated trial. Trial promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

The BICARICU-2 trial will be the first randomised clinical trial to investigate whether sodium bicarbonate infusion is associated with day 90 mortality in critically ill patients with both severe acidemia (pH≤7.20) and moderate-to-severe AKI. We will also explore whether sodium bicarbonate infusion, targeted to maintain an arterial pH equal or greater than 7.30, is associated with less organ support dependence, a shorter length of stay in the ICU and in the hospital.

Whether sodium bicarbonate is beneficial in that subset of patients is a matter of debate in 2023. Since the publication of the BICARICU-1 trial, a few observational studies but no randomised clinical trial have been published. Interestingly, these studies enrolled patients with moderate acidemia (pH≤7.30) instead of severe acidemia (pH≤7.20).

In 18 ICUs in Australia, Japan and Taiwan, 1292 consecutive critically ill adult patients with early and moderate metabolic acidosis (pH≤7.3 and a Base Excess ≤−4 mEq/L, within 24 hours of ICU admission) were evaluated. Among them, 233 (18%) received sodium bicarbonate. The patients who did receive sodium bicarbonate were sicker than the ones who did not. After adjusting for confounders, sodium bicarbonate was associated with higher mean arterial pressure at 6 hours among the patients with vasopressors dependency but not with mortality.[19] In a single centre retrospective study using the open access MIMIC-3 database, 869 patients older than 60 years old with sepsis and moderate metabolic acidosis (pH≤7.3 and bicarbonataemia less than 20 mmol/L) were evaluated according to whether they received sodium bicarbonate or not within 48 hours after the ICU admission.[12] Both ICU and hospital mortality were significantly reduced in the subgroup of patients with moderate metabolic acidemia (7.2<pH<7.3) treated with sodium bicarbonate. Using the same MIMIC-3 database and moderate acidemia (pH<7.30), Wang *et al* suggested that sodium bicarbonate was not associated with survival and that sodium bicarbonate might be associated with worsening organ failure score in a subset of patients with unchanged or deteriorating haemodynamics before sodium bicarbonate infusion.[20]

One strength of the BICARICU-2 trial is the planned enrolment of 640 patients with both severe acidemia (pH≤7.20) and moderate-to-severe acute kidney injury. Contrary to the observational studies that enrolled moderately ill patients with no inclusion criteria about kidney function, we will focus on a very high mortality group of patients. The BICARICU-2 trial is not blinded because first there is no solution with no effect on the acid–base balance and second because it is unethical to blind the caregivers to the pH trend during the first hours of the ICU stay. Blinding them for pH would obligate them to navigate without this crucial information. On the other hand, making the pH available in both groups would

per se give them the information about the group of randomisation.

We believe that, if sodium bicarbonate, a medication worldwide available for almost no additional cost in most of the countries around the globe, is associated with a better outcome it would change the way of treating these critically ill patients.

Trial status

The trial has actively enrolled since November 2019.

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Contributors BJ drafted the manuscript. BJ designed the trial together with SJ. HH and NM wrote the statistical analysis plan and estimated the sample size. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

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