Sodium Bicarbonate for Metabolic Acidosis in the Intensive Care Unit: Results of the pilot randomized double-blind clinical trial

ONLINE SUPPLEMENT

Table of Contents

	Page
eMethods	3
Table S1 – Additional Baseline Characteristics of the Included Patients	6
Table S2 – Characteristics During Study Drug Infusion	7
Table S3 – Clinical Characteristics During the First Seven Days of Follow-Up	8
Figure S1 – Algorithm of Study Intervention	9
Figure S2 – pH, Bicarbonate and Base Excess Levels in the First 24 Hours of Follow-Up (Including the Infusion Period)	10
Figure S3 – pH, Bicarbonate and Base Excess Levels in the First Seven Days of Follow-Up	11
Figure S4 – SOFA in the First Seven Days of Follow-Up	12
Figure S5 – Cumulative Distribution Plots of Duration of Shock, Duration of Vasopressor Infusion and Mean Bicarbonate Levels in the First 24 Hours	13
Figure S6 – Incidence of Metabolic Acidosis and Use of Sodium Bicarbonate in the First Seven Days of Follow-Up	14
Figure S7 – Kaplan-Meier Curves of 28- and 90-Day Survival	15

eMETHODS

Patients

The following exclusion criteria were applied: 1) proven digestive or urinary tract loss of sodium bicarbonate (e.g., acute diarrhoea, ileostomy, or drainage of pancreatic or biliary duct); or 2) diabetic ketoacidosis (DKA); or 3) stage IV or V chronic kidney disease; or 4) use of RRT (acute or chronic); or 5) received sodium bicarbonate within 24 hours of screening; or 6) dysnatraemia (serum Na ≥ 155 mEq/L or < 120 mEq/L); or 7) hypokalaemia (serum K < 2.5 mEq/L); or 8) pulmonary edema with a PaO_2 / FiO_2 < 100; or 9) hypocalcaemia (iCa < 0.8mmol/L); or 10) known or suspected poisoning of antidepressant or antipsychotic drugs or agents that may cause high anion gap acidosis (methanol, PEG, aspirin); or 11) suspected intoxication with unknown aetiology; or 12) pregnancy or breastfeeding; or 13) limitation of medical therapy orders; or 14) imminent or inevitable death; or 15) in the opinion of the treating clinical team the patients will almost certainly receive RRT in the next 6 hours; or 16) traumatic brain injury (or substantial risk for intracranial hypertension); or 17) the clinician believes that being enrolled in either arm is not in the best interest of the patient; or 18) previous enrolment in the study.

Randomization

A centralised, encrypted, web-based system (REDCap) was employed, allowing 24-hour enrolment and random allocation. The random allocation sequence was generated using a computer software program by the project manager at the coordinating centre (ANZIC-RC) and embedded into the REDCap system. Site investigators, site research coordinators, and study participants did not have

access to the allocation sequence throughout the trial. A senior statistician, who performed the trial data analysis, did not have access to the treatment allocation throughout the trial.

Intervention

The intervention was informed by a survey circulated amongst healthcare professionals in the Australian and New Zealand Intensive Care Society – Clinical Trials Group (ANZICS-CTG) (1). Stability of the study drug and feasibility of blinding were validated in two previous studies (2,3).

For preparation, 300 mL of D5W was removed and 300 mL of sodium bicarbonate 8.4% added to prepare the bicarbonate solution in a total volume of 500 mL (final concentration: 600 mEq/L). D5W was chosen as a comparator for this study because it is a readily available intravenous fluid that is commonly used by clinicians, contains no strong ions, and is a common diluent for drug administration. Moreover, D5W has an exemplary safety profile, and does not lead to hyperchloremia (as seen with saline solutions), which exacerbates metabolic acidosis.

The maximum duration of the study infusion was up to 5 hours after commencement, until RRT was started, or ICU discharge, whichever came first. Arterial blood gases were obtained at pre-defined times within the first 5 hours (at 0, 1, 3 [± 0.5 hours], and 5 [± 1 hour] hours after the start of the infusion), and then at 12, 18 and 24 hours after the start of the drug infusion. The study drug was permanently withheld if any contraindication to sodium bicarbonate developed (hypernatremia [Na > 155 mEq/L], hypocalcaemia [iCa < 0.8 mmol/L], hypokalemia refractory to potassium replacement [K < 2.5 mEq/L], clinically

significant fluid overload, or any contra-indication according to the treating physician).

Outcome measures and feasibility aims

The primary focus of the pilot trial was to understand key elements of feasibility (choice of population, choice and design of the intervention, recruitment rate, protocol compliance, safety, between-group separation, and suggestions of biological, physiological and clinical efficacy).

The primary outcome was the number of hours alive and free of vasopressors at day 7 (168 hours) after randomization. This was defined as the time, censored at 7 days, that a patient was both alive and had not received vasopressors for at least 12 hours. If a patient died while receiving vasopressor therapy following the index episode, the patient was assigned zero hours for this outcome. If a patient was weaned from all vasopressors for 12 consecutive hours, then all of the remaining time through day 7 was treated as success, even if the patient died or had vasopressors restarted after weaning within the 7-day period.

Consent strategy

As our population consisted of seriously ill patients, it was not anticipated that any participants would have the capacity to provide prospective consent. Additionally, it is common in these situations that either substitute decision maker is not known, not present, and if contactable is faced with confronting and alarming news. It is a stressful and emotional time for them, and the investigators did not consider it feasible or practicable to sufficiently inform them of the patient's condition and diagnosis, present the research proposal and obtain informed and respectful

consent in these circumstances. In addition to this, the protocol required rapid commencement of the research (randomization to occur within 2 hours of screening, infusion to start within 1 hour of randomization). Given that the intervention only spanned a maximum of 5 hours, we did not expect a change in either the patient or their substitute decision makers' ability to provide informed consent prior to cessation of the infusion. Therefore, we conducted this study using an "opt-out" approach, wherein the participant and/or their decision maker was provided with an information brochure that explained the purpose of the study and how to withdraw/opt-out of further data collection if they wished. This study was deemed to be a comparative effectiveness study, comparing two standard therapies that are approved for the treatment of these patients. Both of the therapies are commonly prescribed in clinical practice and considered to be low risk and minimally invasive. As such, the investigators did not anticipate that participation would confer any additional clinical risk than receiving standard treatment, nor add any discomfort or inconvenience to the patient. All this was approved by the ethics committee in the participating sites.

References

1. Serpa Neto A, Fujii T, El-Khawas K, Udy A, Bellomo R. Sodium Bicarbonate Therapy for Metabolic Acidosis in Critically Ill Patients: A survey of Australian and New Zealand Intensive Care Clinicians. Crit Care Resusc 2020;22:275-80.

2. Jude B, Naorungroj T, Neto AS, Fujii T, Udy A, Bellomo R. Sodium bicarbonate in 5% dextrose: can clinicians tell the difference?. Crit Care Resusc 2020;22:80-82.

3. Naorungroj T, Neto AS, Fujii T, Jude B, Udy A, Bellomo R. Stability of bicarbonate in normal saline: a technical report. Crit Care Resusc 2020;22:83-85.

Table S1 – Additional Baseline Characteristics of the Included Patients

Variables	Overall (*n* = 30)	Sodium Bicarbonate (*n* = 15)	Placebo (*n* = 15)
ICU source of admission – no. (%)			
Emergency department	7 (23.3)	2 (13.3)	5 (33.3)
Ward	3 (10.0)	2 (13.3)	1 (6.7)
Transfer from other ICU	3 (10.0)	2 (13.3)	1 (6.7)
Operating room	17 (56.7)	9 (60.0)	8 (53.3)
APACHE III	68.0 (57.0 - 97.8)	66.0 (56.5 - 86.5)	68.0 (57.5 - 102.5)
Risk of death, %	21.7 (8.5 - 52.5)	14.1 (7.0 - 28.6)	24.0 (13.6 - 61.7)
Mean ± standard deviation	35.4 ± 35.0	30.4 ± 36.4	40.2 ± 34.2
Total SOFA closest to randomization	7.0 (6.0 - 11.0)	7.0 (6.0 - 8.0)	9.0 (6.0 - 12.5)
Modified SOFA*	7.0 (6.0 - 8.0)	7.0 (6.0 - 7.5)	7.0 (6.0 - 10.0)
Respiratory	2.0 (1.0 - 2.0)	2.0 (1.0 - 2.5)	2.0 (1.0 - 2.0)
Coagulation	0.0 (0.0 - 1.0)	0.0 (0.0 - 0.5)	0.0 (0.0 - 1.0)
Liver	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
Cardiovascular	4.0 (4.0 - 4.0)	4.0 (3.5 - 4.0)	4.0 (4.0 - 4.0)
Renal	1.0 (0.0 - 2.0)	1.0 (0.0 - 2.0)	1.0 (0.5 - 2.0)
Neurology	0.0 (0.0 - 1.0)	0.0 (0.0 - 0.8)	0.0 (0.0 - 1.5)
Co-morbidities – no. (%)			
Hepatic failure	1 (3.3)	1 (6.7)	0 (0.0)
Leukemia / Myeloma	1 (3.3)	0 (0.0)	1 (6.7)
Immunosuppression	2 (6.7)	1 (6.7)	1 (6.7)
Liver cirrhosis	2 (6.7)	2 (13.3)	0 (0.0)
Diabetes	7 (23.3)	3 (20.0)	4 (26.7)
Blood gas at eligibility			
PaO_2 / FiO_2	312 (244 - 382)	326 (269 - 394)	275 (219 - 375)
Blood tests closest to randomization			
Urea, mmol/L	9.0 (6.4 - 18.6)	9.1 (7.4 - 12.2)	7.2 (6.2 - 20.0)
At randomization			
Acute kidney injury – no. (%)[a]	17 (56.7)	8 (53.3)	9 (60.0)
Stage 1	6 / 17 (35.3)	4 / 8 (50.0)	2 / 9 (22.2)
Stage 2	4 / 17 (23.5)	1 / 8 (12.5)	3 / 9 (33.3)
Stage 3	7 / 17 (41.2)	3 / 8 (37.5)	4 / 9 (44.4)
Vasopressor[b] – no. (%)	30 (100.0)	15 (100.0)	15 (100.0)
Noradrenaline – no. (%)	28 (93.3)	13 (86.7)	15 (100.0)
Dose, µg/min	16.5 (8.8 - 22.5)	18.0 (7.0 - 21.7)	15.0 (11.0 - 22.4)
Inotropes[c] – no. (%)	3 (10.0)	2 (13.3)	1 (6.7)
Milrinone – no. (%)	3 (10.0)	2 (13.3)	1 (6.7)
Dose, µg/min	10.0 (8.3 - 18.3)	16.7 (11.7 - 21.6)	10.0 (10.0 - 10.0)

Abbreviations: ICU is intensive care unit; APACHE is Acute Physiology and Chronic Health Evaluation; SOFA is Sequential Organ Failure Assessment.

* Modified SOFA was calculated excluding the neurological component.

[a] Based on the creatinine criteria from KDIGO definition. When not available, premorbid creatinine was imputed using the following formula: creatinine = 0.74 − 0.2 [if female] + 0.08 [if African American] + 0.003 × age [in years]

[b] Vasopressor defined as the use of noradrenaline, adrenaline, vasopressin, metaraminol, dopamine, phenylephrine and/or angiotensin II.

[c] Inotrope defined as the use of milrinone, dobutamine or levosimendan.

Table S2 – Characteristics During Study Drug Infusion

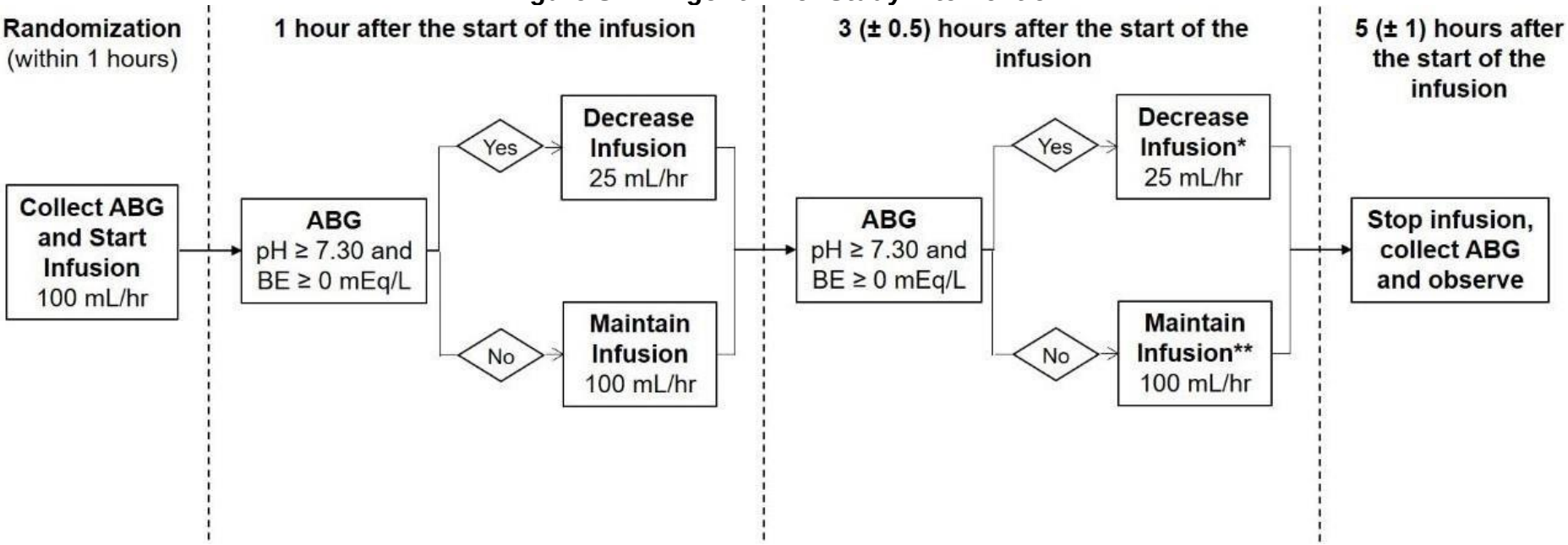
Variables	At the start of the infusion			1 hour after the start of the infusion			3 hours after the start of the infusion			5 hours after the start of the infusion		
	Soda Bic (*n* = 15)	Placebo (*n* = 15)	*p* value	Soda Bic (*n* = 15)	Placebo (*n* = 15)	*p* value	Soda Bic (*n* = 15)	Placebo (*n* = 15)	*p* value	Soda Bic (*n* = 15)	Placebo (*n* = 15)	*p* value
Infusion rate – no. (%)			---			0.483			0.080			0.011
100 mL/h	15 (100.0)	15 (100.0)		13 (86.7)	15 (100.0)		9 (60.0)	14 (93.3)		8 (53.3)	11 (73.3)	
25 mL/h	0 (0.0)	0 (0.0)		2 (13.3)	0 (0.0)		6 (40.0)	1 (6.7)		7 (46.7)	1 (6.7)	
Interrupted	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	3 (20.0)	
Other	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Open sodium bicarbonate – no. (%)	0 (0.0)	0 (0.0)	---	0 (0.0)	0 (0.0)	---	0 (0.0)	1 (6.7)	0.999	0 (0.0)	1 (6.7)	0.999
Blood gas analysis												
pH	7.29 (7.27 - 7.32)	7.26 (7.23 - 7.28)	0.026	7.35 (7.30 - 7.36)	7.26 (7.24 - 7.29)	< 0.001	7.39 (7.36 - 7.44)	7.27 (7.23 - 7.29)	< 0.001	7.39 (7.38 - 7.44)	7.28 (7.26 - 7.30)	< 0.001
Bicarbonate, mmol/L	17.2 (16.0 - 18.5)	17.0 (15.5 - 17.8)	0.589	20.0 (18.7 - 21.6)	16.0 (16.0 - 17.8)	0.004	24.1 (22.9 - 24.9)	17.0 (16.0 - 18.0)	< 0.001	26.0 (24.0 - 27.1)	16.4 (16.0 - 18.5)	< 0.001
Base excess, mmol/L	-7.7 (-9.6 - -6.8)	-9.6 (-10.6 - -8.8)	0.110	-4.5 (-6.3 - -3.4)	-10.1 (-11.0 - -8.6)	0.002	0.0 (-0.9 - 1.4)	-9.3 (-10.6 - -7.7)	< 0.001	1.6 (-0.1 - 2.7)	-9.6 (-10.0 - -7.3)	< 0.001
$PaCO_2$, mmHg	37.0 (32.0 - 40.2)	37.0 (35.2 - 39.6)	0.534	36.0 (34.5 - 39.3)	37.5 (33.5 - 39.9)	0.983	38.2 (35.1 - 43.6)	38.3 (36.0 - 40.8)	0.836	41.0 (36.0 - 43.8)	37.0 (33.9 - 39.5)	0.084
Lactate, mmol/L	2.3 (1.5 - 4.3)	2.5 (1.7 - 4.0)	0.983	2.5 (1.6 - 3.6)	2.5 (1.6 - 4.0)	0.999	2.2 (1.6 - 3.1)	2.2 (1.7 - 3.0)	0.782	2.2 (1.8 - 3.8)	2.3 (1.6 - 2.8)	0.776
Electrolytes												
Sodium, mmol/L	137 (134 - 139)	138 (134 - 138)	0.933	137 (135 - 141)	136 (133 - 138)	0.245	139 (137 - 144)	135 (132 - 137)	0.010	140 (137 - 144)	134 (131 - 136)	0.003
Potassium, mmol/L	4.7 (4.4 - 4.8)	4.6 (4.2 - 5.1)	0.868	4.5 (4.3 - 4.8)	4.5 (4.2 - 4.8)	0.810	4.4 (4.2 - 4.6)	4.6 (4.2 - 4.8)	0.355	4.3 (4.1 - 4.6)	4.6 (4.2 - 4.8)	0.228
Ionized calcium, mmol/L	1.1 (1.1 - 1.1)	1.1 (1.0 - 1.1)	0.413	1.1 (1.0 - 1.1)	1.1 (1.0 - 1.1)	0.678	1.1 (1.0 - 1.1)	1.1 (1.0 - 1.1)	0.883	1.1 (1.0 - 1.1)	1.1 (1.0 - 1.1)	0.222
Vital signs												
Heart rate, bpm	76 (75 - 85)	88 (72 - 106)	0.253	80 (75 - 88)	89 (75 - 95)	0.455	84 (78 - 95)	76 (69 - 93)	0.289	88 (76 - 92)	73 (68 - 101)	0.561
Mean arterial pressure, mmHg	75 (72 - 77)	73 (69 - 82)	0.819	73 (65 - 77)	73.0 (67.0 - 77.5)	0.835	74 (71 - 81)	78 (72 - 79)	0.695	72 (68 - 75)	71 (68 - 77)	0.934
Noradrenaline use – no. (%)	13 (86.7)	15 (100.0)	0.483	13 (86.7)	13 (86.7)	0.999	10 (66.7)	14 (93.3)	0.169	9 (60.0)	13 (86.7)	0.215
Infusion rate, µg/min	16.7 (5.0 - 18.0)	13.0 (6.5 - 19.2)	0.854	18.0 (5.0 - 22.0)	13.0 (9.0 - 15.0)	0.918	13.0 (6.0 - 17.5)	13.0 (8.7 - 18.8)	0.977	11.0 (9.0 - 32.0)	15.0 (8.0 - 15.0)	0.687

Abbreviations: Soda Bic is sodium bicarbonate.

Table S3 – Clinical Characteristics During the First Seven Days of Follow-Up

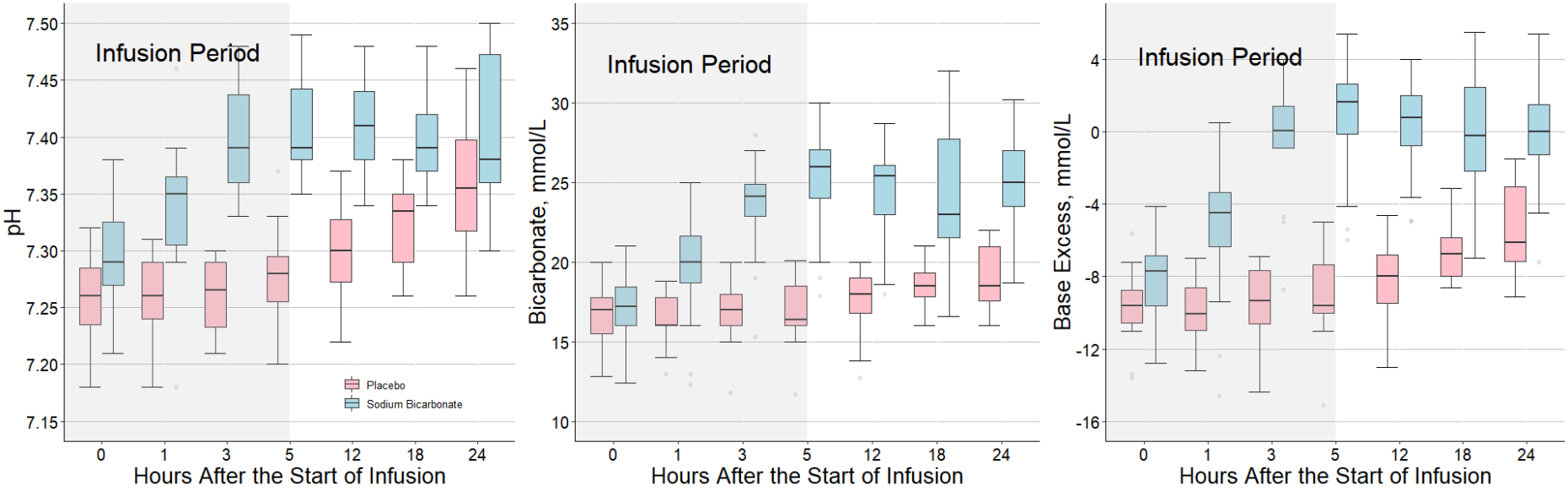
Variables	Overall (*n* = 30)	Sodium Bicarbonate (*n* = 15)	Placebo (*n* = 15)	*p* value
pH				
Lowest	7.32 (7.27 - 7.36)	7.37 (7.33 - 7.41)	7.27 (7.25 - 7.31)	< 0.001
< 7.20 – no. (%)	1 (3.3)	1 (6.7)	0 (0.0)	0.999
Highest	7.42 (7.39 - 7.46)	7.43 (7.40 - 7.46)	7.42 (7.34 - 7.46)	0.546
> 7.45 – no. (%)	10 (33.3)	4 (26.7)	6 (40.0)	0.700
Bicarbonate, mmol/L				
Lowest	18.0 (16.2 - 22.0)	22.0 (20.6 - 24.6)	17.0 (15.5 - 18.0)	< 0.001
Highest	24.0 (21.3 - 26.8)	25.0 (24.0 - 28.2)	24.0 (18.5 - 24.3)	0.036
Base excess, mmol/L				
Lowest	-7.0 (-8.4 - -1.7)	-1.7 (-2.5 - 0.2)	-8.4 (-9.8 - -7.8)	< 0.001
Highest	0.6 (-1.9 - 3.1)	1.4 (-0.9 - 4.0)	0.1 (-5.1 - 1.0)	0.059
$PaCO_2$, mmHg				
Lowest	35.8 (33.0 - 41.7)	38.0 (35.0 - 41.4)	35.0 (32.0 - 39.3)	0.184
Highest	44.9 (40.3 - 47.0)	47.0 (42.5 - 50.5)	43.0 (39.0 - 45.5)	0.097
Sodium, mEq/L				
Lowest	134.0 (131.2 - 138.8)	138.0 (133.5 - 142.5)	134.0 (129.5 - 134.5)	0.047
< 135 mEq/L – no. (%)	17 (56.7)	6 (40.0)	11 (73.3)	0.139
Highest	142.0 (138.0 - 146.0)	145.0 (142.0 - 146.5)	138.0 (135.5 - 142.5)	0.013
> 155 mEq/L – no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	---
Potassium, mEq/L				
Lowest	3.8 (3.6 - 4.1)	3.8 (3.5 - 4.1)	3.8 (3.6 - 4.0)	0.546
< 2.5 mEq/L – no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	---
Replacement – no. (%)	24 (80.0)	11 (73.3)	13 (86.7)	0.651
Days with replacement	2.0 (1.0 - 5.0)	2.0 (0.5 - 5.5)	2.0 (1.0 - 4.0)	0.916
Highest	4.8 (4.5 - 5.1)	4.9 (4.6 - 5.0)	4.8 (4.5 - 5.2)	0.692
> 5.0 mEq/L – no. (%)	8 (26.7)	2 (13.3)	6 (40.0)	0.215
Ionized calcium, mmol/L				
Lowest	1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)	0.657
< 0.8 mmol/L – no. (%)	1 (3.3)	0 (0.0)	1 (6.7)	0.999
Replacement	14 (46.7)	6 (40.0)	8 (53.3)	0.715
Days with replacement	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	1.0 (0.0 - 1.5)	0.496
Highest	1.1 (1.1 - 1.1)	1.1 (1.0 - 1.1)	1.1 (1.1 - 1.1)	0.357
Chloride, mmol/L				
Lowest	104.5 (101.0 - 107.0)	105.0 (99.5 - 107.5)	104.0 (101.0 - 106.5)	0.724
Highest	111.0 (107.2 - 114.8)	110.0 (107.5 - 113.0)	112.0 (107.5 - 115.5)	0.603
Lactate, mmol/L				
Lowest	1.2 (1.0 - 1.7)	1.3 (1.1 - 1.9)	1.2 (0.9 - 1.5)	0.196
Highest	2.1 (1.5 - 3.2)	2.3 (1.6 - 3.2)	2.1 (1.5 - 3.6)	0.771
Cumulative fluid balance, mL	1545 (516 - 3000)	1253 (490 - 2517)	2111 (572 - 4500)	0.468

Figure S1 – Algorithm of Study Intervention



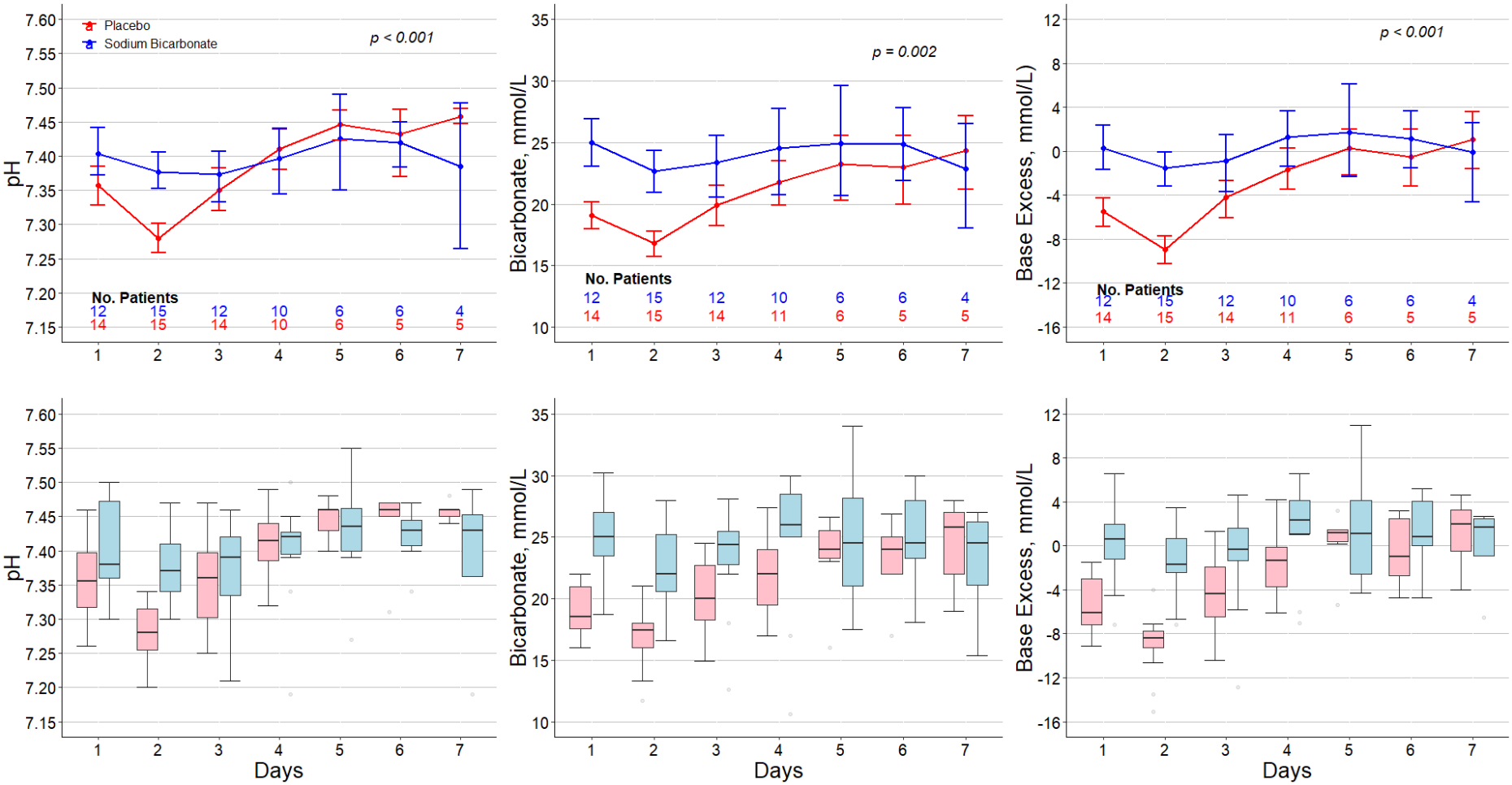
* Or maintain at 25 mL/hr if already decreased in the previous assessment; ** Or increase to 100 mL/hr if receiving 25 mL/hr
Abbreviations: ABG is arterial blood gas; BE is base excess.

Figure S2 – pH, Bicarbonate and Base Excess Levels in the First 24 Hours of Follow-Up (Including the Infusion Period)



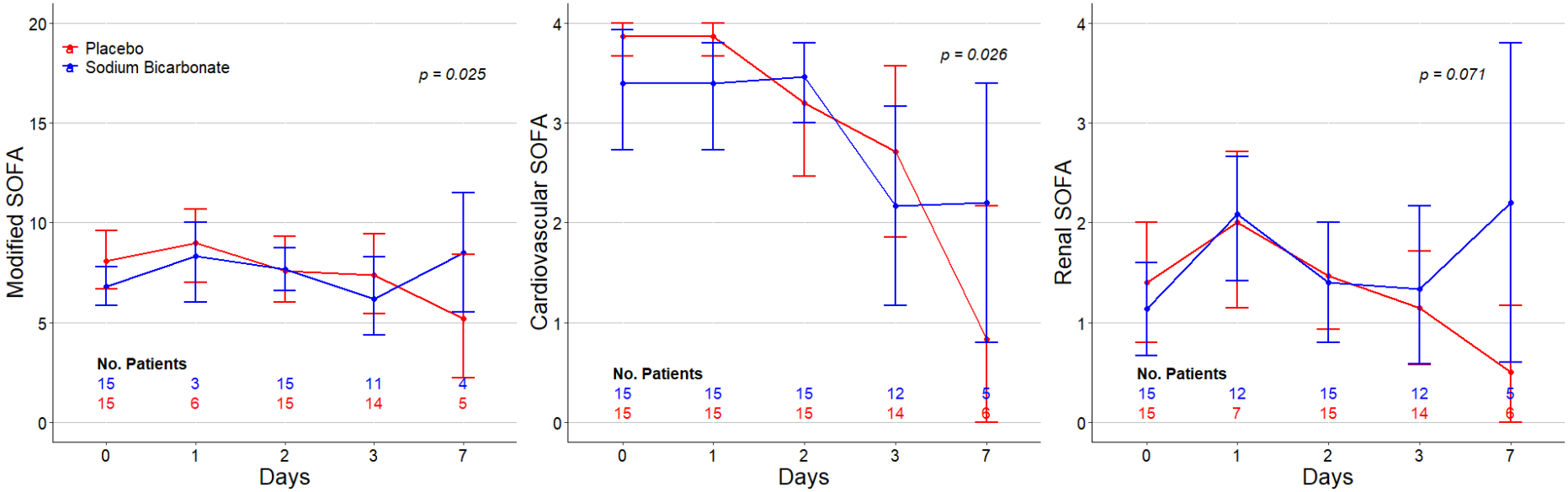
Boxplots presenting the median, interquartile range and amplitude.

Figure S3 – pH, Bicarbonate and Base Excess Levels in the First Seven Days of Follow-Up



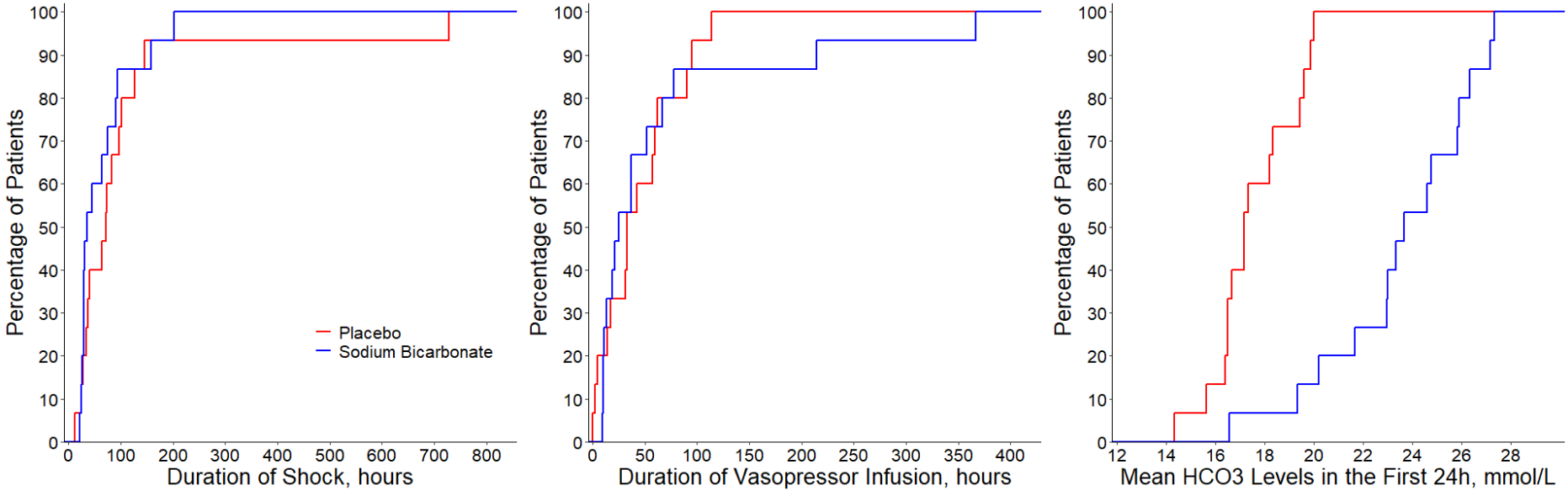
Top panels: Circles are mean and error bars are 95% confidence intervals. *P* values from mixed-effect generalized linear models with Gaussian distribution, and with intervention, days (as continuous variable) and intervention x days interaction added as fixed effect, and with patients added as random effect to account for repeated measurements.
Bottom panels: Boxplots presenting the median, interquartile range and amplitude.

Figure S4 – SOFA in the First Seven Days of Follow-Up



Circles are mean and error bars are 95% confidence intervals. *P* values from mixed-effect generalized linear models with Gaussian distribution, and with intervention, days (as continuous variable) and intervention x days interaction added as fixed effect, and with patients added as random effect to account for repeated measurements.

Figure S5 – Cumulative Distribution Plots of Duration of Shock, Duration of Vasopressor Infusion and Mean Bicarbonate Levels in the First 24 Hours



Curves more to the left represent shorter periods until event, less hours alive and free of vasopressor at day 7 or lower levels of bicarbonate.

Abbreviations: HCO3 is bicarbonate.

Figure S6 – Incidence of Metabolic Acidosis and Use of Sodium Bicarbonate in the First Seven Days of Follow-Up

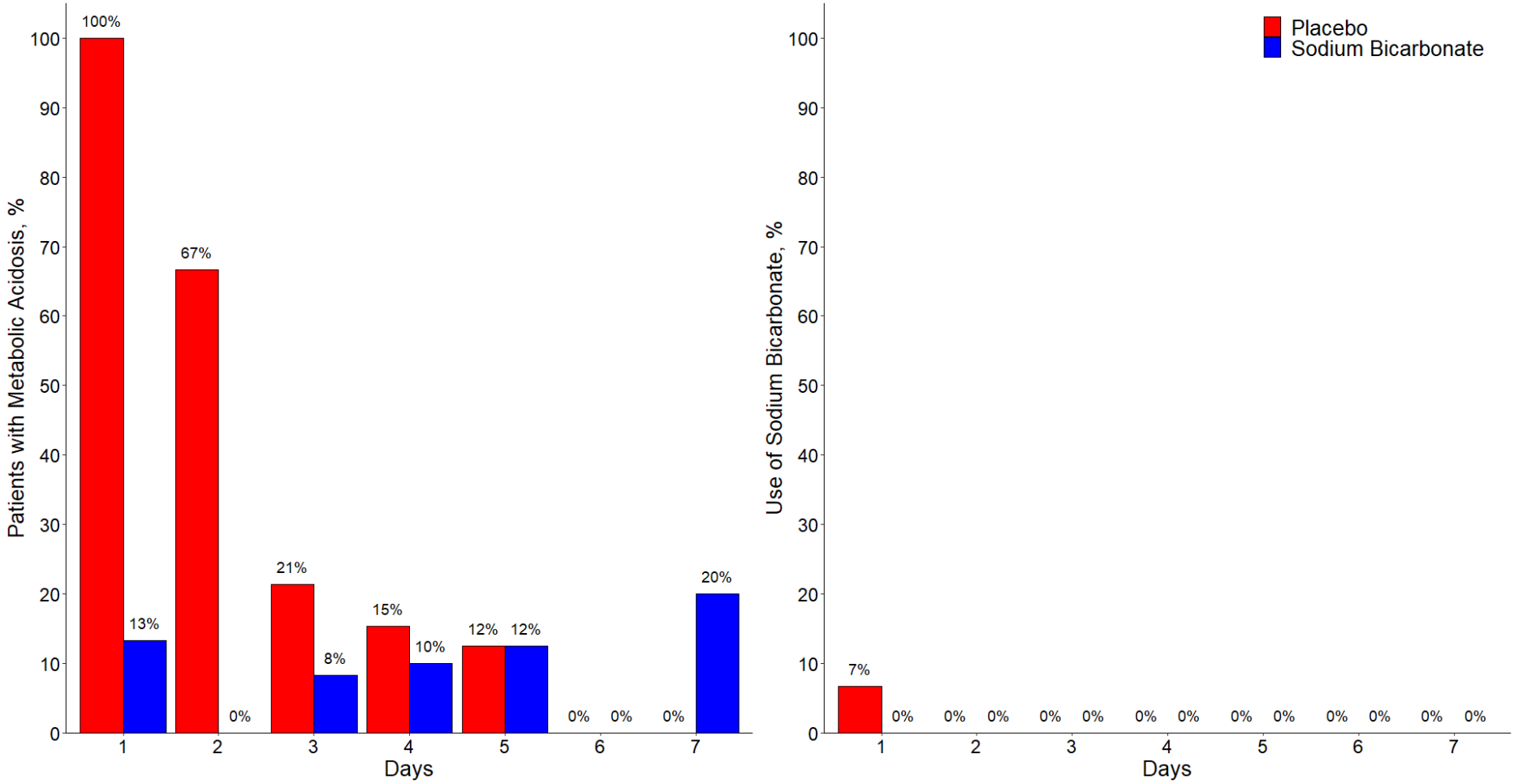
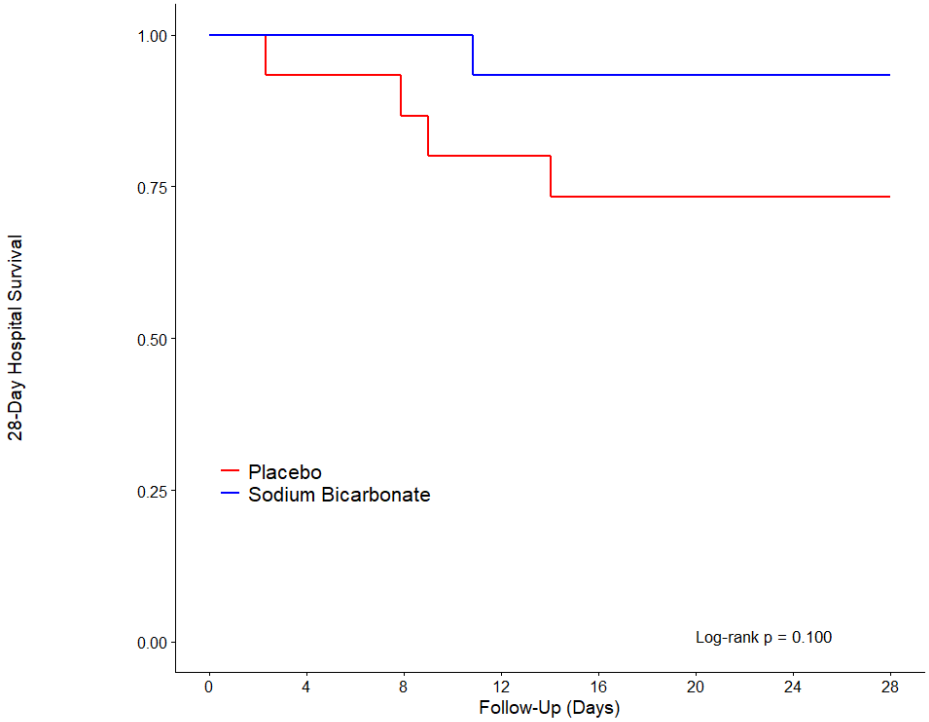
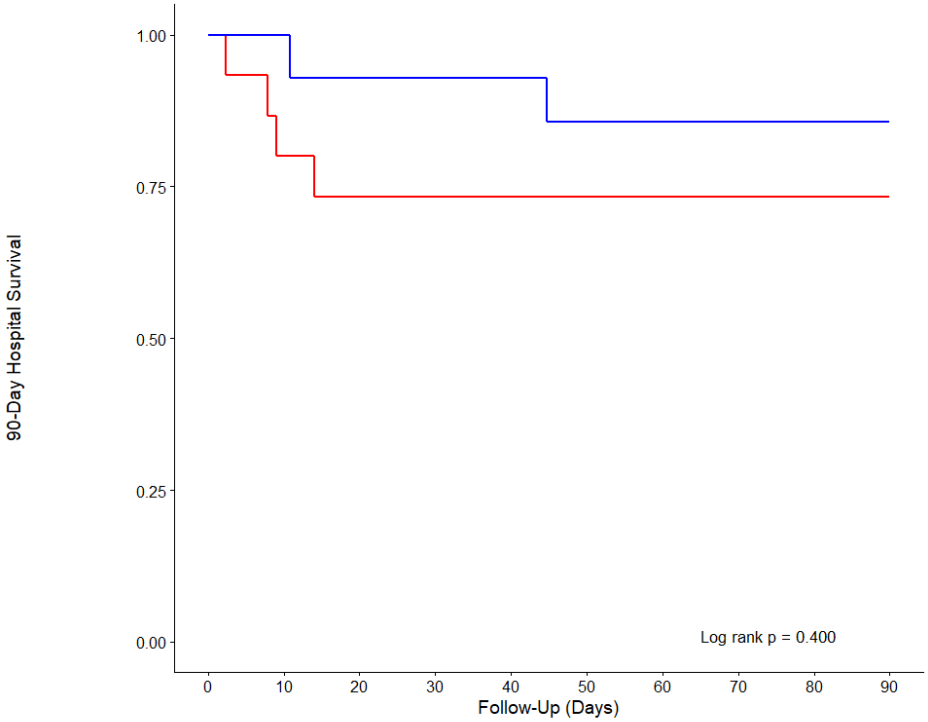


Figure S7 – Kaplan-Meier Curves of 28- and 90-Day Survival



No. at Risk

Placebo	15	14	13	12	11	11	11	11
Sodium Bicarbonate	15	15	15	14	14	14	14	14



No. at Risk

Placebo	15	12	11	11	11	11	11	11	11	11
Sodium Bicarbonate	14	14	13	13	13	12	12	12	12	12

The SODa-BIC Pilot RCT

SODium BICarbonate for metabolic acidosis in the Intensive Care Unit: A pilot, multicentre, randomized, double-blind clinical trial

Chief Investigator:	Prof Andrew Udy Co-Deputy Director Australian and New Zealand Intensive Care Research Centre Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia Telephone: +61 438 755 568 Email: andrew@udy.com
Study Coordinator:	Dr Ary Serpa Neto Senior Research Fellow Australian and New Zealand Intensive Care Research Centre Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia Telephone: +61 04 3274 9435 Email: ary.serpaneto@monash.edu
Coordinating Centre:	Australian and New Zealand Intensive Care Research Centre School of Public Health and Preventive Medicine, Monash Universi Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia Telephone: +61 3 9903 0343 Fax: +61 3 9903 0071 Email: anzicrc@monash.edu
Clinical Trials Number:	ACTRN12620001361998p

TABLE OF CONTENTS

1. ABBREVIATIONS 3
2. SYNOPSIS 4
3. STUDY ADMINSTRATIVE STRUCTURE 6
4. PURPOSE OF THE PROTOCOL 9
5. CLINICAL RATIONALE 10
6. AIMS AND OBJECTIVES 14
7. RESEARCH PLAN 15
8. DATA MANAGEMENT 21
9. SAFETY MONITORING AND REPORT 26
10. ETHICS 28
11. BUDGET 29
12. PUBLICATION AND DISSEMINATION 30
13. RESEARCH TIMELINES 31
14. REFERENCES 32

1. ABBREVIATIONS

ABG	Arterial blood gases
AE	Adverse event
AKI	Acute kidney injury
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ANZICS-CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
APACHE III	Acute Physiology and Chronic Health Evaluation III
AR	Adverse reaction
Atot	Total weak acids
BE	Base excess
CRF	Case report form
D5W	5% dextrose
DKA	Diabetic ketoacidosis
DNI	Do not intubate
DNR	Do not resuscitate
FiO_2	Inspired fraction of oxygen
HREC	Human Research and Ethics Committee
ICU	Intensive care unit
NHMRC	National Health and Medical Research Council's
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
RRT	Renal replacement therapy
SAE	Serious adverse event
SDM	Substitute decision maker
SID	Strong ion difference
SIG	Strong ion gap
SODa-BIC	SODium BICarbonate for metabolic acidosis in the Intensive Care Unit
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected unexpected serious adverse reaction

2. SYNOPSIS

Background

Metabolic acidosis refers to any process that elevates the concentration of hydrogen ions in the body, and is commonly encountered in critical illness. Lactic acidosis, diabetic ketoacidosis, and hyperchloremic acidosis are major examples seen in the intensive care unit (ICU). Metabolic acidosis may impair cardiac function, and sodium bicarbonate can be used to normalise blood pH. Despite being in common clinical usage, the clinical efficacy of sodium bicarbonate is still uncertain. Previous studies exploring the effects of sodium bicarbonate therapy have been limited and of variable quality.

Aim

The trial aims to assess if the infusion of 5% dextrose (D5W) + sodium bicarbonate, in vasopressor-dependent patients with moderate metabolic acidosis admitted to the ICU, increases the number of vasopressor-free hours at day 7, compared to the infusion of D5W alone.

Study Design

Pilot, feasibility, international, multicentre, double-blind, randomized clinical trial.

Settings

ICUs in Australia, New Zealand and Japan.

Participants

Adult patients (≥ 18 years old), admitted to the ICU within 48 hours, receiving a continuous infusion of a vasopressor drug to maintain a mean arterial pressure > 65 mmHg (or a mean arterial pressure target set by the treating clinician), a dedicated line (central or peripheral) is available (or is about to be made available within 1 hour after randomization), and with moderate metabolic acidosis, defined as: 1) pH < 7.30; 2) BE < -4 mEq/L; and 3) $PaCO_2$ < 45 mmHg.

Intervention

Patients will be randomly allocated in a 1:1 ratio to receive either an infusion of D5W + sodium bicarbonate, or D5W alone, as a comparator.

Study drug will be continuously infused targeting a pH ≥ 7.30 and a BE ≥ 0 mEq/L. The infusion will be maintained until this target is achieved and continued by titration thereafter for a maximum of 5 hours (to maintain target pH and base excess levels).

The infusion will start at 100 mL/hr and be kept at this rate until both targets (pH and BE) are achieved, following which, the infusion rate will be decreased to 25 mL/hr and kept constant at this rate until 5 hours has elapsed since the start of the infusion. At this point, the infusion will be stopped, independently, of the results of arterial blood gas analysis.

Arterial blood gases will be obtained at pre-defined times within the first 5 hours (at 0, 1, 3 [± 0.5 hours], and 5 [± 1 hour] hours after the start of the infusion), and then at 12, 18 and 24 hours after the start of the drug infusion. The maximum duration of the study infusion is up to 5 hours after commencement, until RRT is started, or ICU discharge, whichever comes first.

All other aspects of care will be determined by the treating clinical team, including the use of additional fluid therapy, vasopressors, and other organ support modalities. Open-label sodium bicarbonate bolus infusion is allowed in both groups if clinically indicated.

<u>5% dextrose + Sodium bicarbonate group</u>

Sodium bicarbonate 8.4% (1000 mEq/L) will be diluted in a D5W solution (500 mL bag). For preparation, 300 mL of D5W will be removed and 300 mL of sodium bicarbonate 8.4% added

to prepare the bicarbonate solution in a total volume of 500 mL (final concentration: 600 mEq/L).

5% dextrose group
Standard 500 mL bag of D5W.

Primary outcome
The primary outcome of the study is the number of hours alive and free of vasopressor administration up to day 7 (168 hours).

Sample Size
60 patients (30 *per* group).

Period
2 year.

Clinical trial registration
ACTRN12620001361998p.

3. STUDY ADMINSTRATIVE STRUCTURE

3.1 Coordinating Centre and Data Management Centre

3.1.1 Responsibilities

- Overall management of the trial including assistance with human research ethics committee applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of investigators, research coordinators and the trial team
- Trial set-up
- Coordination of data entry and feedback of data enquiries
- Data analysis and collaboration on publications

3.2 Management Committee

3.2.1 Responsibilities

Oversight of all aspects of the study management including:

- Liaison with coordinating centre staff and trial management centre staff
- Funding applications
- Disbursement and administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and trial materials
- Development and approval of data collection tools and methods
- General trial management issues
- Day-to-day management of the study
- Provide clinical insight

3.2.2 Members

Prof Andrew Udy (Chair)
Dr Ary Serpa Neto
Dr Tomoko Fujii
Dr Mikihiro Maeda
Prof Alistair Nichol
Prof Rinaldo Bellomo
Prof Adam Deane
Dr Elisa Licari
Dr Paul Young
Dr Kyle White
Prof Craig French
Prof Yahya Shehabi
Dr Anthony Cross
Dr Matthew Maiden
Dr Umesh Kadam
Dr Khaled El Khawas
Ms Meredith Young

3.3 Study Statistician

3.3.1 Responsibilities

Oversight of all aspects of study statistics:

- Assist in the development of the database and statistical plan

- Provide expertise in complex data analysis

3.3.2 Member

Prof Michael Bailey (Chief)
Dr Ary Serpa Neto

3.5 Contact Details

3.5.1 Chief Investigator

Prof Andrew Udy
Co-Director
Australian and New Zealand Intensive Care Research Centre
Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia
Telephone: +61 438 755 568
Email: andrew@udy.com

3.5.2 Study Coordinator

Dr Ary Serpa Neto
Senior Research Fellow
Australian and New Zealand Intensive Care Research Centre
Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia
Telephone: +61 04 3274 9435
Email: ary.serpaneto@monash.edu

3.5.3 Coordinating Centre

Australian and New Zealand Intensive Care Research Centre
School of Public Health and Preventive Medicine, Monash University
Level 3, 553 St Kilda Road, Melbourne, Victoria 3004, Australia
Telephone: +61 3 9903 0343
Fax: +61 3 9903 0071
Email: anzicrc@monash.edu

3.5.4 Site Principal Investigators

Site	Name	Contact
Austin Hospital	Prof Rinaldo Bellomo	E: Rinaldo.BELLOMO@austin.org.au T: +61 3 9496 5992 A: Intensive Care Unit, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia
The Alfred Hospital	Prof Andrew Udy	E: andrew@udy.com T: +61 4 3875 5568 A: Intensive Care Unit, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia
Wellington Regional Hospital	Dr Paul Young	E: Paul.Young@ccdhb.org.nz T: +64 4 806 0432 A: Intensive Care Unit, Level 3, Wellington Regional Hospital, Riddiford Street, Newtown, Wellington 6021, New Zealand
Jikei University Hospital	Dr Tomoko Fujii	E: tofujii-tky@umin.net T: +81 3 3433 1111 A: Intensive Care Unit, Jikei University Hospital, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo 105-0003, Japan

Royal Melbourne Hospital	Adam Deane	E: adam.deane@monash.edu
Western Health	Craig French	E: craig.french@wh.org.au
University Hospital Geelong	Matthew Maiden	E: mjmaiden@ozemail.com.au
Monash Medical Centre	Yahya Shehabu	E: yshehabi@ozemail.com.au
Northern Hospital	Anthony Cross	E: anthony.cross@nh.org.au
Princess Alexandra Hospital	Kyle White	E: kyle.white@health.qld.gov.au
Ballarat Health Services	Khaled El Khawas	E: khaledelkhawas@gmail.com
Monash Casey Hospital	Umesh Kadam	E: kadamuk2@gmail.com
Werribee Mercy Hospital	Umesh Kadam	E: kadamuk2@gmail.com

3.5.5 Management Committee

Prof	Andrew	Udy	Intensivist	The Alfred & ANZIC-RC
Prof	Rinaldo	Bellomo	Intensivist	Austin Health & ANZIC-RC
Prof	Alistair	Nichol	Intensivist	The Alfred & ANZIC-RC
A/Prof	Adam	Deane	Intensivist	The Royal Melbourne Hospital
Dr	Elisa	Licari	Intensivist	The Alfred
Dr	Paul	Young	Intensivist	Wellington Regional Hospital
Ms	Meredith	Young	Research Coordinator	The Alfred
Dr	Ary	Serpa Neto	Intensivist	ANZIC-RC
Prof	Craig	French	Intensivist	Western Health
Dr	Anthony	Cross	Intensivist	Northern Hospital
Dr	Matthew	Maiden	Intensivist	University Hospital Geelong
Prof	Yahya	Shehabi	Intensivist	Monash Medical Centre
Dr	Tomoko	Fujii	Intensivist	Jikei University, ANZIC-RC
Dr	Kyle	White	Intensivist	Princess Alexandra Hospital
Dr	Umesh	Kadam	Intensivist	Monash Casey Hospital
Dr	Mikihiro	Maeda	Pharmacist	St. Marianna University Hospital

4. PURPOSE OF THE PROTOCOL

This document is a protocol for the SODa-BIC study, which represents a coordinated effort to create a high-quality, detailed, pilot randomized clinical trial of the use of 5% dextrose (D5W) + sodium bicarbonate in critically ill patients with moderate metabolic acidosis, compared with D5W alone, as fluid therapy.

The SODa-BIC study will be conducted in compliance with this protocol, good clinical practice guidelines, university research policies and procedures, hospital and health service policies, and state and federal laws governing privacy and confidentiality. It will be guided by the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research and the Australian Commission of Safety and Quality Health Care Operating Principles.

5. CLINICAL RATIONALE

5.1 Metabolic acidosis

General

Critical illness affects millions of patients each year and is associated with a variety of clinical features, including metabolic acidosis. Metabolic acidosis is a process that elevates the concentration of hydrogen ions in the body due to a change in strong ion difference (SID) or total weak acids (Atot), which can be detected as a negative base excess (BE).[1,2] When SID decreases and/or Atot increases, the plasma concentration of hydrogen ions rises. SID is the difference in concentrations between strong positive ions (i.g. Na^+, K^+, Mg^{++}, Ca^{++}) and strong negative ions (i.g. Cl^-, Lac^-), in which sodium and chloride are dominant. The major weak acids in plasma are albumin (Alb^-) and phosphate (PO^-)[1] which are commonly reduced below normal concentrations in critically ill patients.[3,4] For a detailed review of acid base balance, please see Stewart P. How to Understand Acid-Base: A Quantitative Acid-Base primer for biology and medicine.[1] BE is commonly used to assess the severity of the metabolic acidosis in clinical practice and provides reasonable estimates of these determinants of acid-base balance.[5,6]

Metabolic acidosis is common in patients with sepsis and other critical illness syndromes; however, the general incidence and prevalence of metabolic acidosis have not been established.[7-9] Furthermore, it remains uncertain whether metabolic acidosis per se plays any role in determining patient outcomes, or simply represents an epiphenomenon, reflecting the severity of the underlying illness, or the way in which we manage patients.[10] Importantly, metabolic acidosis is known to be a predictor of poor outcomes in critically ill patients.[11-14]

Pathophysiology of metabolic acidosis in critically ill patients

Critically ill patients may have metabolic acidosis due to a number of discrete aetiologies. Lactic acidosis, diabetic ketoacidosis (DKA), and hyperchloremic acidosis are common precipitants of metabolic acidosis due to a reduced SID.

Lactate is a strong anion as over 99.9% of lactate is ionised in the human body. Lactic acidosis is defined as metabolic acidosis with an elevated plasma lactate concentration, and the cut off concentration has been defined variably in the literature.[15] The incidence varies from 0.5% to 3.8%, with a mortality rate ranging from 30% to 88% depending on the definition used.[16] Lactataemia is now most commonly operationalized as a lactate level > 2mmol/L[17] and elevated lactate is associated with a greater risk of mortality. The risk of death increases with the extent of the derangement in lactate concentration, this is true both of the magnitude of derangement and the duration. Furthermore, abnormal blood lactate concentrations which normalize over time (lactate clearance) is associated with better patient outcomes in observational studies than abnormal lactate concentrations which do not normalize, but the effect of lactate clearance reported in clinical trials is inconsistent.[18-20] Targeting the correction of lactate is thus still controversial.

DKA is a medical emergency of diabetes mellitus that results from insulin deficiency. The criterion that is often used for DKA is blood glucose > 11 mmol/L, moderate ketonuria or ketones > 3mmol/L, and an arterial pH < 7.30 or bicarbonate < 15 mmol/L.[21] The hepatic metabolism of fatty acids produces organic acids such as beta-hydroxybutyrate and acetoacetate, which are strong anions in the human body. Although beta-hydroxybutyrate is usually unmeasurable in clinical settings, the accumulation of these ketoacid anions causes a decrease in SID.[22] Due to osmotic diuresis of hyperglycaemia, patients with DKA present with a marked contraction of their extracellular fluid volume.[23] The mainstay of therapy has empirically focused on the correction of dehydration, insulin deficiency, treatment of precipitating conditions, and the rapid reversal of acidemia.[24,25] The use of sodium bicarbonate has been recommended by some to correct severe metabolic acidosis in these patients. However, no clear consensus exists.

Hyperchloremic acidosis is more commonly encountered as an iatrogenic complication in the critically ill,[26-28] while the other causes of metabolic acidosis are related to the underlying pathology. This is because 0.9% saline, which has a SID of 0 mEq/L, is often been used to treat shock or as a maintenance fluid. Large volume of saline infusion produces metabolic acidosis by a reduction of SID. Balanced crystalloids such as Ringer's lactate and Plasmalyte replace chloride with lactate, acetate, and gluconate. These strong anions are metabolised by the liver, which is faster than renal excretion of chloride. Several observational studies have found that the 0.9% saline or chloride load is associated with metabolic acidosis with increased chloride levels, and increased hospital mortality.[27,29-31] A before-and-after trial suggested that the use of balanced crystalloids is associated with lower rates of acute kidney injury, renal replacement therapy (RRT), and death.[28] It has been suggested that the avoidance of hyperchloremic acidosis may account for the observed benefits.

Metabolic acidosis in patients with acute kidney injury (AKI) may be due to increased weak acids. AKI is an abrupt loss of renal function diagnosed by increased serum creatinine levels or reduction in urine output.[32] AKI is observed in nearly half of ICU patients and is associated with high mortality.[32-35] Among patients with AKI, metabolic acidosis due to elevated unmeasured anions, hyperphosphatemia, and hypoalbuminemia are reported.[36] The management of AKI is mainly to correct causes while providing supportive care for acute complications including metabolic acidosis, hyperkalaemia, and fluid overload.[32] In the most severe cases, the definitive intervention is to provide renal replacement therapy. In less severe cases, medical treatment of acidosis involves administering sodium bicarbonate; however, the efficacy or effectiveness of this intervention has not been rigorously evaluated.[37]

Consequences of metabolic acidosis

Although the physiological performance of several organs and systems are impaired by severe acidaemia, the impact on cardiac function has been suggested to be the most critical. The observation of the effect of acidaemia on the response to catecholamines goes back to 1950s.[38] In these studies, sodium lactate injection in patients with acidosis from septic shock increased the response to catecholamine's and increased mean arterial pressure.[38] Subsequent experimental and clinical studies have focused on the effect of acidaemia on cardiovascular function. Several experimental studies using isolated cardiac muscle and heart preparations suggest that the low arterial pH may decrease the cardiac contractile force and diminish the contractile response to catecholamines.[39-41] A correlation between the severity of acidaemia and degree of cardiac depression was observed in whole animal experiments as well. In the intact animal, cardiac output decreased when blood pH was decreased to less than 7.20.[42,43] Several cellular processes which may underlie the impairment of cardiac contractility during severe acidaemia have been suggested, including high-energy phosphate metabolic intermediates in the myocardial cell,[44] reduction or elevation in intracellular calcium levels,[45] or impairment of actin-myosin cross-bridge formation by H_2PO^-.[46]

4

5.2 Treatment of metabolic acidosis

General

In critically ill patients requiring vasopressor support, due to underlying shock and metabolic acidosis, the cornerstone of treatment is early fluid therapy. Nevertheless, the best fluid therapy strategy (type and rate of administration) in this setting, is still not clear, with clinicians utilising a variety of options. D5W may be employed, as it; a) is a readily available intravenous fluid, b) contains no strong ions, and c) is regularly used as a diluent for drug administration. Moreover, clinicians are familiar with its use, and it has an exemplary safety profile. Most importantly, as excess chloride worsens acidosis (as is seen with the use of saline solutions), D5W infusion avoids exacerbating the acid-base disturbance.

In addition, administration of "buffer" solutions is common in critically ill patients with significant metabolic acidosis, under the assumption that this might restore normal cardiovascular function and oxygen delivery to tissues, by raising extracellular pH. In this respect, sodium bicarbonate is the most common agent used.[47,48] The administration of sodium bicarbonate raises extracellular SID principally through the delivery of sodium ions; however, it is unclear whether this leads to improvements in patient-centred outcomes. Effects of sodium bicarbonate on acid-base status and haemodynamics in critically ill patients with lactic acidosis have been examined in several small studies, which showed increased blood pH but no changes in cardiac index.[49,50] Interestingly, there are several studies of animals with hypoxic lactic acidosis where bicarbonate administration resulted in a decrease in cardiac output and increased $PaCO_2$,[51,52] and decreased intracellular pH of the liver.[52]

Clinical evidence

Our recent systematic review examining the use of bicarbonate therapy for metabolic acidosis,[53] identified two randomised controlled trials examining the effect of sodium bicarbonate for metabolic acidosis in the ICU.[54,55] Hoste et al.[54] compared the biochemical changes of a single dose of sodium bicarbonate and THAM (a buffering solution) for mild metabolic acidosis. Jaber et al.[55] examined the effect of repeated sodium bicarbonate infusion to maintain the arterial pH above 7.30 and usual care for moderate to severe metabolic acidosis. In these trials, sodium bicarbonate administration normalized arterial pH, serum bicarbonate, base excess, and sodium and decreased potassium values.

Jaber et al.[55] suggested that intravenous sodium bicarbonate reduced the need for RRT by the risk ratio of 0.83 (95%CI 0.68 to 1.02). However, this result should be interpreted cautiously, as they used blood pH as an indication for RRT. Sodium bicarbonate obviously increases blood pH as previous studies have shown. Of note, this trial did not show any clinical effectiveness of sodium bicarbonate on hemodynamic indices regardless of the highly quoted rationale for using sodium bicarbonate to restore cardiovascular function by improving pH. Furthermore, the treatment regimen of bicarbonate therapy was not standardised, which limits the generalisability of the results.

The SODA-BIC investigators completed an international observational study, demonstrating that metabolic acidosis was common in Australian and Japanese ICUs, and early intravenous sodium bicarbonate was variably used in such patients across the study ICUs (not published yet). Most patients receiving sodium bicarbonate did so as a bolus dose. However, the prescription was not adjusted for body weight or the severity of metabolic acidosis. Patients who received sodium bicarbonate had a higher severity of critical illness and more severe metabolic acidosis. However, their biochemical parameters and PaO_2/FiO_2 ratio improved more rapidly than for patients who did not receive bicarbonate. Early sodium bicarbonate was not significantly associated with improved clinical outcomes overall. However, in patients with vasopressor dependency at diagnosis, sodium bicarbonate was associated with higher mean arterial pressures within 6 hours and a favourable, but not statistically significant, odds ratio for ICU mortality.

In summary, there is currently insufficient data to support the routine use of sodium bicarbonate to normalize pH in the context of metabolic acidosis.

5.3 Importance of the present study

The worsening or persistence of metabolic acidosis has been associated with a poor prognosis, with a mortality rate as high as 57% when pH stays below 7.20. Clinicians often recognise this as an emergency, as persistent metabolic acidosis is associated with a cascade of deleterious effects, such as haemodynamic instability and organ dysfunction, and if not treated could result in death. As a result, many therapies are administered urgently in this context, in order to prevent further deterioration and serious permanent damage to health. Despite being

approved for the treatment of metabolic acidosis, the use of sodium bicarbonate in the ICU is highly heterogeneous among clinicians, and this lack of consensus could be explained by two factors: 1) a lack of definitive evidence for any patient centred benefits (particularly with moderate metabolic acidosis); and 2) the potential adverse effects associated with the therapy (e.g. electrolyte abnormalities and intracellular acidosis). As such, the use of sodium bicarbonate infusion is not mandated, and most clinicians will utilise other fluid therapy, and use sodium bicarbonate only in patients with severe acid-base derangement.

However, a recent large open-label RCT suggested a potential role for this therapy, with a signal towards improved outcomes in patients with severe acidosis (pH < 7.20), albeit the study was underpowered and grossly confounded by lack of blinding and selection of outcomes. As such, the results of this study have not been widely translated into clinical care in Australia. The present study aims to generate more robust evidence, and also to test the efficacy of sodium bicarbonate when administered earlier (pH < 7.30), in patients receiving a vasopressor infusion, compared with D5W alone, as fluid therapy. Critically, this is an urgent, time-sensitive situation, as worsening metabolic acidosis is strongly associated with adverse outcomes.

6. AIMS AND OBJECTIVES

6.1 Aim

The trial aims to assess if the infusion of D5W + sodium bicarbonate in vasopressor-dependent patients with moderate metabolic acidosis admitted to the ICU increases the number of vasopressor-free hours at day 7 (168 hours), compared with D5W alone.

6.2 Hypothesis

We hypothesize that conducting a double-blind randomized clinical trial aiming to correct moderate metabolic acidosis with sodium bicarbonate in critically ill vasopressor-dependent patients is feasible, and leads to an increase in the number of hours alive and free of vasopressor administration up to day 7 (168 hours) compared with D5W alone, as fluid therapy.

7. RESEARCH PLAN

7.1 Study design

Pilot, feasibility and physiological efficacy international, multicentre, randomized, double-blind clinical trial.

7.2 Study setting

Study participants will be enrolled in ICUs in Australia, New Zealand and Japan. The ANZIC-RC, Monash University will be the coordinating centre. This study is to be conducted over a 2-year period.

7.3 Study population

The target population is vasopressor-dependent, adult critically ill patients, with moderate metabolic acidosis.

Inclusion criteria

All the diagnostic criteria of moderate metabolic acidosis below have to be fulfilled within the last 2 hours before randomization, and a vasopressor is being infused continuously at the time of randomization.

1. Adult patients (≥ 18 years);
2. Patient is within 48 hours of admission to the ICU;
3. Patient is receiving a continuous infusion of a vasopressor drug to maintain mean arterial pressure > 65 mmHg (or a mean arterial pressure target set by the treating clinician);
4. A dedicated line (central or peripheral) is available (or is about to be made available within 1 hour after randomization); and
5. Patient has at least a moderate metabolic acidosis, defined as:
    a. pH < 7.30; and
    b. BE < -4 mEq/L; and
    c. $PaCO_2$ < 45 mmHg.

Exclusion criteria

1. Proven digestive or urinary tract loss of sodium bicarbonate (e.g., acute diarrhoea, ileostomy, or drainage of pancreatic or biliary duct); or
2. DKA; or
3. Stage IV or V chronic kidney disease; or
4. Using renal replacement therapy (acute or chronic); or
5. Received sodium bicarbonate within 24 hours of screening; or
6. Dysnatraemia (serum Na ≥ 155 mEq/L or < 120 mEq/L); or
7. Hypokalaemia (serum K < 2.5 mEq/L); or
8. Pulmonary oedema with PaO_2 / FiO_2 < 100; or
9. Hypocalcaemia (iCa < 0.8mmol/L); or
10. Known or suspected poisoning of antidepressant or antipsychotic poisoning agents that may cause high anion gap acidosis (methanol, PEG, aspirin); or
11. Suspected intoxication with unknown aetiology; or
12. Pregnancy or breastfeeding; or
13. Limitation of medical therapy orders (DNR, DNI); or
14. Imminent or inevitable death; or
15. In the opinion of the treating clinical team the patients will almost certainly receive RRT in the next 6 hours; or
16. Traumatic brain injury (or substantial risk for intracranial hypertension); or

17. Clinician believes that being enrolled in intervention or control arm is not in the best interest of the patient; or
18. Previous enrolment in this study ever.

7.4 Screening and enrolment

Adult patients (≥ 18 years) admitted to a participating ICU, and who meet all the inclusion criteria will be screened for enrolment. A screening log is designed to monitor patient recruitment at the participating sites. The log will be maintained at each participating site by the research coordinator to record patients evaluated for enrolment. The log will provide a record of all patients assessed for eligibility, either enrolled in the study or deemed ineligible for the study. When a patient is considered ineligible, the reason(s) will be noted in the log.

7.5 Randomization

Eligible patients will be randomised as soon as possible after fulfilling the criteria for enrolment. A permuted block randomisation with stratification by study site will be used. Patients will be allocated in a 1:1 ratio to either the D5W + Sodium Bicarbonate Group or D5W Group. A centralised, web-based system (REDCap) will be employed, allowing 24-hour enrolment and random allocation. The random allocation sequence will be generated using a computer software program by the project manager at the coordinating centre (ANZIC-RC) and embedded into the REDCap system. Site investigators, site research coordinators, or study participants do not have access to the allocation sequence throughout the trial. A senior statistician does not have access to the treatment allocation throughout the trial.

7.6 Consent and legal issues

Since all eligible patients will be seriously ill (requiring a vasopressor infusion in the setting of life-threatening metabolic acidosis), we do not anticipate they will have capacity to provide prospective consent. Moreover, it is highly conceivable that the patient's legally authorised representative (LAR) is not known, not present, nor sufficiently informed of the patient's condition and diagnosis to consider the proposal and give consent in a timely manner. Enrolment into the study represents an opportunity to receive potentially life-saving therapy. Given persistent metabolic acidosis is associated with a cascade of deleterious effects, such as haemodynamic instability, organ dysfunction, and death, clinicians administer therapies urgently in this context, in order to prevent further deterioration and serious permanent damage to health. While sodium bicarbonate can be used, its use in treating metabolic acidosis in ICU is highly heterogeneous, due to a lack of definitive evidence. The present study aims to not only generate more robust evidence, but also test the efficacy of D5W + sodium bicarbonate when administered earlier (pH < 7.30) in patients receiving a vasopressor infusion, compared with D5W alone, as fluid therapy. Critically, this is an urgent, time-sensitive situation. As such, enrolment in this project for patients in Victoria, Australia will be performed under Section 53 of the Medical Treatment Planning and Decisions (MTPD) Act 2016. Consent will not be sought from the patients or their LAR prior to enrolment in the study. A waiver of consent has been granted by the HREC for this jurisdiction for the collection of data associated with the medical research procedure. Elsewhere, we propose enrolment as emergency care research where permitted by jurisdictional law, in line with the National Statement Guideline 4.4.13.

In designing the SODa-BIC trial we have carefully considered potential risks and benefits for trial participants. We have specifically designed the study protocol to ensure that trial participants will benefit from trial participation irrespective of the specific treatment that they are allocated to (see section 7.8 of the protocol). Sodium bicarbonate is an established therapy in ICU patients. While acid-base and electrolyte disturbances can occur with its use, these are common problems in ICU patients more generally, and, as outlined in section 7.8,

our study protocol has been specifically designed so that the risk of such disturbances becoming severe enough to have clinical consequences should be lower in trial participants than they are in usual clinical care. Also, we are conscious that clinicians have obligations to ensure that patients receive services of an appropriate standard. The protocolised management outlined in section 7.8 of the protocol exceeds this standard. In particular, the protocolised monitoring of arterial blood gases we will use should minimise the risk of electrolyte derangements and increase safety compared to usual care in both study treatment groups. The intensity of monitoring specified in the protocol can only be achieved with the assistance of research coordinators. In addition, patients allocated to the comparator group will receive early fluid therapy with D5W, a strategy that could also potentially improve acid- base and electrolyte disturbances, and outcomes in this group of patients.

As soon as practicable following recruitment, the patient and/or LAR will be informed about the trial. Given the 'research procedure' in this trial will span a maximum of 5-hours, this will most likely occur after the procedure has been completed. In our experience with trials in critically ill patients, patients and LARs often find it confusing to provide written consent when the research procedure has already taken place and they frequently perceive that more invasive procedures are required. Further, data will be collected from the medical record only (no data from patients or out-of-hospital data will be required). Therefore, subject to local approval, we will provide an information brochure to the patient and/or LAR together with a verbal presentation of information. The brochure will provide contact details should the patient/LAR require a more detailed explanation or wish to withdraw from the study. We will also request that the waiver for the requirement of consent to collect data be extended to participants who succumb to their illness prior to such time that they or their LAR can be informed of their inclusion and presented with the information brochure. A condolence letter will be sent from the principal investigator at participating sites in Victoria, Australia to the family/relatives of participants who die prior to the provision of an information brochure. This letter will be sent 6 weeks after the death.

7.7 Co-enrolment with other studies

We will seek agreement from other trials about inclusion or exclusion for co-enrolment of patients participating in this study.

7.8 Intervention

This study is a double-blind randomized clinical trial. The intervention was shaped based on a survey circulated among healthcare professionals in the ANZICS-CTG.[56] The stability of the study drug and feasibility of blinding were validated in two previous studies.[57,58] In both arms the infusion of the study drug must be started within one hour of randomization. The study drug will be prepared by an ICU nurse or pharmacist not involved in the care of the patient. All other management will be at the discretion of the attending clinicians in charge.

Study drug

5% Dextrose + Sodium bicarbonate group

Sodium bicarbonate 8.4% (1000 mEq/L) will be diluted in a D5W solution (500 mL bag). For preparation, 300 mL of D5W will be removed and 300 mL of sodium bicarbonate 8.4% added to prepare the bicarbonate solution in total volume of 500 mL (final concentration: 600 mEq/L).

5% Dextrose group

Standard 500 mL D5W bag. We have chosen D5W as a comparator for this study because it; a) is a readily available intravenous fluid that is commonly utilised by clinicians, b) contains no strong ions, and c) is regularly used as a diluent for drug administration. Moreover, D5W has

an exemplary safety profile, and will not lead to hyperchloraemia (as seen with saline solutions), which exacerbates metabolic acidosis.

Study drug administration

Study drug will be continuously infused targeting a pH ≥ 7.30 and a BE ≥ 0 mEq/L. The infusion will be maintained until this target is achieved and continued by titration thereafter for a maximum of 5 hours (to maintain target pH and base excess levels).

The infusion will start at 100 mL/hr and be kept at this rate until both targets (pH and BE) are achieved, following which, the infusion rate will be decreased to 25 mL/hr and kept constant at this rate until 5 hours has elapsed since the start of the infusion. At this point, the infusion will be stopped, independently, of the results of arterial blood gas analysis (**Figure 1**).

Arterial blood gases will be obtained at pre-defined times within the first 5 hours (at 0, 1, 3 [± 0.5 hours], and 5 [± 1 hour] hours after the start of the infusion), and then at 12, 18 and 24 hours after the start of the drug infusion. The maximum duration of the study infusion is up to 5 hours after commencement, until RRT is started, or ICU discharge, whichever comes first.

Arterial blood gases provide data on the patient's pH, HCO3-, BE, CO2, sodium, potassium, and lactate. As outlined in section 7.6 of the protocol, the level of monitoring prescribed by this protocol exceeds current standards of care and would not be achievable without support of research coordinators. Assiduous monitoring of sodium and potassium levels will allow for more prompt correction of disturbances of these electrolytes than could be achieved in usual practice. Monitoring of lactate levels may provide clinicians with important collateral information about clinical trajectories that would not usually be available. These benefits of trial participation will occur irrespective of which study treatment participants are assigned to.

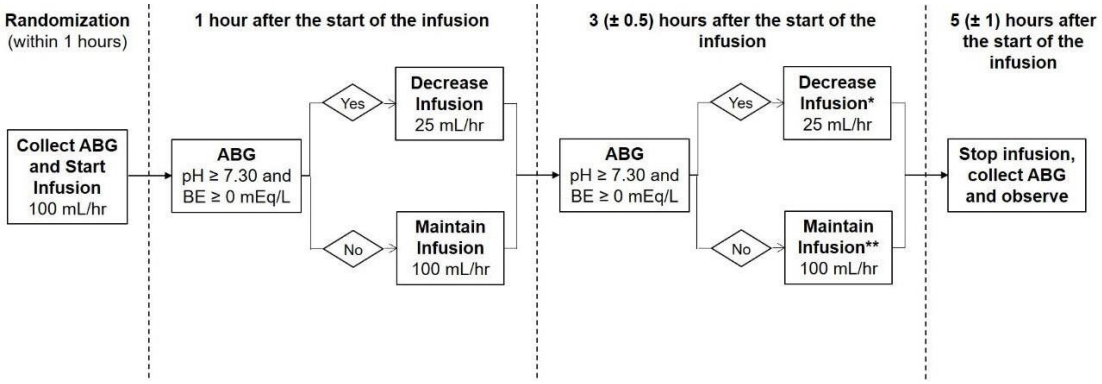


Figure 1 - Study intervention

* or maintain at 25 mL/hr if already decreased in the previous assessment

** or increase to 100 mL/hr if receiving 25 mL/hr

All other aspects of care will be determined by the treating clinical team, including the use of additional fluid therapy, vasopressors, and other organ support modalities. Open-label sodium bicarbonate bolus infusion is allowed in both groups if clinically indicated.

Permanent withholding criteria

Study drug will be permanently withheld for any of the following reasons:

1. Contraindication to sodium bicarbonate arisen:
    a. Development of dysnatraemia (Na > 155 mEq/L);
    b. Hypocalcaemia (iCa < 0.8 mmol/L);
    c. Hypokalaemia refractory to potassium replacement (K < 2.5 mEq/L);
    d. Clinically significant fluid overload (e.g., lung oedema); or
    e. Any contra-indication according to the treating physician.

7.9 Outcome measures

Primary outcome

The primary outcome is the number of hours alive and free of vasopressors at day 7 (168 hours) after randomization. This is defined as the time, censored at 7 days, that a patient was both alive and had not received vasopressors for at least 12 hours. If a patient died while receiving vasopressor therapy following the index episode, the patient is assigned zero hours for this outcome. If a patient was weaned from all vasopressors for 12 consecutive hours, then all of the remaining time through day 7 was treated as success, even if the patient died or had vasopressors restarted after weaning within the 7-day period.

Key feasibility outcome

The key secondary outcomes of this pilot study are to establish the feasibility of the study design, including:

1. Correct patient selection by demonstrating effective application of the eligibility criteria across multiple study centres;
2. Recruitment rate;
3. Protocol compliance;
4. Time from eligibility criteria to the first dose of sodium bicarbonate; and
5. Enrolment-to-screening ratio.

Clinical secondary outcomes

1. Time to correction of BE;
2. Time to correction of pH;
3. Recurrence of moderate metabolic acidosis (defined as pH < 7.30, BE < -4 mEq/L and $PaCO_2$ < 45 mmHg) in the first 7 days after randomization;
4. Mean bicarbonate levels in the first 24 hours of infusion (at 0, 1, 3, 5, 12, 18 and 24 hours after start of infusion);
5. Incidence and the maximum stage of acute kidney injury in the first 7 days after randomization (according to KDIGO criteria);
6. Receipt of renal replacement therapy in the first 28 days;
7. 28-day cumulative vasopressor-free days;
8. 28-day renal replacement therapy–free days;
9. Change in Sequential Organ Failure Assessment (SOFA) score at day 3 after randomization;
10. ICU length of stay;
11. Hospital length of stay;
12. ICU mortality;
13. Hospital mortality;
14. 28-day in-hospital mortality;
15. 90-day in-hospital mortality;
16. Adverse events during study drug infusion, including:
    a. Hypokalaemia needing correction;
    b. Hypocalcaemia needing correction; and
    c. Dysnatraemia (Na > 155 mEq/L).

Physiological tertiary outcomes

1. SID and SIG in the first 24 hours of infusion;
2. pH at 0, 1, 3, 5, 12, 18 and 24 hours after the start of the infusion;
3. BE at 0, 1, 3, 5, 12, 18 and 24 hours after the start of the infusion; and
4. $PaCO_2$ at 0, 1, 3, 5, 12, 18 and 24 hours after the start of the infusion.

7.10 Statistical analysis

Sample size calculation

No previous data for the calculation of the sample size is available. In the absence of accurate, current data, the estimate of the standard deviation was based on a previous study in a similar population.[59] Considering a standard deviation on the primary outcome of 55 hours, an expected difference of 44 hours, a power of 80%, a two-sided alpha of 0.05, and an inflation of 15% due to the possibility of using rank-sum tests, 60 patients (30 in each arm) is needed. The estimation of the standard deviation will be updated from the pooled SD from the first 50 patients, and a blinded sample size recalculation is planned.

Statistical analysis plan

A senior statistician at Monash University Department of Epidemiology and Preventive Medicine will perform data analysis on an intention-to-treat basis. Summary statistics will be used to describe the clinical data and presented as mean ± SD, median with interquartile range or percentages as appropriate. Chi-squared analysis with Fisher's exact test (when appropriate), and Student's t-test (Mann Whitney U test for non-normal distributions) will be used to compare data between the active treatment group and the control group with statistical significance declared for probability values of less than 0.05. A full statistical analysis plan will be prepared before the final of the recruitment.

Recruitment feasibility

With an expected conservative eligibility rate of 3 patient/week and participation of 6 ICUs we estimate 72 eligible patients/month. Assuming a randomization to eligibility rate of 0.3, we expect to randomize 22 patients/month. Thus, we expect to achieve the target population in less than one year.

8. DATA MANAGEMENT

8.1 Data collection methods

Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including baseline demographics, primary diagnoses, physiological parameters, therapeutic interventions, documentation of deaths and other adverse events, and the feasibility of the trial intervention. All data will be collected by trained staff at each study site and will be entered into the web database, REDCap (an electronic CRF). Randomised patients will be followed up to hospital discharge, death or 90 days post-randomisation whichever occurs first. All data will be collected from hospital clinical records.

Study day 1 commences on randomisation and concludes at the 06.59AM. Then, each day will start at 07.00AM and end at 06.59AM. Data will be collected for all randomised patients (**Figure 2**).

Data management will be performed by Monash University. The system is capable of collecting high volumes of patient data. Data is entered by participating sites. A paper CRF worksheet will be available for use by sites if desired. Access to the SODa-BIC database is based on the defined role of the user. The SODa-BIC Project Manager and Project Officer has access to all data contained in the database and the ability to assign access to new users. Responsibility for updating the database currently resides with the Project Manager. This will be reviewed periodically as the SODa-BIC increases in size.

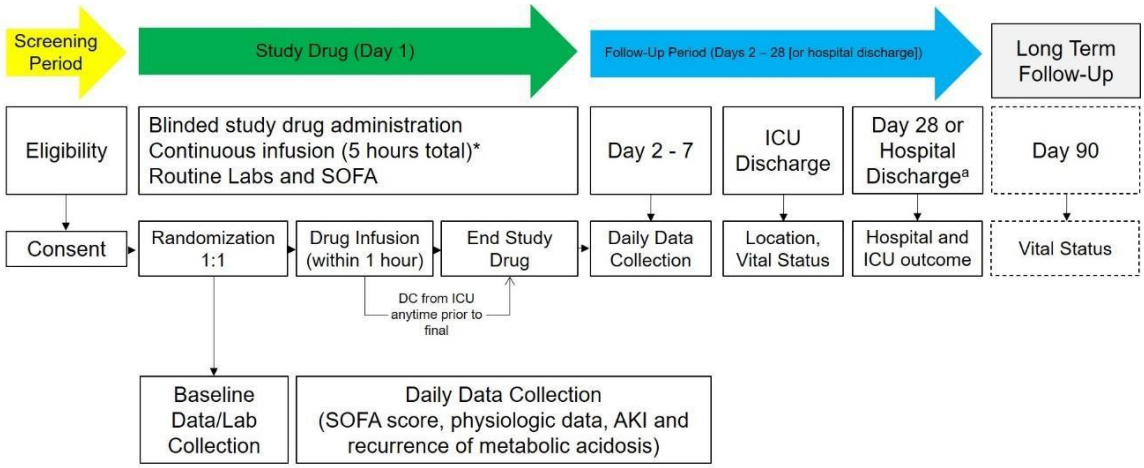


Figure 2 - Overview of study progression

* study drug infusion up to 5 hours after randomization; [a] whichever comes first

8.2 Data variables collected

All data variables are defined in the SODa-BIC data dictionary. The following data variables will be collected at each participating site:

Demographics

- Age;
- Sex (female *or* male);
- Height (centimetres);
- Weight (kilograms);
- Co-existing disorders (yes *or* no):
  - Hypertension;
  - Diabetes;
  - Chronic respiratory disease;
  - Chronic kidney disease Stage I to III;
  - Active cancer;

    - Heart failure;
    - Chronic liver disease.
- APACHE III severity of illness score;
- Type of admission (medical *or* surgical);
- ICU admission source;
- Scheduled admission (yes *or* no);
- Reason for ICU admission (as defined by APACHE III severity of illness scoring system);
- Possible aetiology of metabolic acidosis;
- Receipt of mechanical ventilation (yes *or* no);
- SOFA score;
- Type and dose of vasopressor;
- Most recent creatinine measured within 3 months and more than 7 days prior to the ICU admission.

Intervention details

- Date and time of start of infusion;
- Date and time of stop of infusion;
- Date and time of first pH ≥ 7.30;
- Date and time of first BE ≥ 0 mEq/L;
- Reason for stopping study drug;
- At 0, 1, 3 (± 0.5), 5 (± 1), 12, 18 and 24 hours after randomization:
    - Arterial blood gas analysis (pH, PaO_2, $PaCO_2$, BE, HCO_3, Na, K, Cl, iCa, lactate);
    - Heart rate;
    - Mean arterial pressure.

ICU daily data (collected during the first 7 days in the ICU)

- Receipt of mechanical ventilation (yes *or* no);
- Use of vasopressor;
- Six-hourly dosage of intravenous vasopressor infusion;
- Arterial blood gas analysis (minimum and maximum value in 24 hours of pH, PaO_2, $PaCO_2$, FiO_2, BE, HCO_3, Na, K, Cl, iCa, lactate)
- Heart rate;
- Mean arterial pressure;
- Blood (minimum and maximum value in 24 hours of white blood cell count, haemoglobin, platelets);
- Serum (minimum and maximum value in 24 hours of total bilirubin, albumin, creatinine, magnesium, phosphate);
- SOFA score;
- Daily cumulative number of vasopressor free hours;
- Total fluid input;
- Urine output;
- Fluid balance;
- Need of potassium supplementation;
- Need of calcium supplementation;
- Need of renal replacement therapy.

Admission and discharge data

- ICU admission and discharge dates and times;
- ICU discharge destination;
- Hospital admission and discharge dates;
- Hospital discharge destination;

- Treatment limitations/withdrawal.

Outcome data

- Time alive and free of vasopressors at day 7 (168 hours) after randomisation;
- Length of ICU and hospital stay;
- Duration of intravenous vasopressor infusion (hours);
- Duration of mechanical ventilation (hours);
- Duration of renal replacement therapy (hours);
- Last day of renal replacement therapy during hospital stay;
- Presence and timing of acute kidney injury (defined using the KDIGO criteria; namely, an increase of the serum creatinine > 26.4 µmol/L (0.3 mg/dL) or a level > 1.5 times the baseline value within 48 hours. If the baseline serum creatinine is not known a value > 132 µmol/L (1.5 mg/dL) will be regarded as diagnostic of acute kidney injury);
- Vital status at:
    - ICU discharge;
    - Hospital discharge;
    - 28-day post-randomization;
    - 90-day post-randomization.
- Last serum creatinine measured during hospital admission.

Safety data

- Adverse events until 72 hours after randomisation;
- Adverse reactions until 72 hours after randomisation; and
- Serious adverse events until 72 hours after randomisation.

Consent data

- Date of consent (if applicable);
- Date of consent withdraw (if applicable).

Feasibility data

- Time from meeting the eligibility to the first dose of the main study drug;
- Monthly recruitment rate;
- Number of patients screened;
- Randomised to the screened patient ratio;
- Reasons for exclusion;
- Protocol deviations.

8.3 Patient identification

Each patient will be given a unique identifier. Research Coordinators at each site will compile an enrolment log, which will not leave the site, including patient's name, year of birth, hospital identification number, unique identifier and date of randomization. All data entered into the SODa-BIC trial will be identified using the unique identifier. No identifying patient information will be entered into the SODa-BIC database. At study completion only re-identifiable data is kept in the secure SODa-BIC folder on the secure drive at Monash University.

8.4 Data handling and security

Monash REDCap security is maintained using encryption of data, a managed and audited protocol for access, training and accreditation of personnel, role-based access and authentication of data. Monash REDCap is managed in an ISO 27001 certified environment.

The ISO 27001 certification incorporates the Privacy Act (1988) and Health Records Act (2001) within its Applicability Statement.

8.5 Data access and data release

Access to information collected and collated by the SODa-BIC trial is guided by strict protocols and procedures to protect against potential breaches of privacy and to ensure appropriate ethical integrity is maintained at all times and by written request to the Management Committee.

8.6 Data access for clinicians, researchers, industry and TGA

Access to data is subject to the approval of the SODa-BIC Management Committee. When considering the approval of access to SODa-BIC data, the Management Committee seeks to balance the importance of privacy protection and the significant public health interest from the proposed research. Ethical approval must be obtained prior to the transfer of SODa-BIC data. If the value of the proposed activity is deemed to be inadequate, access will be denied. If an approval is granted the data transferred will be sent via secure file transfer and all data will be in a re-identifiable format.

8.7 Data management

Data management will be coordinated by the project manager, at the ANZIC-RC including programming (online study database design) and data management support (including data monitoring, database questions, technical issues, data queries, query resolution).

8.8 Data quality and monitoring

Several procedures to ensure data quality and protocol standardisation will help to minimise bias and to optimise data quality. These include:

- A site initiation teleconference will be conducted before site activation to ensure consistency in procedures;
- A detailed data dictionary will define the data to be collected and entered into the eCRF;
- The coordinating centre will perform timely validation of data entered into the eCRF, queries and corrections

The SODa-BIC trial database will be developed with tools to reduce data entry error. Range and reliability checks activated as data will be entered into the database to reduce the opportunity for data errors. Intuitive checks will be built into the database. For example:

- Dates recorded cannot be in the future date;
- Patients under 18 years will be queried;
- Logic checks in place based on data previously entered;
- User receives a warning if they try to leave a page without saving data

The study will be monitored by quality control reviews of protocol compliance, data queries, safety reporting, protocol deviations, and key outcomes. On-site or online video monitoring will only be performed on a case by case basis if quality control issues are flagged by electronic review of data. Medical records, any other relevant source documents and the site investigator files must be made available to the monitoring representative for these monitoring visits during the study and at the completion of the study as needed.

8.9 Protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

Given that the investigator is responsible for patient safety and care he/she may deviate or change the protocol to eliminate an immediate hazard to trial patients without prior Human Research and Ethics Committee (HREC) approval. The implemented deviation or change must be reported in a protocol deviation form. The deviation must be reported via the study website by the principal investigator. A six-monthly summary of protocol deviations will be reported to the coordinating HREC; a serious breach will be reported ASAP.

The following events will be considered a protocol deviation (and justification will be provided):

- Patient enrolled and randomized, who is in fact not eligible;
- Intentional withhold of the protocol;
- Infusion rate not adjusted based on arterial blood gases and according to the protocol;
- Infusion not started within 1 hours of randomization; and
- Infusion extended beyond 6 hours after the start of infusion.

8.10 Retention of records

If the SODa-BIC trial is transferred to another custodian, the data will be provided to the new custodian in a mutually agreed file format. Data will be transferred within 90 days after the appointment of the new custodian provided that it can demonstrate compliance with security arrangements equivalent to or more sophisticated than the existing SODa-BIC trial security arrangements. The SODa-BIC Management Committee must approve transfer of data to the new custodian in writing.

If the SODa-BIC trial ceases to operate, data will be held by the custodian in accordance with the Australian Code for the Responsible Conduct of Research.

9. SAFETY MONITORING AND REPORT

9.1 Data monitoring and safety reporting

A duly constituted DSMB will be formed, as per standard ANZIC-RC and NHMRC guidelines.

9.2 (S)AE, (S)AR, and SUSAR reporting

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment. It is recognised that the patient population with critical illness will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are considered to be of concern or related to the study or the intervention in the investigator's clinical judgement. In the present study, the following adverse events will be recorded until 72 hours after randomisation:

- Hypokalaemia needing correction;
- Hypocalcaemia needing correction; and
- Dysnatraemia (Na > 155 mEq/L).

An adverse reaction (AR) is defined as any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting site investigator or the coordinating centre as having a reasonable possibility of a causal relationship to an investigational medicinal product will qualify as adverse reactions.

A serious adverse event (SAE) or serious adverse reaction is in general defined as any adverse event/reaction that results in death, is life-threatening, requires hospitalisation or prolongation of current hospitalisation, or results in persistent or significant disability or incapacity. However, death is an expected outcome among critically ill patients with metabolic acidosis. Therefore, death will not be considered a serious adverse event in this trial. Standard care of critically ill patients includes a host of complications that fit the definition of an SAE. Medical and scientific judgement will be exercised by the site principal investigator in deciding whether an adverse event/ reaction will be classified as serious in other situations to avoid over-reporting. Specific serious adverse reaction in this trial is suspected or confirmed anaphylactic/anaphylactoid reaction towards sodium bicarbonate solution.

Suspected unexpected serious adverse reaction (SUSAR) is defined as being an adverse reaction that is both serious and unexpected.

9.3 Reporting (S)AE, (S)AR, and SUSAR

Adverse events/reactions and serious adverse events/reactions will be recorded on a case report form. SAEs should be reported to the coordinating centre within 24 hours of study staff becoming aware of the event.

Minimum information on the report form will include:

- Patient initials and study number;
- Nature of the event;
- Commencement and cessation of the event;
- An investigator's opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitively related); and
- Whether treatment was required for the event and what treatment was administered.

The coordinating centre staff will be responsible for following-up all events to ensure all details are available. The coordinating centre is also responsible for reporting directly to HRECs and investigators, who forward any relevant information to their institution. It is the

responsibility of each principal investigator to inform the local or lead HREC of all SUSAR events which occur at their hospital, by local requirements. Copies of any reporting and correspondence to and from the local HREC or RGO should also be sent to the coordinating centre. All SUSARs occurring in Australian participants will be reported to the Therapeutic Goods Administration:

- For fatal or life-threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days; and
- For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case.

The coordinating centre will provide the principal HREC with an annual safety report. Instead of submitting individual reports of AEs, SAEs and SUSARs, the outcomes of the coordinating centre's analyses of accumulating safety data will be provided to the HREC and the participating institutions.

9.4 Contact phone number for SAE advice

Chief Investigator (Prof Andrew Udy): +61 438 755 568

ANZIC-RC (Dr Ary Serpa Neto): +61 432 749 435

9.5 Post-trial care

Post-trial care for compensation to those who suffer harm from trial participation will be covered by Monash University Insurance.

https://www.intranet.monash/finance/our-services/insurance/certificatesofcurrency

10. ETHICS

10.1 Guiding principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, NHMRC National Statement on Ethical Conduct in Research Involving Humans 2007 (Updated 2018), and the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000).

10.2 Ethics committee approval

Each participating site will submit this protocol, and any other relevant study documentation to the responsible local or national constituted HREC (or equivalent). Approval of the protocol plans for obtaining consent, and related documents will be obtained before the start of the study at each site. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC (or equivalent) as required by that committee.

10.3 Confidentiality

After randomisation, patients will be allocated a unique study number. The site research coordinator will compile an enrolment log including the patient's name, date of birth, hospital identification number, unique study number and date and time of randomisation. Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately. Study data will be entered into a password protected REDCap database managed by ANZIC-RC (Monash University). No identifying data will be entered into the database.

Similarly, hard copies of enrolment log and study data collected on paper CRF's will be stored separately in the locked office of the principal investigator or research coordinator. Only the research team will have access to this information, and they will not disclose this information to any other person or entity. When archiving, the study site principal investigators will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The site principal investigator will maintain the confidentiality of all study documentation and take measures to prevent the accidental or premature destruction of these documents. The site principal investigator will retain the study documents at least 15 years after the completion or discontinuation of the study. The site principal investigator must notify the study management committee prior to destroying any essential study documents following the study completion or discontinuation.

If any principal investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the coordinating centre or another investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

10.4 Declaration of interests

All the staff member in the coordinating centre for this trial, all the site principal investigators, all the management committee members do not have any significant conflict of interest regarding the trial.

11. BUDGET

Funding is being sought to support the study.

12. PUBLICATION AND DISSEMINATION

The study will be conducted in the name of the management committee. The principal publication from the study will be in the name of the management committee with full credit assigned to all collaborating investigators, research coordinators, and institutions. Funding bodies will be acknowledged in the publication.

13. RESEARCH TIMELINES

Expected timeframe	Milestone
November 2020	HREC application submitted
December 2020	Database built
May 2021	First patient enrolled in the SODa-BIC Study
November 2022	Hospital follow ups complete
January 2023	Study completion and publication

14. REFERENCES

1. A. Stewart P. How to Understand Acid-Base: A Quantitative Acid-Base primer for biology and medicine. New York: Elsevier North Holland; 1981.
2. Kellum J a, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care. 1995;10:51–5.
3. Zazzo JF, Troché G, Ruel P, Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: Efficacy of phosphorus therapy on myocardial function. Intensive Care Med. 1995;21(10):826–31.
4. Suzuki S, Egi M, Schneider AG, Bellomo R, Hart GK, Hegarty C. Hypophosphatemia in critically ill patients. J Crit Care [Internet]. Elsevier Inc.; 2013;28(4):536.e9-536.e19. Available from: http://dx.doi.org/10.1016/j.jcrc.2012.10.011
5. Gilfix B, Bique M, Magder S. A physical chemical approach to the analysis of acid-base Balance in the Clinical Setting. J Crit Care. 1993;8(4):187–97.
6. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. 2003;2333–44.
7. Jung B, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, et al. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. a prospective, multiple-center study. Crit Care [Internet]. BioMed Central Ltd; 2011;15(5):R238. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc10487
8. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care [Internet]. Elsevier Inc.; 2012;27(2):132–7. Available from: http://dx.doi.org/10.1016/j.jcrc.2011.07.071
9. De Corte W, Vuylsteke S, De Waele JJ, Dhondt AW, Decruyenaere J, Vanholder R, et al. Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. J Crit Care [Internet]. Elsevier Inc.; 2014;29(4):650–5. Available from: http://dx.doi.org/10.1016/j.jcrc.2014.02.019
10. Kellum JA. Metabolic Acidosis in Patients with Sepsis : Epiphenomenon or Part of the Pathophysiology ? :197–203.
11. Azevedo LCP, Choi H, Simmonds K, Davidow J, Bagshaw SM. Incidence and long-term outcomes of critically ill adult patients with moderate-to-severe diabetic ketoacidosis: Retrospective matched cohort study. J Crit Care [Internet]. Elsevier Inc.; 2014;29(6):971–7. Available from: http://dx.doi.org/10.1016/j.jcrc.2014.07.034
12. McCluskey S a, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg [Internet]. 2013 Aug [cited 2013 Oct 2];117(2):412–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23757473
13. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients : a retrospective multi-centre study. Crit Care. 2010;14:R25.
14. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJC, Libório AB, et al. Metabolic acidosis in patients with severe sepsis and septic shock: A longitudinal quantitative study. Crit Care Med. 2009;37(10):2733–9.
15. Fall PJ, Szerlip HM. Lactic acidosis: From sour milk to septic shock. J Intensive Care Med. 2005;20(5):255–71.
16. Luft D, Deichsel G, Schmülling R, Stein W, Eggstein M. Definition of clinically relevant lactic acidosis in patients with internal diseases. Am J Clin Pathol. 1983;80(4):484–9.
17. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama

[Internet]. 2016;315(8):801–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26903338
18. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler J a, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004;32(8):1637–42.
19. Lee SM, Kim SE, Kim E Bin, Jeong HJ, Son YK, An WS. Lactate Clearance and Vasopressor Seem to Be Predictors for Mortality in Severe Sepsis Patients with Lactic Acidosis Supplementing Sodium Bicarbonate: A Retrospective Analysis. PLoS One. 2015;10(12):1–14.
20. Jones AE. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy<subtitle>A Randomized Clinical Trial</subtitle> Jama [Internet]. 2010;303(8):739. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2010.158
21. Dhatariya K, Savage M. The Management of Diabetic ketoacidosis in adults [Internet]. Joint British Diabetes Societies Inpatient care group. 2013. Available from: http://www.diabetes.org.uk/Documents/About Us/What we say/Management-of-DKA-241013.pdf
22. Lopes AD, Maciel AT, Park M. Evolutive physicochemical characterization of diabetic ketoacidosis in adult patients admitted to the intensive care unit. J Crit Care [Internet]. Elsevier Inc.; 2011;26(3):303–10. Available from: http://dx.doi.org/10.1016/j.jcrc.2010.08.013
23. Kamel KS, Halperin ML. Diabetic ketoacidosis: Evaluation and treatment. N Engl J Med. 2015;372:546–54.
24. Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis - a systematic review. Ann Intensive Care [Internet]. Springer Open Ltd; 2011 Jan [cited 2013 Sep 22];1(1):23. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3224469&tool=pmcentrez&rendertype=abstract
25. Chua HR, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care [Internet]. Elsevier Inc.; 2012;27(2):138–45.Available from: http://dx.doi.org/10.1016/j.jcrc.2012.01.007
26. Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med [Internet]. Elsevier Inc.; 2011;29(6):670–4. Available from: http://dx.doi.org/10.1016/j.ajem.2010.02.004
27. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid Saline Infusion Produces Hyperchloremic Acidosis in Patients Undergoing Gynecologic Surgery. Anesthesiology. 1999;90:1265–70.
28. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury. JAMA. 2012;308(15):1566–72.
29. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-lyte. Ann Surg. 2012;255(5):821–9.
30. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40(12):1897–905.
31. Wilkes NJ, Woolf R, Mutch M, Mallett S V, Peachey T, Stephens R, et al. The Effects of Balanced Versus Saline-Based Hetastarch and Crystalloid Solutions on Acid-Base and Electrolyte Status and Gastric Mucosal Perfusion in Elderly Surgical Patients. 2001;
32. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl [Internet]. 2012;2(1):1–138. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4089764&tool=pmcentrez&rende

rtype=abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4089619&tool=pmcentrez&rendertype=abstract%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.

33. Hoste E a. J, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med [Internet]. 2015;41(8):1411–23. Available from: http://link.springer.com/10.1007/s00134-015-3934-7

34. Nisula S, Kaukonen K-M, Vaara ST, Korhonen A-M, Poukkanen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med [Internet]. 2013 Mar [cited 2013 Apr 22];39(3):420–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23291734

35. Fujii T, Uchino S, Doi K, Sato T, Kawamura T; JAKID study group. Diagnosis, management, and prognosis of patients with acute kidney injury in Japanese intensive care units: The JAKID study. J Crit Care. 2018 Oct;47:185-191. doi: 10.1016/j.jcrc.2018.07.007.

36. Rocktaeschel J, Morimatsu H, Uchino S, Goldsmith D, Poustie S, Story D, et al. Acid- base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. Crit Care. 2003;7(4):R60.

37. Hewitt J, Uniacke M, Hansi NK, Venkat-Raman G, McCarthy K. Sodium bicarbonate supplements for treating acute kidney injury. Cochrane Database Syst Rev. 2012 Jun 13;(6):CD009204. doi: 10.1002/14651858.CD009204.pub2.

38. CAMPBELL, HOULE DB, CRISP NW, WEIL MH, BROWN EB. Depressed response to intravenous sympathicomimetic agents in humans during acidosis. Dis Chest [Internet]. 1958 Jan;33(1):18–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13501085

39. Cingolani HE, Faulkner SL, Mattiazzi AR, Bender HW, Graham TP. Depression of human myocardial contractility with “respiratory” and “metabolic” acidosis. Surgery [Internet]. 1975 Mar;77(3):427–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1124498

40. Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol [Internet]. 1988 Jan;254(1 Pt 2):H20-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2827525

41. Orchard CH, Hamilton DL, Astles P, McCall E, Jewell BR. The effect of acidosis on the relationship between Ca2+ and force in isolated ferret cardiac muscle. J Physiol. 1991;436(1):559–78.

42. Wildenthal K, Mierzwiak DS, Myers RW, Mitchell JH. Effects of acute lactic acidosis on left ventricular performance. Am J Physiol. 1968;214(6):1352–9.

43. Graf H, Leach W, Arieff AI. Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs. Am J Physiol Physiol [Internet]. 1985;249(5):F630–5. Available from: http://www.physiology.org/doi/10.1152/ajprenal.1985.249.5.F630

44. Zhou HZ, Malhotra D, Shapiro JI. Contractile dysfunction during metabolic acidosis: role of impaired energy metabolism. Am J Physiol [Internet]. 1991;261(5 Pt 2):H1481-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1951735

45. Poole-Wilson PA. Is Early Decline of Cardiac Function in Ischæmia Due To Carbon-Dioxide Retention? Lancet. 1975;306(7948):1285–7.

46. Miller RG, Boska MD, Moussavi RS, Carson PJ, Weiner MW. 31P nuclear magnetic resonance studies of high energy phosphates and pH in human muscle fatigue. Comparison of aerobic and anaerobic exercise. J Clin Invest. 1988;81(4):1190–6.

47. Henriksen OM, Prahl JB, Roder ME, Svendsen OL. Treatment of diabetic ketoacidosis in adults in Denmark: a national survey. Diabetes Res Clin Pract 2007;77:113–9.

48. Kraut J a., Kurtz I. Use of base in the treatment of acute severe organic acidosis by nephrologists and critical care physicians: Results of an online survey. Clin Exp Nephrol 2006;10:111–7. doi:10.1007/s10157-006-0408-9.

49. Cooper D, Walley K. Bicarbonate Does Not Improve Hemodynamics in Critically Ill Patients Who Have Lactic Acidosis. Ann Intern … [Internet]. 1990;112(7):492–8. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/2156475%5Cnhttp://annals.org/article.aspx?articleid=703775
50. Mathieu D, Neviere R, Billard V, Fleyfel M, Wattel F. Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study. Vol. 19, Critical Care Medicine. 1991. p. 1352–6.
51. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science. 1985;227:754–6.
52. Arieff AI, Leach W, Park R, Lazarowitz VC. Systemic effects of NaHCO3 in experimental lactic acidosis in dogs. Am J Physiol. 1982;242(6):F586-91.
53. Fujii T, Udy A, Licari E, Romero L, Bellomo R. Sodium bicarbonate therapy for critically ill patients with metabolic acidosis: a scoping and a systematic review. [Personal communication]
54. Hoste EA, Colpaert K, Vanholder RC, Lameire NH, De Waele JJ, Blot SI, Colardyn FA. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. J Nephrol. 2005;18(3):303-7.
55. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandière M, Asehnoune K, Dellamonica J, Velly L, Abback PS, de Jong A, Brunot V, Belafia F, Roquilly A, Chanques G, Muller L, Constantin JM, Bertet H, Klouche K, Molinari N, Jung B; BICAR-ICU Study Group. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 2018;392(10141):31-40. doi: 10.1016/S0140-6736(18)31080- 8.
56. Serpa Neto A, Fujii T, El-Khawas K, Udy A, Bellomo R. Sodium Bicarbonate Therapy for Metabolic Acidosis in Critically Ill Patients: A survey of Australian and New Zealand Intensive Care Clinicians. Crit Care Resusc 2020;[in press]
57. Jude B, Naorungroj T, Neto AS, Fujii T, Udy A, Bellomo R. Sodium bicarbonate in 5% dextrose: can clinicians tell the difference?. Crit Care Resusc. 2020 Mar;22(1):80-82.
58. Naorungroj T, Neto AS, Fujii T, Jude B, Udy A, Bellomo R. Stability of bicarbonate in normal saline: a technical report. Crit Care Resusc. 2020 Mar;22(1):83-85.
59. Fujii T, Luethi N, Young PJ, 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; 323:423-431.