Sodium bicarbonate therapy for metabolic acidosis in critically ill patients: a survey of Australian and New Zealand intensive care clinicians

Ary Serpa Neto, Tomoko Fujii, Khaled El-Khawas, Andrew Udy and Rinaldo Bellomo

ABSTRACT

Objective: To help shape the design of a future double blind placebo-controlled randomised clinical trial of bicarbonate therapy for metabolic acidosis, based on opinions of intensive care clinicians in Australia and New Zealand.

Design: An online survey was designed, piloted and distributed electronically to members of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) mailing list. The survey sought to collect information about choice of placebo, method of bicarbonate administration, and acid-base monitoring.

Main outcome measures: Responses to six questions in the following domains were sought: 1) solution to be used as placebo; 2) method of administration; 3) target of the intervention; 4) timing of arterial blood gases to monitor the intervention; 5) duration of therapy; and 6) rate of bolus therapy (if selected as the best option).

Results: One in every eight ANZICS CTG members completed the survey (118/880, 13.4%). Compound sodium lactate was the preferred solution for placebo (54/118, 45.8%), and continuous infusion of bicarbonate (80/118, 67.8%) was the most frequently selected method of administration. A pH > 7.30 was the preferred target (50/118, 42.4%), while monitoring with arterial blood gas analysis every 2 hours until the target is reached and then every 4 hours was the most favoured option (40/118, 33.9%). The preferred duration of therapy was until the target is achieved (53/118, 44.9%).

Conclusions: This survey offers important insights into the preferences of Australian and New Zealand clinicians in regards to any future randomised controlled trial of bicarbonate therapy for metabolic acidosis in the critically ill.

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Metabolic acidosis is common in critically ill patients and is associated with worse outcomes.[1-4] Administration of "buffer" solutions is relatively common in patients with significant metabolic acidosis, under the assumption that it might restore normal cardiovascular function and oxygen delivery to tissues by raising extracellular pH.[5,6] Sodium bicarbonate is the most commonly used agent,[5,6] and its administration raises extracellular strong ion difference (SID) mainly through the delivery of sodium ions; however, it is unclear whether this leads to improvements in patient-centred outcomes. The 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 or other clinical outcomes.[7,8]

A recent systematic review examining the use of bicarbonate therapy for metabolic acidosis in the intensive care unit (ICU)[9] identified two published randomised controlled trials concerning this topic.[10,11] The first study compared the biochemical changes of a single dose of sodium bicarbonate and trometamol; tris-hydroxymethyl aminomethane (THAM) for mild metabolic acidosis.[10] The second study examined the effect of repeated sodium bicarbonate infusion to maintain the arterial pH above 7.30 in moderate to severe metabolic acidosis.[11] In both trials, bicarbonate administration normalised arterial pH, serum bicarbonate, base excess (BE) and sodium, and decreased potassium values. Furthermore, in one of the studies the use of bicarbonate therapy was associated with decreased need of renal replacement therapy.[11]

The available evidence in the field is scarce and mainly derived from small and underpowered studies. In addition, the findings from the largest study to date should be interpreted with caution,[11] since it was a non-blinded study and the use of bicarbonate was not standardised. Altogether, these findings suggest the need for a well powered randomised clinical trial to assess the impact of

bicarbonate therapy on patients with metabolic acidosis. However, it is currently unclear whether the method of administration, the targets, and the duration of bicarbonate therapy used in previous studies are valid in Australia and New Zealand. Thus, more information is required so as to design a clinically acceptable trial in this field.

The aim of this study was to collect information to help shape the design of a future double blind placebo-controlled randomised clinical trial based on opinions and practice of intensive care clinicians in Australia and New Zealand.

Methods

Study design

A prospective web-based survey of Australian and New Zealand intensive care clinicians was conducted in March 2020.

Survey instrument

A structured, closed-question survey was developed by the study investigators, and then piloted by senior consultant staff at two tertiary-level, metropolitan ICUs in Melbourne, Australia, to check the clarity of the questionnaire. The survey questions (Table 1) were then entered into the Research Electronic Data Capture (REDCap) tool hosted at Monash University (the full survey is available in the Online Appendix).[12,13]

Participant population

The survey was distributed via email using the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) mailing list. At the time of the survey, the list included 880 members. The survey remained open for 15 days.

Ethical considerations

Ethics approval was obtained from the Human Research and Ethics Committee of the Alfred Hospital (248/20). Participation in the survey was strictly voluntary and all responses were anonymous.

Definition of consensus

The definition of consensus was established a priori to avoid biasing the results towards the beliefs of the research team. In all questions, the response that was selected most frequently was deemed the preferred option.

Statistical analysis

There are no recommendations on the panel size for this type of study — studies have been conducted with virtually any panel size. The sample size has been researcher- and situation-specific, and more often than not, convenience samples have been chosen dependent on availability of experts and resources. All members of the ANZICS CTG mailing list were invited and the final sample size includes all those who responded.

All statistics employed are completely descriptive and summarise the answers for each one of the questions as counts and percentages. All reports and graphs were done in R v.3.6.3 (R Core Team, Vienna, Austria).

Results

Between 19 March and 2 April 2020, 118 surveys responses were received from 880 sent, representing a response rate of 13.4%. All answers were complete and were included in analysis.

Control arm

Compound sodium lactate was the preferred solution for placebo in the control arm (54/118, 45.8%), followed by 5% dextrose (36/118, 30.5%), and then by normal saline (28/118, 23.7%) (Figure 1, A).

Bicarbonate administration

The preferred method of administration was as a continuous infusion (80/118, 67.8%) (Figure 1, B).

Target

A pH > 7.30 was the preferred target for therapy (50/118, 42.4%), followed by a combination of pH > 7.30 and BE > 0 mEq/L (36/118, 30.5%) and by BE > 0 mEq/L only (14/118, 11.9%) (Figure 1, C). The options of normal pH and normal pH combined with BE > 0 mEq/L were selected by less than 10% of respondents respectively.

Monitoring

Monitoring with arterial blood gas analysis every 2 hours until the target is reached and then every 4 hours was the most commonly selected option (40/118, 33.9%), followed by every 2 hours for the first 6 hours and then every 4 hours (33/118, 28.0%), and by 1 hour after the first dose has started, then every 2 hours until the target is reached and then every 4 hours (29/118, 24.6%) (Figure 1, D).

Duration

The preferred duration of therapy for the majority of the responders was until the target is achieved (53/118, 44.9%), followed by 24 hours (21/118, 17.8%) and by 48 hours (13/118, 11.0%) (Figure 1, E). All other options received less than 10% of positive answers.

Bolus specific

In this domain specific to bolus therapy, the preferred rate of infusion was over 2 hours (46/1185, 39.0%) and over 4

Table 1. Summary of survey questions

Domains	Questions	Answers
Control arm	Which solution do you think is best as placebo?	a. 5% dextrose (D5W) b. Normal saline (N/S) c. Compound sodium lactate (CSL)
Administration	How do you think sodium bicarbonate should be delivered?	a. As repeated boluses (eg, every 60 min until target is achieved) b. As a continuous infusion (at a rate of 50 mmol/h)
Target	What should be the target for the intervention?	a. Normal pH (7.35–7.45) b. pH > 7.30 c. BE > 0 mEq/L d. Combination of normal pH (7.35–7.45) and BE > 0 mEq/L e. Combination of pH > 7.30 and BE > 0 mEq/L
Monitoring	How often should arterial blood gases be taken during the intervention period?	a. Every 2 hours for the first 6 hours and then every 4 hours b. Every 2 hours until target is reached and then every 4 hours c. One hour after the first dose has started, then every 2 hours for the first 6 hours and then every 4 hours d. One hour after the first dose has started, then every 2 hours until the target is reached and then every 4 hours
Duration	How long should the intervention be applied?	a. 6 hours b. 8 hours c. 12 hours d. 24 hours e. 48 hours f. 72 hours g. Ceased when the target is achieved h. Until ICU discharge
Bolus specific	In considering bolus dosing of bicarbonate, this is estimated at 1 mmol/kg × 0.4 for each 1 mEq/L increase in BE. Thus, for example, in a person weighing 80 kg, with a base deficit of 6 mEq/L and a BE target of 0 mEq/L, this would approximate an initial dose of 80 × 0.4 × 6 = 192 mmol of bicarbonate. How fast would you prefer to give such a dose?	a. Over 1 hour b. Over 2 hours c. Over 3 hours d. Over 4 hours

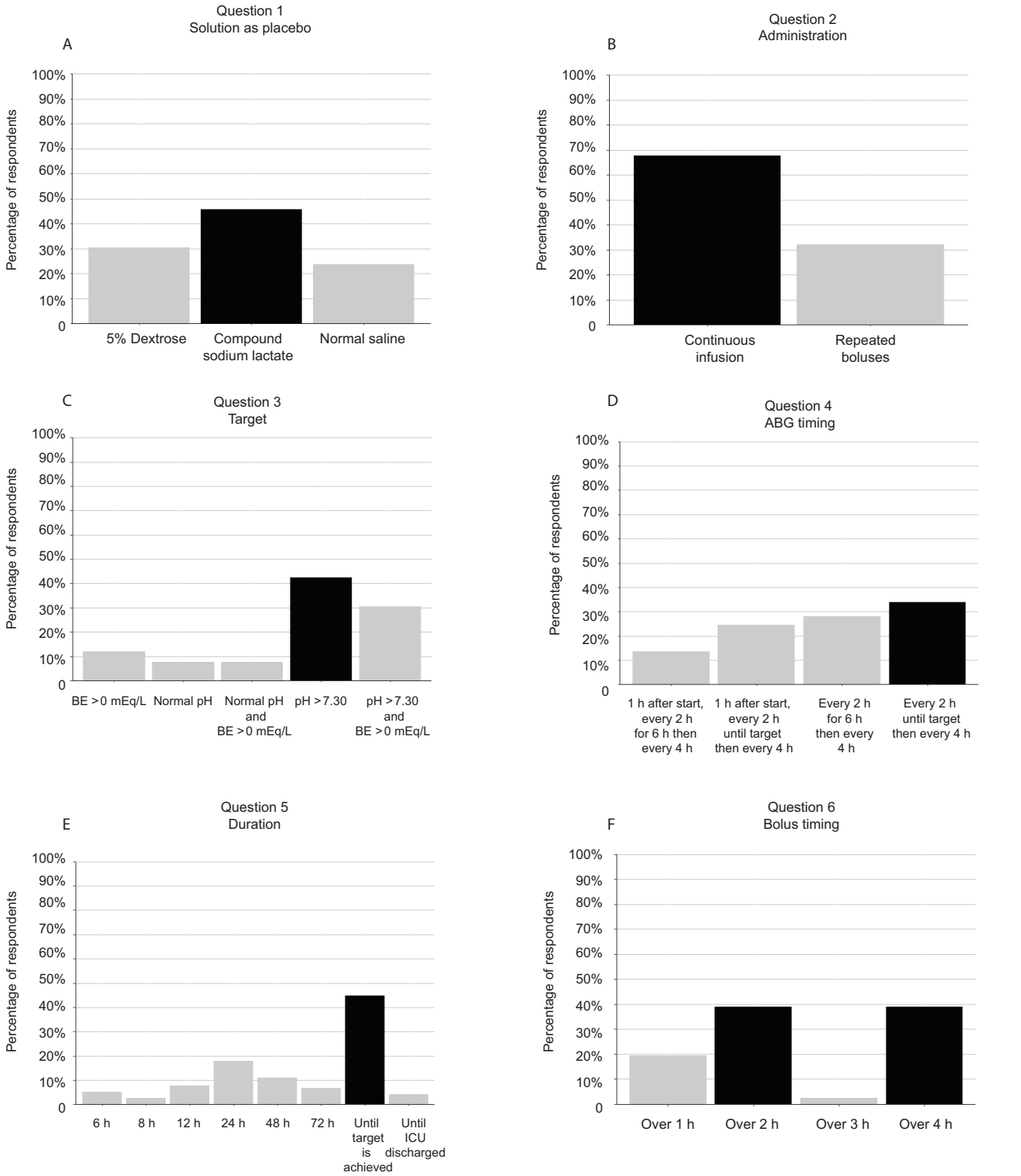
BE = base excess; ICU = intensive care unit.

hours (46/118, 39.0%) and then by over 1 hour (23/118, 19.5%) (Figure 1, F).

Discussion

In this survey of 118 ICU clinicians from Australia and New Zealand, it was found that compound sodium lactate was the preferred solution for the placebo arm of any future trial, and that a continuous infusion of bicarbonate therapy was the most favoured option for the administration of the intervention. The most common target was a pH > 7.30 monitored with arterial blood gas analysis every 2 hours until reached, and then every 4 hours for the first 24 hours. Also, the intervention should be used until the target is achieved, as selected by the majority of responders.

Figure 1. Frequency of the answers in each domain



ABG = arterial blood gas; BE = base excess; ICU = intensive care unit.

To date, no placebo-controlled, double blind randomised clinical trial has been conducted in this field.[10,11] However, recent evidence from our group suggests that such a design is feasible. In a study with 60 health care professionals, we showed that, when 100 mL of 8.4% sodium bicarbonate was diluted in 150 mL of 5% dextrose within a 250 mL polyolefin bag, clinicians were unable to correctly identify the contents of the bags.[14] In a second technical study, we also found that when 100 mL of 8.4% sodium bicarbonate was diluted in 150 mL of normal saline within a 250 mL polyolefin bag, changes in pH and arterial partial pressure of carbon dioxide ($Paco_2$) over a 24–48 hour period were small and bicarbonate concentration remained stable over this period.[15] These findings imply that sodium bicarbonate therapy can be successfully blinded and it is stable for at least 24 hours.

Opposite to previous trials, clinicians from Australian and New Zealand ICUs preferred a continuous infusion of bicarbonate for the treatment arm. Previously, sodium bicarbonate and THAM were administered as a bolus infusion over 30 minutes to 1 hour. Indeed, prescription of bicarbonate therapy is heterogeneous among ICUs around the world.[16] Only one recent study in the literature reported the use of bicarbonate therapy as a continuous infusion, with a rate of 0.1–0.2 mmol/kg predicted body weight per hour in patients with septic shock and elevated blood lactate levels.[17] In this prospective non-randomised study, the use of continuous infusion of bicarbonate therapy resulted in shorter time to weaning of mechanical ventilation and a shorter ICU length of stay. Despite potentially more cumbersome for the health professional, a continuous infusion of bicarbonate has the potential to decrease the risk of adverse effects associated with this therapy, such as transient drops in blood pressure and cardiac output, a decrease in ionised calcium, arrhythmia, and volume overload.

A target pH > 7.30 was the most frequent option selected by ICU clinicians. This target is in line with the previous largest randomised trial in this area.[11] However, other studies reported different targets, such as normalising acidaemia,[10] keeping a pH between 7.35 and 7.45,[17] and achieving a pH > 7.20.[16,18] Trying to normalise the pH in this scenario is problematic for several reasons, including the amount of bicarbonate that must be used, potentially increasing the risk of hypernatraemia and other adverse effects. Specifically to bolus therapy, we found a bimodal distribution in the answers, with 39% of the responders supporting an infusion over 2 hours or over 4 hours. However, there is no current evidence to support or justify neither of these infusion rates.

Our study has both limitations and strengths. The low response rate does limit the generalisability of our results to the wider Australian and New Zealand ICU community. Nevertheless, the present survey provided an opportunity for all ANZICS CTG members to participate regardless of location, unit size, experience or background. The accuracy of the responses to the survey could not be independently verified; however, there was no reason for clinicians not to report their preferences as accurately as possible, and an approach based on self-report was also used by other surveys.[10,19] More than one member from the same ICU may have completed the survey, possibly creating clusters of answers increasing the risk of over-representation of any one unit in the final data. Also, no information about the participants, such as years of experience, was collected. Thus, we cannot exclude that the practice reported could be different according to characteristics of the respondents such as the level of experience. Finally, among all 880 emails in the list, some are probably no longer available.

Conclusions

This survey offers an important insight into bicarbonate therapy preferences in critically ill patients with metabolic acidosis in Australian and New Zealand ICUs. In addition, it helps shape the design of a future double blind placebo-controlled randomised clinical trial. According to the results of the present survey, any future trial should consider compound sodium lactate solution as the placebo in the control arm, and the intervention with bicarbonate therapy should be given as a continuous infusion, targeting a pH > 7.30, monitored with arterial blood gas analysis every 2 hours until the target is reached, and stopped once this is achieved.

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Competing interests

None declared.

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