Effects of sodium bicarbonate infusion on mortality in medical–surgical ICU patients with metabolic acidosis—A single-center propensity score matched analysis

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\textbf{KEYWORDS}
Sodium bicarbonate; Metabolic acidosis; Mortality; Critical illness; ICU

\textbf{Abstract}

\textbf{Objective:} Metabolic acidosis is associated with high mortality. Despite theoretical benefits of sodium-bicarbonate (SB), current evidence remains controversial. We investigated SB-related effects on outcomes in ICU patients with metabolic acidosis.

\textbf{Design:} Retrospective analysis.

\textbf{Setting:} Academic medical center.

\textbf{Patients or participants:} 971 ICU patients with metabolic acidosis defined as arterial pH < 7.3 and CO\textsubscript{2} < 45 mmHg treated between 2012 and 2016. A propensity score (PS) was estimated using logistic regression. Patients were matched in pairs using the PS.

\textbf{Interventions:} 441 patients were treated with SB 8.4% (SB-group) and n = 530 patients were not (control group).

\textbf{Main variables of interest:} Primary outcome was all-cause mortality at ICU-discharge. Average Treatment Effect (ATE), Average Treatment effect in Treated (ATT), and estimated relative survival effects at 20 days were computed.

\textbf{Results:} In the full cohort, we observed considerable differences in pH, base excess, additional acidosis-related indices, and ICU mortality (controls 31% vs. SB-group 56%, p < .001) at baseline between the two groups. After PS-matching (n = 174 in each group), no significant difference in ICU mortality was observed (controls 32% vs. SB-group 41%; p = .07). Odds ratios (OR) for ATE and ATT showed no association with ICU mortality (OR ATE: 1.08, 95%-CI 0.99–1.17; p = .08; OR ATT 1.09; 95%-CI 0.99–1.2; p = .09). Hazard ratios at 20-days (multivariable HR, matched sample n = 348: 1.16, 95%-CI 0.86–1.56, p = .33) showed similar survival in the two study groups.

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Introduction

Metabolic acidosis (arterial pH < 7.3) is observed in about 8% of intensive care unit (ICU) admissions\(^1\) and is associated with particularly high mortality (up to 57%).\(^1,2\) The etiology of severe metabolic acidosis typically includes tissue hypoxemia, shock, diabetic ketoacidosis, hepatic and renal failure, and intoxications.\(^2\) Metabolic acidosis has numerous deleterious consequences on various physiological systems, including enzyme-/protein functionality, tissue metabolism, and increased production of nitric oxide leading to vasodilatation,\(^3\) which may further amplify organ dysfunction. Furthermore, acidosis is associated with reduced adrenoceptor function on cellular surfaces,\(^3\) depression of myocardial function including contractility and relaxation,\(^3,4\) cardiac arrhythmia,\(^3\) and a shift of the oxyhemoglobin dissociation curve.\(^3\)

Previous data show that low serum bicarbonate levels predict mortality at ICU admission in e.g. cardiogenic shock patients.\(^5,6\) Intravenous sodium bicarbonate can be applied to rapidly correct metabolic acidosis and reports indicate that about two thirds of North American critical care specialists prescribe sodium bicarbonate for this purpose.\(^7\) However, it remains uncertain whether metabolic acidosis should be corrected using sodium bicarbonate (or other buffers).\(^8,9\) Importantly, there are concerns that sodium bicarbonate therapy could lead to sodium and/or fluid overload, increased lactate and/or carbon dioxide production, and/or decreased ionized serum calcium.\(^10\) Thus, sodium bicarbonate might theoretically worsen the outcome of affected patients.\(^11\)

Current evidence on whether sodium bicarbonate impacts on mortality in the critically ill is controversially discussed, with sparse data from mostly retrospective studies\(^12-14\) available.

Conclusions: We did not observe effects of SB infusion on all-cause mortality in critically ill patients with metabolic acidosis.

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PALABRAS CLAVE
Bicarbonato de sodio; Acidosis metabólica; Mortalidad; Enfermedad crítica; UCI

Efectos de la infusión de bicarbonato de sodio sobre la mortalidad en pacientes de UCI médico-quirúrgica con acidosis metabólica: un análisis de puntuación de propensión en un solo Centro

Resumen
Objetivo: La acidosis metabólica se asocia con una alta mortalidad. A pesar de los beneficios teóricos del bicarbonato de sodio (BS), la evidencia actual sigue siendo controvertida. Investigamos los efectos relacionados con el BS sobre los resultados en pacientes de la UCI con acidosis metabólica.

Diseño: Análisis retrospectivo.

Ámbito: Centro médico académico.

Pacientes o participantes: Se incluyeron 971 pacientes de la Unidad de Cuidados Intensivos (UCI) con acidosis metabólica (pH < 7,3, CO2 < 45 mmHg) tratados entre 2012 y 2016. Se calculó una puntuación de propensión (PS) mediante regresión logística. Los pacientes se emparejaron utilizando el PS.

Variables de interés principales: Intervenciones; 441 pacientes fueron tratados con BS 8,4% (grupo BS) y n = 530 pacientes no (grupo control).

Resultados: El resultado primario fue la mortalidad por todas las causas al alta de la UCI. Se calcularon el efecto promedio del tratamiento (ATE), el efecto promedio del tratamiento en los tratados (ATT) y los efectos de supervivencia relativa estimados a los 20 días. En la cohorte completa se observaron diferencias considerables en el pH, el exceso de bases y la mortalidad en la UCI (control 31% vs. grupo BS 56%, p < 0,001) al inicio del estudio entre los grupos. Después del emparejamiento de PS (n = 174 en cada grupo), no se observaron diferencias significativas en la mortalidad en la UCI (control 32% vs. grupo BS 41%; p = 0,07). Los odds ratios (OR) para ATE y ATT no mostraron asociación con la mortalidad en la UCI (OR ATE: 1,08, IC 95%; 0,99-1,17; p = 0,08; OR ATT 1,09; IC 95%; 0,99-1,2; p = 0,09). Los coeficientes de riesgo a los 20 días (HR multivariable, muestra emparejada n = 348: 1,16, IC 95%; 0,86-1,56, p = 0,33) mostraron una supervivencia comparable.

Conclusiones: No observamos efectos de la infusión de BS sobre la mortalidad por todas las causas en pacientes con acidosis metabólica.

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As most of the available studies are performed in aci- 
dotic patients with sepsis\textsuperscript{15,15} or hyperlactatemia,\textsuperscript{12,16} we 
thus embarked to perform a retrospective analysis with the 
primary objective to investigate whether infusion of sodium-
bicarbonate impacts on all-cause mortality in critically ill 
patients with all-cause metabolic acidosis including but not 
limited to septic and lactic acidosis.

Patients and methods

Patients

A monocentric propensity-score matched analysis of elec- 
tronic patient charts was performed. Patients were treated 
at the Department of Intensive Care Medicine, University 
of Bern, Switzerland, between January 2012 and December 
2016. Patients were excluded when any of the following 
criteria was met I) refusal to provide general consent for use of 
electronic health care data for patients treated after Janu- 
ary 1st 2015 (standardized general consent [GC] procedure 
established in the Department of Intensive Care Medicine), 
and II) patients with incomplete basic datasets in regard 
to age, gender, Acute Physiology and Chronic Health Eval- 
uation (APACHE) II-score at ICU-admission, discharge data 
and/or ICU mortality data. Routinely recorded data from 
electronic patient charts was assessed (Centricity Critical 
Care; General Electriccs, Helsinki, Finland).

The study was approved by the local Ethics Committee 
on Human Research (Kantonale Ethikkomission, KEK, Bern, 
Nr. 2018-01829), who waived the need for individual written 
infomation consent due to the GC procedure described above. 
Patients were grouped for treatment with sodium bicarbo- 
ate 8.4% during the ICU stay vs. without sodium-bicarbonate 
to sodium bicarbonate (SB) and control groups (noSB). We 
chose the sodium bicarbonate 8.4% concentration as this is 
the formulation of choice in our ICU to treat severe acidemia 
if necessary. For the preliminary data selection, we used the 
available basic dataset age, gender, and APACHE II scores at 
ICU admission) to pair control patients to sodium bicarbon- 
ate treated patients in a 3:1 ratio to gain a meaningful subset 
of ICU patients with comparable baseline disease severity.

Primary and secondary outcomes

Primary outcome was all-cause mortality (crude and 
adjusted) at ICU-discharge and all-cause mortality at hos- 
pital discharge in patients with (non-respiratory) metabolic 
acidos (defined as pH $\leq$ 7.3, pCO$_2$ $< 45$ mmHg) treated with 
versus without sodium bicarbonate infusion. Secondary 
objectives were excess mortality (mortality beyond ICU mor-
tality) at 30 days, at one year following ICU discharge and 
excess mortality after more than one year until the last-
possible follow-up (hospital discharge until September 2019) 
to better differentiate a short term effect from a hypothet- 
ical long term effect.

Variables collected/study data

Data was derived from electronic patient charts. Source data 
were double checked by two individual ICU physicians (JW 
and BH) before extraction. Inconsistencies were discussed and 
a consensus was sought between the two examiners. The 
following routinely collected data were available: patient 
age, diagnostic and comorbidity groups (APACHE IV diag-
nostic groups), body mass index (BMI), APACHE II scores, 
time of ICU admission/discharge, time of hospital admis-
sion/discharge, cumulative dose of sodium-bicarbonate 
received, laboratory data at admission including arterial pH, 
arterial carbon dioxide (paCO$_2$), base excess (BE), bicar- 
bonate (HCO$_3^-$), lactate, sodium, potassium, hemoglobin 
(Hb), creatinine, time on and cumulative dose of vasopres-
sors/inotropes (noradrenaline, adrenaline, dobutamine), 
total volume of packed red blood cells (RBC) and fresh frozen 
plasma (FFP), need for renal replacement therapy (RRT), 
time on mechanical ventilation (in- to extubation), length of 
stay (LOS) in ICU/hospital, vital status at ICU- and hospital 
discharge (alive/dead), time of death.

Statistical analysis

We explored the marginal univariate distributions of the 
treatment variables in the ‘‘crude’’ data set (Suppl. Fig. 1). 
Due to asymmetry in the continuous variables we report the 
p-values of Kolmogorov-Smirnov test for continuous vari- 
ables and chi-squared test for categorical variables (for the 
null hypothesis of equal frequencies between two groups). 
The p-values are to be interpreted as measure of dissimilarity 
(p-values close to 0 correspond to high dissimilarity).

A propensity score (PS) $\hat{e}(x)$ was estimated using logistic 
regression in which the SB treatment status was regressed on 
$pH$, paCO$_2$ and HCO$_3^-$. Pairs of treated and untreated 
patients were matched on the propensity score using a 
caliper of width 0.3 of the standard deviation of the logit of 
the propensity score (using the R package ‘‘Matching’’ 
by Diamond and Sekhon, 2013). We considered mortality 
at ICU discharge as well as death outcomes at hospital dis-
charge, after 30 days, at one year and death after more than 
one year (after hospital discharge until maximum follow-
up (the latter without ICU-mortality). Mortality occurrences 
were regressed on the set of covariates with logit logistic 
regression. The covariates for the full weighted sample were 
SB treatment status, propensity score, sex, age, BMI and 
APACHE II scores. In the matched sample, given that treated 
patients and controls were paired with respect to propensi-
sity scores (as well as pH, paCO$_2$ and HCO$_3^-$ ), the covariates 
set was restricted to SB treatment status, sex, age, BMI and 
APACHE II.

The Average Treatment effect in Treated (ATT) is the 
expected effect of the treatment for individuals in the treat- 
ment group,\textsuperscript{17} while the average treatment effect (ATE) is 
the expected effect of the treatment across all individu- 
als in the population. Randomized Clinical Trials (RCTs) are 
usually organized in such way that ATE equals ATT (unless 
explicitly specified exceptions). Difference between ATE 
and ATT would indicate that the treatment assignment was 
not random or not random enough in the study consider-
ing covariates of interest. We computed the ATE Odds Ratio 
(OR) and ATT OR\textsuperscript{18} with standard errors by Abadie and Imbens 
(2006) on a matched sample\textsuperscript{18}; as well as the ATE OR on the 
full sample with inverse weighting by ATE weights\textsuperscript{18} given 
by $1/(\hat{e}(x))$ for the treated subjects and by $1/(1 - \hat{e}(x))$ for
untreated; finally we provide an ATT OR on a full sample with inverse weighting by ATT weights given by 1 for the treated subjects and by \( \hat{e}(x)/(1 - \hat{e}(x)) \) for untreated.

We estimated survival curves and relative effects using Cox regression models by regressing survival on SB treatment status, sex, age, BMI and APACHE II. Both analyses were done for the maximum follow-up as well as for a 20 days follow-up as for the majority of patients (97.5%) the ICU stay was below 20 days. In the "crude" unmatched dataset, we added the propensity score to the covariates set. We used a robust variance estimator to account for the clustering within the matched set and weighting in the "crude" samples.

Results

A total of 18,754 admissions of ICU patients were screened in the study interval. After removal of duplicates and patients with incomplete data sets, 16,966 data sets remained. Of these, 749 patients received sodium bicarbonate (SB group) during ICU stay. We performed a 1:3 pairing of patients with regard to age, gender and APACHE II score at ICU admission to narrow further data search on patients with comparable disease severity. For respective \( n = 2165 \) patients, further data collection was performed. While exploring the data, we removed \( n = 69 \) very extreme outliers with aberrant values (eventually data entry mistakes) in ICU length of stay and very high vasopressor support in addition to patients without acidosis (pH > 7.3, \( n = 1125 \)). 441 (SB) and 530 (noSB) patients remained in the final "crude" dataset. A Consort flow chart is given (Fig. 1).

Patient characteristics of this "crude" data set are given in Table 1. Median dose of sodium bicarbonate 8.4% given in the SB group was 100 ml (interquartile range [IQR] 100–242 ml). Patients received SB after a median time of 5.14 h following ICU admission (IQR 14.64 h). The SB group had lower APACHE II scores than the noSB group (median 30; IQR 11 vs. 32; IQR 19; \( p < 0.001 \)). Further, statistically significant differences were observed between groups regarding pH (SB median 7.17; IQR 0.15 vs. noSB 7.23; IQR0.09; \( p < 0.01 \)), arterial HCO\(_3^−\) (SB median 12.4 mmol/l; IQR 8.11 vs. noSB 17.7 mmol/l; IQR 5.28; \( p < 0.001 \)) and additional acidosis-related indices (Table 1). Patients in the SB group differed significantly from nonSB patients in regard to admission diagnosis such as sepsis, metabolic disorders, intoxications, need for vasoactives and blood products, and need for RRT (all \( p < 0.05 \)). ICU mortality was higher in the sodium-bicarbonate group (SB 46% vs noSB 31%; \( p < 0.001 \)) (Table 1). Median time to death in non-survivors was 7.66 days (IQR 279.3 days) in the noSB-Group vs. 3.32 days in the SB-group (IQR 37.53 days) (\( p < 0.001 \)).

The ORs for the ATT with regard to (all-cause) ICU mortality and (all-cause) in-hospital excess mortality (mortality beyond ICU mortality) in the "crude" dataset adjusted for SB treatment status, sex, age, BMI and APACHE scores were 1.56 (95% confidence interval [CI] 1.17–2.07; \( p = 0.002 \)) resp. 0.67 (95%CI 0.43–1.03; \( p = 0.07 \)). The ATT OR for excess mortality at 30 days, between day 31 and 364 and over one year are 0.52 (95%CI 0.32–0.84; \( p = 0.007 \)), 1.31 (95%CI 0.74–2.31; \( p = 0.357 \)) and 0.72 (95%CI 0.47–1.09; \( p = 0.121 \)) respectively (Supplement Table 1).

Propensity score analysis

We constructed the PS model that fitted to 971 observations and explained 34% of variability in treatment prescription. While dropping 615 observations (described in Suppl. Table 2), we achieved a sound matching between the treatment and control groups (Suppl. Fig. 2.).

Using propensity scores, we obtained a dataset with 348 patients equally split between the control and sodium bicarbonate groups. Patient characteristics are given (Fig. 1, Table 2). Median cumulative dose of sodium bicarbonate was 100 ml (IQR 100, 200) applied after a median of 8.77 h following ICU admission (IQR 2.56, 23.51). ICU-mortality, in-hospital excess mortality and excess mortality after hospital discharge as well as median time-to-death did not differ significantly (\( p \) for all > 0.05) (Table 2). Median hospital LOS was longer in the SB group than in the noSB group (9 days; IQR 17.2 days vs. 6 days; IQR16 days; \( p = 0.01 \)).

In the matched data set, we observed no association of sodium bicarbonate with ICU-mortality or death outcomes neither in the ATE OR nor in the ATT OR (Table 3).

As for the majority of patients (97.5%), ICU length of stay was below 20 days, we estimated crude Kaplan–Meier survival curves up to 20 days (i.e. if death did not occur after 20 days from admission, we reported it as no death event during 20 days). The Kaplan–Meier estimate of the "crude" data showed that the patients who received the sodium bicarbonate treatment had considerably lower survival probability (log-rank test: \( p = 0.005 \); Fig. 2), while using the matched data, there was no significant difference (stratified log-rank test \( p = 0.53 \)). Applying the ATE and ATT weights in the "crude" sample (n = 971) did not result in a difference in probability of survival (stratified log-rank test \( p = 0.91 \) and .98, respectively) (Fig. 2). Estimating Kaplan–Meier survival curves for the whole follow-up time showed no different results (Suppl. Fig. 3).

Cox regression modeling did not reveal a significant difference in survival at 20 days (Hazard ratio [HR] (multivariable, matched sample, \( n = 348 \): 1.16; 95%CI 0.86–1.56; \( p = 0.33 \)) (Table 4).

Discussion

In this monocentric propensity score matched analysis, we observed no influence of sodium bicarbonate infusion on ICU-mortality in critically ill patients with metabolic acidosis.

In critically ill patients, it appears that sodium bicarbonate infusion is mostly prescribed as symptomatic measure aiming to influence effects of severe metabolic acidosis (e.g. on the cardiovascular system) until a more causal therapy (e.g. improvement of tissue oxygenation, source control strategies, and/or antibiotics) becomes effective. Currently, there is uncertainty whether SB infusion would impact on patient survival beneficially or whether it would e.g. induce sodium and/or fluid overload, increase \( \text{PaCO}_2 \) production, and would potentially be detrimental. Previous studies supported this assumption and showed that SB administration in metabolic acidosis may actually increase mortality. In contrast, the BICAR-ICU-trial and a retrospective study of Zhang et al. showed no impact on mortality when sodium bicarbonate was administered to
Figure 1   Flowchart of patient selection.
In addition, and in accordance with previous data, our study did not observe mortality benefits in patients with sodium bicarbonate infusion. However, although speculative, e.g. negative SB-induced effects could theoretically be counterweighted by beneficial effects such as improved cardiac contractility and/or vascular responsiveness to catecholamine therapy, without effects on the mortality

Table 1 Patient demographics, ICU treatment, and follow-up data of "crude" patient population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n(all) = 971</th>
<th>n(noSB) = 530</th>
<th>n(SB) = 441</th>
<th>n avail. obs.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>318 (33%)</td>
<td>164 (31%)</td>
<td>154 (35%)</td>
<td>971</td>
<td>.21</td>
</tr>
<tr>
<td>Male</td>
<td>633</td>
<td>366</td>
<td>527</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.12 ± 6</td>
<td>26.12 ± 5.95</td>
<td>26.23 ± 6.26</td>
<td>971</td>
<td>.77</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 17</td>
<td>67 ± 17</td>
<td>66 ± 18</td>
<td>971</td>
<td>.12</td>
</tr>
<tr>
<td>APACHE II</td>
<td>31 ± 10.5</td>
<td>32 ± 19</td>
<td>30 ± 11</td>
<td>971</td>
<td>.18</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>342 (35%)</td>
<td>191 (36%)</td>
<td>151 (34%)</td>
<td>971</td>
<td>.61</td>
</tr>
<tr>
<td>Respiratory</td>
<td>176 (18%)</td>
<td>114 (22%)</td>
<td>62 (14%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>107 (11%)</td>
<td>49 (9%)</td>
<td>58 (13%)</td>
<td>971</td>
<td>.07</td>
</tr>
<tr>
<td>Neurological</td>
<td>80 (8%)</td>
<td>63 (12%)</td>
<td>17 (4%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trauma &amp; TBI</td>
<td>42 (4%)</td>
<td>31 (6%)</td>
<td>11 (2%)</td>
<td>971</td>
<td>.02</td>
</tr>
<tr>
<td>Metabolic &amp; Intox</td>
<td>62 (6%)</td>
<td>16 (3%)</td>
<td>46 (10%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Haematologic disease</td>
<td>17 (2%)</td>
<td>9 (2%)</td>
<td>8 (2%)</td>
<td>971</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>16 (2%)</td>
<td>8 (2%)</td>
<td>8 (2%)</td>
<td>971</td>
<td>.91</td>
</tr>
<tr>
<td>Sepsis</td>
<td>99 (10%)</td>
<td>40 (8%)</td>
<td>59 (13%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>apH</td>
<td>7.21 ± 0.13</td>
<td>7.23 ± 0.09</td>
<td>7.17 ± 0.15</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>aHCO₃ (mmol/L)</td>
<td>15.5 ± 6.4</td>
<td>17.5 ± 5.28</td>
<td>12.4 ± 8.11</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>aLactate (mmol/L)</td>
<td>1 ± [1]</td>
<td>0.9 [0.6]</td>
<td>1.2 [2.4]</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>apCO₂ (mmHg)</td>
<td>28.7 ± 8.8</td>
<td>30.55 ± 7.28</td>
<td>26.1 ± 8</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BE</td>
<td>−10.9 [-8]</td>
<td>−8.15 [-6.3]</td>
<td>−14.7 [7.7]</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hc</td>
<td>0.27 ± 0.07</td>
<td>0.28 ± 0.08</td>
<td>0.26 ± 0.07</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>3.6 ± 0.7</td>
<td>3.6 ± 0.7</td>
<td>3.6 ± 0.8</td>
<td>957</td>
<td>.21</td>
</tr>
<tr>
<td>CreaS (mmol/L)</td>
<td>110 ± 94.5</td>
<td>101 ± 88.5</td>
<td>120 ± 109</td>
<td>920</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adrenaline (y/n)</td>
<td>440 (45%)</td>
<td>193 (36%)</td>
<td>247 (56%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adrenaline CD (µg)</td>
<td>3980.35 ± 6</td>
<td>1661.96 ± 5</td>
<td>6310.7 ± 10</td>
<td>944</td>
<td>.40</td>
</tr>
<tr>
<td>Noradrenaline (y/n)</td>
<td>676 (70%)</td>
<td>340 (64%)</td>
<td>336 (76%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Noradrenaline CD (µg)</td>
<td>3091.9 ± 6</td>
<td>2133.7 ± 6</td>
<td>4614.3 ± 5</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ventilation (y/n)</td>
<td>640 (66%)</td>
<td>372 (70%)</td>
<td>268 (61%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood products (y/n)</td>
<td>512 (53%)</td>
<td>234 (44%)</td>
<td>278 (63%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RRT (y/n)</td>
<td>222 (23%)</td>
<td>88 (17%)</td>
<td>134 (30%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>2.57 ± 4.6</td>
<td>2.57 ± 4.26</td>
<td>2.58 ± 4.91</td>
<td>971</td>
<td>.59</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>8 ± 15</td>
<td>7 ± 15</td>
<td>8 ± 16</td>
<td>937</td>
<td>.14</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>366 (38%)</td>
<td>164 (31%)</td>
<td>202 (46%)</td>
<td>971</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>In-hospital excess mortality</td>
<td>103 (11%)</td>
<td>63 (12%)</td>
<td>40 (9%)</td>
<td>971</td>
<td>.19</td>
</tr>
<tr>
<td>30-day excess mortality</td>
<td>84 (9%)</td>
<td>54 (10%)</td>
<td>30 (7%)</td>
<td>971</td>
<td>.08</td>
</tr>
<tr>
<td>Excess mortality d31-365</td>
<td>69 (7%)</td>
<td>40 (8%)</td>
<td>29 (7%)</td>
<td>971</td>
<td>.64</td>
</tr>
<tr>
<td>Excess mortality at last follow up</td>
<td>122 (13%)</td>
<td>74 (14%)</td>
<td>48 (11%)</td>
<td>971</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to death (days)</td>
<td>5.23 ± 9.4</td>
<td>7.66 ± 279.3</td>
<td>3.32 ± 375</td>
<td>722</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Median values [interquartile ranges] or numbers (percentages) are given. ‘p’ refers to Kolmogorov–Smirnov test for continuous variables, or to chi-squared test for categorical variables (for the null hypothesis of equal categorical frequencies between two groups). Laboratory data are at admission to ICU. NoSB, non sodium-bicarbonate recipients; SB, sodium-bicarbonate recipients; avail.obs., available observations; APACHE II, Acute Physiology and Chronic Health Evaluation-II Score; DG, Diagnosis Group is referring to the APACHE IV-classification of diagnosis ad admission with a separate sepsis group (all groups include operative and non-operative diagnoses); Cardiovasc., Cardiovascular; Gastroint., Gastrointestinal; Haemat., Hematological; BE, base excess; Hc, hematocrit; Na, sodium; K, potassium; CreaS, serum creatinine; TBI, traumatic brain injury; NA, noradrenaline; CD, cumulative dose; RRT, renal replacement therapy; ICU, intensive care unit; d, day; y, yes; n, no.

A p value < 0.05 was considered statistically significant.

A last follow up: September 2019. Please note that excess mortality is given for in-hospital mortality and mortality at d30, d31–365 and at last follow up (mortality is excess mortality plus ICU mortality).

Critically ill patients with metabolic acidosis. In line with the aforementioned studies, we did not observe an increased mortality after sodium bicarbonate treatment. In contrast to the BICAR-study and the study of Zhang, however, we likely studied a rather broad population of ICU patients with metabolic acidosis as we included not only patients with acidosis and hyperlactatemia and/or septic patients.

695
Table 2  Patient demographics, ICU treatment, and follow-up data of propensity score matched patient population (n = 348).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n(no SB) = 174</th>
<th>n(SB) = 174</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female: 55 (32%)</td>
<td>Female: 50 (29%)</td>
<td></td>
<td>.64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 [6.25]</td>
<td>26.83 [7.91]</td>
<td>.2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 [16]</td>
<td>68 [17]</td>
<td>.94</td>
</tr>
<tr>
<td>APACHE II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>68 (39%)</td>
<td>55 (32%)</td>
<td>.18</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18 (10%)</td>
<td>33 (19%)</td>
<td>.03</td>
</tr>
<tr>
<td>Neurological</td>
<td>27 (16%)</td>
<td>26 (15%)</td>
<td>1</td>
</tr>
<tr>
<td>Trauma incl. TBI</td>
<td>15 (9%)</td>
<td>10 (6%)</td>
<td>.41</td>
</tr>
<tr>
<td>Metabolic &amp; Intox</td>
<td>9 (5%)</td>
<td>5 (3%)</td>
<td>.41</td>
</tr>
<tr>
<td>Hemic disease</td>
<td>10 (6%)</td>
<td>13 (7%)</td>
<td>.67</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15 (9%)</td>
<td>18 (10%)</td>
<td>.71</td>
</tr>
<tr>
<td>apH</td>
<td>7.23 [0.08]</td>
<td>7.23 [0.09]</td>
<td>1</td>
</tr>
<tr>
<td>aHCO₃⁻ (mmol/L)</td>
<td>15.1 [3.4]</td>
<td>15.25 [3.7]</td>
<td>1</td>
</tr>
<tr>
<td>aLactate (mmol/L)</td>
<td>1 [0.8]</td>
<td>1 [1.0]</td>
<td>.45</td>
</tr>
<tr>
<td>Hc</td>
<td>0.27 [0.07]</td>
<td>0.26 [0.07]</td>
<td>.98</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>3.6 [0.7]</td>
<td>3.6 [0.8]</td>
<td>.98</td>
</tr>
<tr>
<td>CreaS (mmol/L)</td>
<td>118 [84.5]</td>
<td>125 [131]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adrenaline (y/n)</td>
<td>76 (44%)</td>
<td>85 (49%)</td>
<td>.39</td>
</tr>
<tr>
<td>Noradrenaline (y/n)</td>
<td>109 (63%)</td>
<td>135 (78%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Noradrenaline CD (µg)</td>
<td>2471.82 [6512.9]</td>
<td>3330.52 [13,183.4]</td>
<td>.09</td>
</tr>
<tr>
<td>Ventilation (y/n)</td>
<td>126 (72%)</td>
<td>111 (64%)</td>
<td>.11</td>
</tr>
<tr>
<td>Blood Products (y/n)</td>
<td>91 (52%)</td>
<td>111 (64%)</td>
<td>.04</td>
</tr>
<tr>
<td>RRT (y/n)</td>
<td>44 (25%)</td>
<td>43 (25%)</td>
<td>1</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>2.65 [4.2]</td>
<td>2.87 [5.1]</td>
<td>.54</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>6 [16]</td>
<td>9 [17.2]</td>
<td>.01</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>55 (32%)</td>
<td>72 (41%)</td>
<td>.07</td>
</tr>
<tr>
<td>InHospital excess mortality</td>
<td>22 (13%)</td>
<td>18 (10%)</td>
<td>.61</td>
</tr>
<tr>
<td>30d excess mortality</td>
<td>20 (11%)</td>
<td>11 (6%)</td>
<td>.13</td>
</tr>
<tr>
<td>Excess mortality d31–365</td>
<td>12 (7%)</td>
<td>15 (9%)</td>
<td>.69</td>
</tr>
<tr>
<td>Excess mortality at last follow up</td>
<td>26 (15%)</td>
<td>23 (13%)</td>
<td>.76</td>
</tr>
<tr>
<td>Time to death (days)</td>
<td>5.22 [274.9]</td>
<td>6.25 [47.3]</td>
<td>.91</td>
</tr>
</tbody>
</table>

Median values [interquartile ranges] or counts (percentages) are given. *p* refers to Kolmogorov-Smirnov test for continuous variables, or to chi-squared test for categorical variables (for the null hypothesis of equal categorical frequencies between two groups). Laboratory data are at admission to ICU. DG, Diagnosis Group is referring to the APACHE IV-classification of diagnosis ad admission with a separate sepsis group (all groups include operative and non-operative diagnoses); Cardiovasc., Cardiovascular; Gastroint., Gastrointestinal; Haemat., Hematological; NoSB, non sodium bicarbonate recipients; SB, sodium-bicarbonate recipients; APACHE II, Acute Physiology and Chronic Health Evaluation II Score; Hc, hematocrit; Na, sodium; K, potassium; CreaS, serum creatinine; TBI, traumatic brain injury; CD, cumulative dose; RRT, renal replacement therapy; ICU, intensive care unit.

A p value < 0.05 was considered statistically significant.

*α* Last follow up: September 2019. Please note that excess mortality is given for in-hospital mortality and mortality at d30, d31–365 and at last follow up (mortality is excess mortality plus ICU mortality).

Median values [interquartile ranges] or counts (percentages) are given. *p* refers to Kolmogorov-Smirnov test for continuous variables, or to chi-squared test for categorical variables (for the null hypothesis of equal categorical frequencies between two groups). Laboratory data are at admission to ICU. DG, Diagnosis Group is referring to the APACHE IV-classification of diagnosis ad admission with a separate sepsis group (all groups include operative and non-operative diagnoses); Cardiovasc., Cardiovascular; Gastroint., Gastrointestinal; Haemat., Hematological; NoSB, non sodium bicarbonate recipients; SB, sodium-bicarbonate recipients; APACHE II, Acute Physiology and Chronic Health Evaluation II Score; Hc, hematocrit; Na, sodium; K, potassium; CreaS, serum creatinine; TBI, traumatic brain injury; CD, cumulative dose; RRT, renal replacement therapy; ICU, intensive care unit.

A p value < 0.05 was considered statistically significant.

*α* Last follow up: September 2019. Please note that excess mortality is given for in-hospital mortality and mortality at d30, d31–365 and at last follow up (mortality is excess mortality plus ICU mortality).

endpoints. Further, effects (whether beneficial or not) could theoretically be short- rather than long-lived.

Importantly, about 50% or more patients who received sodium bicarbonate did not have a “severe” metabolic acidosis with pH ≤ 7.2 (Tables 1 and 3). However, when compared to other investigations, our results (median pH of 7.17 in “crude” and 7.23 in matched groups) may be considered rather comparable to other retrospectives studies (e.g. Kim et al.: mean pH 7.244 ± 0.168)\(^{16}\); Zhang et al.: minimum mean pH 7.16 ± 0.1\(^{13}\)). Moreover, the median arterial PCO₂ in the matched groups was 28 mmHg. Therefore, the observed pH at admission may be respiratory compensated and true pH in fact considerably lower.

Further, one might assume that SB patients would have had a higher risk of death. However, in our subset of ICU patients, SB treated patients had a slightly, but statistic-
Table 3  Odds ratios (OR) for treatment effects for mortality in the matched dataset.

<table>
<thead>
<tr>
<th></th>
<th>ATE (matched sample), $n = 348$</th>
<th>p-Value</th>
<th>ATT (matched sample), $n = 348$</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>1.08 (0.991, 1.17)</td>
<td>.08</td>
<td>1.09 (0.987, 1.2)</td>
<td>.09</td>
</tr>
<tr>
<td>In Hospital excess mortality</td>
<td>0.982 (0.924, 1.04)</td>
<td>.55</td>
<td>0.984 (0.92, 1.05)</td>
<td>.62</td>
</tr>
<tr>
<td>30d excess mortality</td>
<td>0.96 (0.91, 1.01)</td>
<td>.13</td>
<td>0.958 (0.903, 1.02)</td>
<td>.16</td>
</tr>
<tr>
<td>Excess mortality d31-365</td>
<td>1.02 (0.968, 1.08)</td>
<td>.44</td>
<td>1 (0.94, 1.06)</td>
<td>.98</td>
</tr>
<tr>
<td>Excess mortality at last follow-up(a)</td>
<td>0.994 (0.935, 1.06)</td>
<td>.82</td>
<td>0.993 (0.928, 1.06)</td>
<td>.83</td>
</tr>
</tbody>
</table>

Reported are the odds ratios (OR) for the treatment effects for mortality at various stages in presence of sodium bicarbonate treatment. Estimated by logit logistic regressions, regressing mortality outcome on SB treatment status, sex, age, BMI and APACHE.

\(a\) Last follow up was in September 2019. ATE, Average Treatment Effect; ATT, Average Treatment effect in Treated. Please note that excess mortality is given for in-hospital mortality and mortality at d30, d31–365 and at last follow up (mortality is excess mortality plus ICU mortality).

![Figure 2](image)

Figure 2  Kaplan–Meier survival curves (20 days) obtained using different propensity score methods. In the top-left panel crude Kaplan–Meier survival curves for treated and untreated subjects in the “crude” sample ($n = 971$; log-rank test: $p = 0.005$). In the top-right panel Kaplan–Meier survival curves for treated and untreated subjects in the propensity score matched sample ($n = 348$ stratified log-rank test $p = 0.53$). In the bottom-left and bottom-right panels survival curves in the sample weighted using the ATE weights ($n = 971$) and the sample weighted using the ATT weights ($n = 971$) are reported (adjusted log-rank test with $p$-values 0.91 and 0.98). ATE, Average Treatment Effect; ATT, Average Treatment effect in Treated.

A number of important additional limitations of our analysis deserve discussion. First, limitations arise from the retrospective, single-center, and exploratory design of this study and all respective inherent limitations apply that are driven by study design. In this retrospective study, even if...
mortality analyses were adjusted for typical potential confounders, our data may theoretically be subject to some degree of unmeasured confounding. Additionally, by definition, the matched sample analysis required extensive exclusion of patients of the overall sample, which may preclude introduction (e.g. selection) bias. Moreover, this may point to heterogeneity of the total cohort and may be one reason why respective patients were particularly challenging to treat. By deliberately curtailing our ICU data set to a subset of patients and by removing some outliers that aimed for a comparable subset of ICU patients, it may theoretically be possible that some degree of selection bias was introduced. Second, we only considered intravenous sodium bicarbonate formulations of 8.4% for analysis and might have missed other preparations, including e.g. chronic oral bicarbonate used in few patients with chronic kidney disease. Third, mortality may not be an optimal endpoint to examine effects of an early single intervention in a critically ill population, which may also underline our interest in early outcomes of our cohort (i.e. 20 days of ICU stay). It appears that endpoints related to therapy-induced effects (e.g. increase in pH) might be particularly interesting in subsequent investigations. Fourth, our retrospective study design made it impossible to identify the medical reason for the (independent treating) physician to prescribe sodium bicarbonate and for the timing of the prescription. We can thus not exclude with certainty that SB was also given for aetologies of metabolic acidosis with a better prognosis (e.g. diabetic ketoacidosis, intoxications) or other reasons than for metabolic acidosis only, e.g. in cases of additional rhabdomyolysis. Although the current analysis may be one of the largest investigations available, it appeared that the sample size was too limited to conclude back on effects of SB dose and/or exact timing as well as to conclude on subgroups of critically ill patients (e.g. acute kidney injury [AKI] or sepsis patients, patient’s post-surgical interventions). Thus, the presented analysis may theoretically be ‘underpowered’. Fifth, we did not evaluate other important covariates such as interventions during the ICU stay (e.g. emergency hemodialysis) as well as respective urgency nor the impact of fluid intake other than sodium bicarbonate including fluid balance. Sixth, the presented mortality data reflects all-cause mortality and we are unable to conclude back on specific acidosis and/or treatment-related adverse effects or on different causes of death. Seventh, as our retrospective analysis made it impossible to conclude back on acid base analysis after sodium bicarbonate infusion we cannot describe any influence of sodium bicarbonate on the pH and the bicarbonate level after treatment. Moreover, we refrained from estimating dose-effects of the sodium bicarbonate given.

Conclusion

In this propensity score matched analysis, intravenous administration of sodium bicarbonate did not appear to effect on mortality in ICU patients with metabolic acidosis. Additional prospective controlled clinical investigations seem required to further determine potential effects of sodium bicarbonate infusion in subgroups of patients with metabolic acidosis, including potential high-risk groups, such as critically ill patients with AKI.

Authors’ contributions

JW: Designed the study, performed data collection and assessment, wrote the first draft, coordinated the input of all authors, supervised the study and revised the manuscript for important intellectual content.

BH: Designed the study, performed data collection and assessment, wrote the first draft, coordinated the input of all authors, and revised the manuscript for important intellectual content.

LC: Contributed to data interpretation, revised the manuscript for important intellectual content.

II: Performed all statistical analyses, revised the manuscript for important intellectual content.

CAP: Co-designed the study, contributed to data interpretation, supervised the study, and revised the manuscript for important intellectual content.

JCS: Co-designed the study, contributed to data interpretation, supervised the study and revised the manuscript for important intellectual content.

All authors approved the final version of the manuscript.
Conflict of interests


II is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern’s conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html

The additional authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medin.2021.04.010.

References