The biochemical effects of restricting chloride-rich fluids in intensive care (ClinicalTrials.gov NCT 00885404)

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Objective: **To determine the biochemical effects of restricting the use of chloride-rich intravenous fluids in critically ill patients.**

Design: **Prospective, open-label, before-and-after study.**

Setting: **University-affiliated intensive care unit.**

Patients: **A cohort of 828 consecutive patients admitted over 6 months from February 2008 and cohort of 816 consecutive patients admitted over 6 months from February 2009.**

Interventions: **We collected biochemical and fluid use data during standard practice without clinician awareness. After a 6-month period of education and preparation, we restricted the use of chloride-rich fluids (0.9% saline, Gelofusine, and Albumex 4) in the intensive care unit and made them available only on specific intensive care unit specialist prescription.**

Measurements and Main Results: **Saline prescription decreased from 2411 L in the control group to 52 L in the intervention group ($p < .001$), Gelofusine from 538 to 0 L ($p < .001$), and Albumex 4 from 269 to 80 L ($p < .001$). As expected, Hartmann's lactated solution prescription increased from 469 to 3205 L ($p < .001$), Plasma-Lyte from 65 to 160 L ($p < .05$), and chloride-poor Albumex 20 from 87 to 268 L ($p < .001$). After intervention, the incidence of severe metabolic acidosis (standard base excess < -5 mEq/L) decreased from 9.1% to 6.0% ($p < .001$) and severe acidemia (pH <7.3) from 6.0% to 4.9% ($p < .001$). However, the intervention also led to significantly greater incidence of severe metabolic alkalosis (standard base excess >5 mEq/L) and alkalemia (pH >7.5) with an increase from 25.4% to 32.8% and 10.5% to 14.7%, respectively ($p < .001$). The time-weighted mean chloride level decreased from 104.9 ± 4.9 to 102.5 ± 4.6 mmol/L ($p < .001$), whereas the time-weighted mean standard base excess increased from 0.5 ± 4.5 to 1.8 ± 4.7 mmol/L ($p < .001$), mean bicarbonate from 25.3 ± 4.0 to 26.4 ± 4.1 mmol/L ($p < .001$) and mean pH from 7.40 ± 0.06 to 7.42 ± 0.06 ($p < .001$). Overall fluid costs decreased from $15,870 (AUD) to $4121.**

Conclusions: **In a tertiary intensive care unit in Australia, restricting the use of chloride-rich fluids significantly affected electrolyte and acid-base status. The choice of fluids significantly modulates acid-base status in critically ill patients. (Crit Care Med 2011; 39:000–000)**

Key Words: chloride; hyperchloremia; acid-base balance; base excess; bicarbonate; acidemia; saline; acidosis; critical care; intensive care

Metabolic acidosis is common in critically ill patients and is an independent predictor of outcome (1, 2). As such, metabolic acidosis attracts considerable research and clinical interest and there is controversy over its pathogenesis (3).

The physicochemical approach (Stewart approach) to acid-base analysis suggests a stronger role of chloride in acid-base homeostasis than previously appreciated. According to this approach, the hydrogen ion concentration $[H^+]$ in blood depends on three independent variables: strong ion difference, partial pressure of CO_2, and weak acid concentration (4, 5). A relative increase in chloride will decrease the strong ion difference, which, in turn, should produce metabolic acidosis.

The logical implication of this approach is that chloride-rich intravenous fluids, i.e., those which chloride concentrations are both supraphysiological and high relative to sodium, may contribute to metabolic acidosis by increasing serum chloride concentration and decreasing the strong ion difference (6). In many countries, such fluids include 0.9% saline (chloride 154 mmol/L, sodium 154 mmol/L), succinylated gelatin (Gelofusine: chloride 120 mmol/L, sodium 154 mmol/L), and albumin in sodium chloride (Albumex 4: chloride 128 mmol/L, sodium 140 mmol/L).

The effects on acid-base status of rapid intravenous loading with chloride-rich fluids have been explored in human volunteers and perioperative studies (7–10) and a small study has shown a correlation between intravenous chloride load in the intensive care unit (ICU) and acid-base status (11). However, no large studies have explored the broader effects of these fluids in critically ill patients when prescribed at variable infusion rates on a daily basis throughout the ICU stay.

In this study, we aimed to investigate the biochemical, acid-base, and cost effects of restricting the use of chloride-rich fluids in a multidisciplinary tertiary ICU in Australia. We hypothesized that such restriction would be associated with decreased plasma chloride concentration and decreased incidence of metabolic acidosis and acidemia.

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Table 1. Electrolyte composition of studied fluids

	0.9% NaCl[a]	Hartmann's[a]	Gelofusine[b]	Plasma-Lyte 148[a]	Albumex4[c]	Albumex 20[c]
Sodium	154	129	154	140	140	48–100
Potassium	0	5	0	5	0	0
Chloride	154	109	120	98	128	0
Calcium	0	2	0	0	0	0
Magnesium	0	0	0	1.5	0	0
Lactate	0	29	0	0	0	0
Acetate	0	0	0	27	0	0
Gluconate	0	0	0	23	0	0
Octanoate	0	0	0	0	6.4	32

[a]Baxter, Toongabie, NSW, Australia; [b]B Braun, Melsungen, Germany; [c]CSL Limited, Broadmeadows, VIC, Australia.

All concentrations in mmol/L.

PATIENTS AND METHODS

We conducted the study in the 22-bed multidisciplinary ICU of the Austin Hospital, a tertiary referral hospital affiliated with the University of Melbourne. The Austin Health Human Research Ethics Committee approved the study and waived the need for informed consent.

We applied no exclusion criteria to this study because intravenous fluids were part of standard patient care in the ICU. All consecutive patients admitted to the ICU from February 18, 2008, through August 17, 2008 (6 months) formed the control (before) group.

During this period, ICU clinicians (residents, fellows, registrars, specialists) were free to use any intravenous fluids based on clinical preference. None of the clinicians was aware of the plan to conduct a trial involving removal of chloride-rich fluids from ICU practice. The fluids available (Table 1) included 0.9% saline, Gelofusine, Albumex 4 (4% albumin), Hartmann's solution, Plasma-Lyte 148, and Albumex 20 (20% albumin).

The next 6 months, between August 18, 2008, and February 17, 2009, were then used to announce a decision to implement a change and to allow a "washout" period before the intervention. We spent the latter 3 months of this "washout" period educating and preparing all ICU staff for the forthcoming shift in fluids practice. Similar policies were implemented in the emergency department and the operating room at the same time.

The intervention period started on February 18, 2009, and ended on August 17, 2009, to replicate the same season of the year with all consecutive ICU admissions during this period enrolled into the intervention group.

ICU clinicians were no longer allowed to use 0.9% saline, Gelofusine, or Albumex 4 in their routine practice. In replacement, they were encouraged to use existing lower chloride fluids, namely Hartmann's solution, Plasma-Lyte 148, and Albumex 20. However, chloride-rich fluids were allowed under exclusive and specific prescription by an ICU specialist for conditions which might be considered likely to benefit from their use (e.g., hyponatremia, cerebral edema, marked hypochloremic alkalosis).

To avoid confusion, the use of 4% dextrose 0.18% saline as maintenance fluids was disallowed in the intervention period despite its low chloride contents (chloride 30.8 mmol/L). The use of 5% dextrose as maintenance was, however, permitted. There was no change in the drug delivery vehicles used during both control and intervention periods. All drugs were delivered using 5% dextrose, except for insulin, for which 0.9% saline was used. A dosage of 0.9% saline was also retained as the fluids used to flush blood transfusion intravenous lines.

Data were collected from all ICU blood gas analyses performed during the control and intervention periods. Blood samples were collected in heparinized blood gas syringes and analyzed in the ICU blood gas analyzer (RapidLab 1265; Siemens Healthcare Diagnostics, Deerfield, IL). The analyzer measured samples at 37°C. ICU nursing staff trained in the use of the analyzer by support technical staff performed all analyses. The ICU laboratory facilities comply with the standards of the Australian National Association of Testing Authorities (12).

We collected the following data from the analyzer output: pH, partial pressure of carbon dioxide, bicarbonate, standard base excess (SBE), sodium, chloride, potassium, ionized calcium, and lactate. The analyzer calculated the bicarbonate and SBE concentrations according to the recommendations from the National Committee for Clinical Standards (13). Sodium, chloride, potassium, and ionized calcium were measured using ion-selective electrodes, whereas lactate was measured using an enzymatic substrate-specific electrode. No additional sampling was required. The analyzer output data were electronically stored and available for computer-based retrieval.

The reference ranges of the blood gas analyzer were: chloride: 98–106 mmol/L, sodium: 135.0–148.0 mmol/L, pH: 7.350–7.450, and SBE: ±2 mEq/L. Severe abnormalities were predefined as marked and equidistant changes from reference values in either direction. Severe hypochloremia was defined as a chloride level <90 mmol/L and severe hyperchloremia as a chloride level >114 mmol/L, severe hyponatremia as a sodium level <127 mmol/L, and severe hypernatremia as a sodium level >156 mmol/L. We labeled each measurement outside of these predefined boundaries as severe dyschloremia or dysnatremia. Similarly, we defined severe acidemia as a pH <7.3, severe alkalemia as a pH >7.5, severe metabolic acidosis as a SBE <−5 mmol/L, and severe metabolic alkalosis as a SBE >5 mmol/L. We labeled any values outside of these boundaries as severe pH derangement and severe metabolic acid-base derangement.

We obtained demographic data of patients enrolled: age, sex, Acute Physiology and Chronic Health Evaluation II score, and type of admission. The pharmacy department monitored delivery of intravenous fluids to the ICU during the control and intervention periods and provided data on their use in liters/month. To study in more detail how fluids might have been used during the two periods, we randomly selected 100 patients from each of the control and intervention groups using computer-generated random numbers and collected detailed information on intravenous fluid intake.

Statistical Analysis. All statistical analysis was performed with commercially available statistical programs (Stata; StataCorp LP, College Station, TX) and SAS Version 9.2 (SAS Institute, Cary, NC). Binomial data were compared using chi-square tests. We used the Student's *t* tests for normally distributed data and Wilcoxon's rank sum test for nonparametric data. To account for the multiple biochemical measurements for each patient, repeat measures were reduced to single measurement per patient using both arithmetic and time-weighted means with results reported as means with SDS or as medians with interquartile ranges as appropriate. Time-weighted means were used to minimize any bias caused by increased surveillance and were calculated by measuring the average of each pair of consecutive measurements and multiplying it by the length of time in minutes between the two measurements (14). Changes over time during the first week of ICU stay were determined using repeat-measures analysis of variance with each patient being treated as a random effect. Models were fitted with a group effect, a time effect, and an interaction between group and time to determine whether the two groups behaved differently over time. All statistical comparisons were two-sided and

Table 2. Baseline characteristics of (*A*) the two groups and of (*B*) 100 randomly selected patients from each group

A

Characteristics	Control Group (n = 828)	Intervention Group (n = 816)	*p*
Age, mean (SD)	61 (17)	60 (18)	.78
Male gender, no. (%)	509 (62)	503 (62)	.94
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	16.0 (7.5)	16.2 (7.8)	.61
Emergency admissions, no. (%)	603 (73)	585 (72)	.61
Postoperative admissions, no. (%)	393 (48)	400 (49)	.46

B

Characteristics	Control Group (n = 100)	Intervention Group (n = 100)	*p*
Age, mean (SD)	61 (16)	60 (19)	.68
Male gender, no. (%)	62 (62)	64 (64)	.77
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	15.6 (7.1)	15.9 (7.4)	.83
Emergency admissions, no. (%)	69 (69)	66 (66)	.65
Postoperative admissions, no. (%)	50 (50)	51 (51)	.89

Table 3. Intravenous fluids intake and fluids balance during intensive care unit stay of 100 randomized patients from each group

	Control Group (n = 100)	Intervention Group (n = 100)	*p*
0.9% saline, mL	695 (165–1681)	0 (0–0)	<.001
Succinylated gelatin (Gelofusine), mL	50 (0–825)	0 (0–0)	<.001
Albumin 4% in sodium chloride (Albumex 4), mL	0 (0–275) (405)[a]	0 (0–0) (44)[a]	<.001
Hartmann's solution, mL	0 (0–0)	1840 (770–3611)	<.001
Plasma-Lyte 148, mL	0 (0–0) (41)[a]	0 (0–0) (205)[a]	<.01
Albumin 20% (Albumex 20), mL	0 (0–100)	200 (0–300)	<.001
Total intravenous fluids intake, mL	2277 (885–3916)	2590 (980–5185)	.62
Total urine output, mL	5163 (2743–8051)	4215 (2130–6723)	.323

[a]Means are shown to highlight differences because both medians are zero.

Data are expressed as medians (interquartile ranges). *p* value represents comparison between the two groups.

Table 4. Cost comparisons based on prices per unit between the two groups[a]

	Control, AUD $	Intervention, AUD $
0.9% saline	2821	61
Succinylated gelatin (Gelofusine)	12,374	0
Hartmann's solution	549	3750
Plasma-Lyte 148	126	310
Total	15,870	4121

[a]In Australia, albumin solutions are provided by the Australian Red Cross Blood Services to hospitals because blood products and are free from charge prices per unit: 0.9% saline 1 L: $1.17; Gelofusine 500 mL: $11.50; Hartmann's 1 L: $1.17; Plasma-Lyte 148: $1.94.

a $p < .05$ was considered to indicate statistical significance.

RESULTS

We studied 1644 patients (Table 2*A*). The two groups were similar with regard to age, sex, Acute Physiology and Chronic Health Evaluation II scores, and type of admission. Likewise, the baseline characteristics of the two groups of 100 randomly selected patients (Table 2*B*) were similar.

There was a significant change in fluid prescription with a 98% reduction in 0.9% sodium chloride, 100% reduction in Gelofusine, and a 70% reduction in Albumex 4 administration (all $p < .001$). As expected, total volume prescribed increased for Hartmann's lactated solution (6.8-fold), Albumex 20 (3.1-fold), and Plasma-Lyte 148 (2.5-fold) ($p < .001$ for Hartmann's and Albumex 20 and $p < .05$ for Plasma-Lyte 148).

These significant differences were confirmed by the findings of detailed intravenous fluids intake in 100 randomly selected patients from each of the control and intervention groups (Table 3). Pharmacy fluid costs decreased during the intervention (Table 4).

The incidence of severe hyperchloremia and hypernatremia was significantly lower in the intervention group with a significant decrease in dyschloremia and dysnatremia (Table 5). On the other hand, although the incidence of severe metabolic acidosis and acidemia significantly decreased, there was a significantly greater incidence of metabolic alkalosis and alkalemia, which was responsible for an increase in the incidence of marked derangements of metabolic acid-base balance and pH in the intervention group.

The time-weighted mean of serum chloride concentration (Table 6) decreased during the intervention group, whereas the time-weighted mean of the sodium chloride difference increased. Correspondingly, the time-weighted mean of SBE, bicarbonate, and median of pH were also significantly higher in the intervention period. Finally, lactate levels were also higher in the intervention period.

For the four variables, sodium chloride difference, SBE, pH, and lactate (Fig. 1), there was a significant interaction ($p < .001$) between groups and the first 7 days of hospital admission indicating that the behavior during the first week of admission was significantly different between the groups. It is, however, important to note that the magnitude of the data used for this analysis (>30,000 data points) ensures that only a slight deviation between groups was required to achieve a high level of statistical significance. The sodium chloride difference, SBE, and pH (Fig. 2) remained consistently different for the duration of the first 7 days ($p < .001$). Lactate in the intervention group, however, was higher than the control group only for the first 2 days.

DISCUSSION

Key Findings. We performed a before-and-after study of the biochemical, acid-

Table 5. Comparisons of severe derangements in chloride, sodium, pH, and standard base excess measurements between the two groups

	Control (21,694 Measurements)	Intervention (19,807 Measurements)	*p*
Severe hypochloremia, chloride <90 mmol/L, no. (%)	205 (0.9%)	287 (1.4%)	<.001
Severe hyperchloremia chloride >114 mmol/L, no. (%)	1353 (6.2%)	465 (2.3%)	<.001
Severe dyschloremia, no. (%)	1558 (7.2%)	752 (3.7%)	<.001
Severe hyponatremia, sodium <127 mmol/L, no. (%)	543 (2.5%)	543 (2.7%)	.129
Severe hypernatremia, sodium >156 mmol/L, no. (%)	205 (0.9%)	31 (0.2%)	<.001
Severe dysnatremia, no. (%)	748 (3.4%)	574 (2.9%)	.001
Standard base excess <−5 mEq/L, no. (%)	1964 (9.1%)	1185 (6.0%)	<.001
Standard base excess >5 mEq/L, no. (%)	5500 (25.4%)	6491 (32.8%)	<.001
Severe metabolic acid-base derangements, no. (%)	7464 (34.4%)	7676 (38.8%)	<.001
pH <7.3, no. (%)	1309 (6.0%)	973 (4.9%)	<.001
pH >7.5, no. (%)	2275 (10.5%)	2909 (14.7%)	<.001
Severe pH derangements, no. (%)	3584 (16.5%)	3882 (19.6%)	<.001

Table 6. Time-weighted mean (SD) [Range] of biochemical variables of the two groups

Biochemical Variables	Control Group (n = 828)	Intervention Group (n = 816)	*p*
Chloride, mmol/L	104.9 (4.9) [81.5–122.8]	102.5 (4.6) [79.5–120.5]	<.001
Sodium, mmol/L	137.1 (4.7) [108.3–159.1]	136.7 (4.6) [104.1–149.7]	.11
Sodium-chloride difference, mmol/L	32.2 (4.2) [19.4–78.0]	34.2 (4.4) [15.6–50.5]	<.001
Potassium, mmol/L	4.1 (0.4) [2.9–6.5]	4.1 (0.5) [2.2–7.1]	.20
Ionized calcium, mmol/L	1.11 (0.07) [0.85–1.42]	1.13 (0.07) [0.74–1.48]	<.001
Bicarbonate, mmol/L	25.3 (4.0) [7.8–43.3]	26.4 (4.1) [5.6–41.8]	<.001
pH	7.40 (0.06) [7.03–7.53]	7.42 (0.06) [7.04–7.58]	<.001
Standard base excess, mmol/L	0.5 (4.5) [−26.7–19.5]	1.8 (4.7) [−28.5–17.2]	<.001
Lactate, mmol/L	1.79 (1.57) [0.51–23.06]	2.05 (1.61) [0.59–17.86]	.002

base, and cost effects of restricting the use of chloride-rich fluid in a multidisciplinary tertiary ICU in Australia to test the hypothesis that such restriction would be associated with decreased plasma chloride concentration and decreased incidence of metabolic acidosis and acidemia. We found that this restriction was associated with a significant decrease in hyperchloremia, hypernatremia, severe metabolic acidosis, and acidemia. However, we also found such restriction led to a significantly higher incidence of severe metabolic alkalosis and alkalemia. Blood lactate concentrations were also significantly and transiently increased. In our unit, these changes decreased the cost of fluids.

Comparison With Previous Studies. To our knowledge, this is the first study to explore the biochemical and acid-base consequences over days to weeks of ICU treatment of restricting chloride-rich fluids. As such, it cannot be directly compared with previous investigations. Our findings, however, appear biologically plausible and are consistent with previous acute treatment studies, which were conducted in the perioperative or experimental setting (9, 10, 15). In particular, our study demonstrates that, consistent with theoretical predictions (16), there is an association between higher chloride intake with increased serum chloride concentration, decreased strong ion difference (predominantly contributed by sodium chloride difference), decreased base excess, bicarbonate, and pH. It also shows that these effects can occur in response to the choice of fluids outside of the acute situation of large-volume fluid resuscitation. Our observations also show that the acid-base changes over time, shown for up to 120 mins in a study by Scheingraber et al (9), can persist for up to 1 wk during an ICU stay, even when these lower chloride fluids are used episodically or at lower infusion rates for minor volume expansion or "maintenance" therapy.

Significance of Study Findings. Our findings provide strong additional data that "routine" ICU intravenous fluid therapy has significant effects on the electrolyte and acid-base status of critically ill patients. In particular, we found that replacing chloride-rich fluids with lower chloride fluids moves acid-base status toward alkalosis. Although the clinical importance of this phenomenon is unclear (and currently under investigation in our unit), the appreciation of these effects is useful to clinicians making choices about fluid therapy in a variety of settings. In particular, it should enable clinicians who consider that in a particular patient, acidemia or alkalemia may be undesirable, to regulate fluid therapy accordingly. Furthermore, our results suggest that routine use of lactate fluids such as Hartmann's or Ringer's lactate is associated with a detectable iatrogenic increase in lactate in the first 48 hrs after ICU admission, when, presumably, lactate clearance is less effective. Finally, we also found this restriction of chloride-rich fluids reduced the cost of care with at least no significantly detrimental biochemical effects. Although cost was a secondary element of our study, the potential impact on healthcare costs is worthy of consideration.

Strengths and Limitations. To our knowledge, this is the first study of a restrictive approach to the use of chloride-rich fluids in a broad and heterogeneous population of critically ill patients. Our findings, therefore, are likely to carry a degree of external validity. The biochemical measurements were extended throughout the whole ICU admission as opposed to the immediate perioperative or periresuscitation period as done in previous studies. The biochemical data were electronic in nature, minimizing the risk of error or manipulation. We further validated the bulk data of intravenous fluids use by analyzing the detailed intravenous fluids intake of 100 randomly selected patients from each group.

On the other hand, this is not a randomized trial. However, our sample size was relatively large and the baseline characteristics did not show any significant difference between the two groups. Furthermore, there were no other changes in

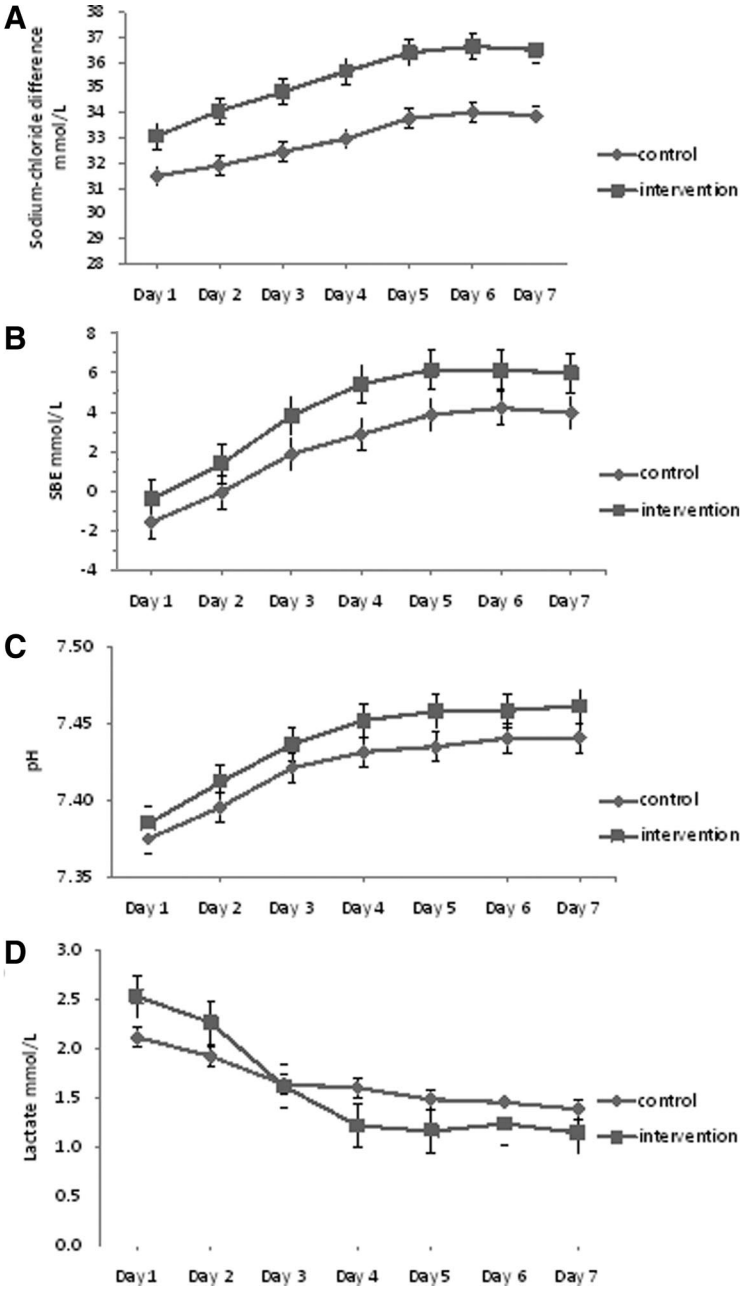

Figure 1. Changes of daily means (SES) in sodium chloride difference (*A*), standard base excess (*B*), pH (*C*), and lactate (*D*) for the first seven intensive care unit days.

unit practice during the time of the study.

The continuing use of dextrose 5% as maintenance and drug delivery vehicle in the intervention period might have affected our results. Although not chloride-rich, dextrose preparations still lowers the strong ion difference through the absence of both strong cations and anions, thus the potential to shift the acid-base results toward acidosis. Our patients also received Gelofusine in the control period, a gelatin colloidal fluid that is not available in North America but widely available elsewhere in the world. However, this fluid has been shown, at least on ex vivo hemodilution, to cause metabolic acidosis of identical severity to standard starch preparations (17) that are widely available in North America. This equivalent tendency toward acidosis, despite the lower chloride content of Gelofusine, has been attributed to the weak acid properties of gelatin countering the lower strong ion difference of the saline vehicle of starch colloids (18). Our cost comparisons are also not applicable to other countries because, in Australia, 4% albumin and 20% albumin are supplied to hospitals by the Australian Red Cross Blood Services as a free blood product. Finally, our use of albumin solutions may also be higher than in other centers because our hospital is a state referral center for liver failure and liver transplantation.

Future Studies. The findings of this study suggest the need to explore the effects of restricting the use of chloride-rich fluids on other commonly measured biochemical (liver function and renal function tests) and hematologic variables. We are currently undertaking such a study. Similarly, whether this intervention and the associated decrease in acidosis/acidemia and increase in alkalosis/alkalemia can improve or worsen clinical outcomes is of great interest. We are currently conducting such a study over a longer period of intervention to increase our statistical power to detect a difference in outcome, if such a difference exists.

CONCLUSION

We conducted a before-and-after study comparing the biochemical and acid-base effects of restricting the administration of chloride-rich fluids in critically ill patients. We found that such restriction was associated with a significant decrease in the incidence of metabolic acidosis and acidemia and significantly lower incidence of severe hyperchloremia and hypernatremia. On the other hand, it increased the incidence of metabolic alkalosis and alkalemia. Further studies are now needed to assess the physiological and clinical impact of these biochemical and acid-base changes. In the meantime, however, clinicians can use this information to estimate the impact of the choice of intravenous fluids on electrolytes and acid-base status and, when appropriate, individualize patient fluid therapy.

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