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Nor'azim Mohd Yunos
Rinaldo Bellomo
Neil Glassford
Harvey Sutcliffe
Que Lam
Michael Bailey

Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis

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Take-home message: We extended a previous study of chloride restriction and AKI to 12 months and found the renal impact remained. However, other unidentified confounders may have contributed to the findings.

Electronic supplementary material
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N. M. Yunos · R. Bellomo (✉) · N. Glassford · H. Sutcliffe · Q. Lam · M. Bailey
Austin Health, Heidelberg, Australia
e-mail: rinaldo.bellomo@austin.org.au

Abstract *Purpose:* In a previous study, restricting intravenous chloride administration in ICU patients decreased the incidence of acute kidney injury (AKI). To test the robustness of this finding, we extended our observation period to 12 months. *Methods:* The study extension included a 1-year control period (18 August 2007 to 17 August 2008) and a 1-year intervention period (18 February 2009 to 17 February 2010). During the extended control period, patients received standard intravenous fluids. During the extended intervention period, we continued to restrict all chloride-rich fluids. We used the Kidney Disease: Improving Global Outcomes (KDIGO) staging to define AKI. *Results:* We studied 1,476 control and 1,518 intervention patients. Stages 2 and 3 of KDIGO defined AKI decreased from 302 (20.5 %; 95 % CI, 18.5–22.6 %) to 238 (15.7 %; 95 % CI, 13.9–17.6 %) ($P < 0.001$) and the use of RRT from 144 (9.8 %; 95 % CI, 8.3–11.4 %) to 103 (6.8 %; 95 % CI, 5.6–8.2 %) ($P = 0.003$). After adjustment for relevant covariates, liberal chloride therapy remained associated with a greater risk of KDIGO stages 2 and 3 [hazard ratio 1.32 (95 % CI 1.11–1.58); $P = 0.002$] and use of RRT [hazard ratio 1.44 (95 % CI 1.10–1.88); $P = 0.006$]. However, on sensitivity assessment of each 6-month period, KDIGO stages 2 and 3 increased in the new extended intervention period compared with the original intervention period. *Conclusions:* On extended assessment, the overall impact of restricting chloride-rich fluids on AKI remained. However, sensitivity analysis suggested that other unidentified confounders may have also contributed to fluctuations in the incidence of AKI.

Keywords Chloride · Saline · Creatinine · Acute kidney injury · Critical care · Intensive care

Introduction

Intravenous fluid therapy may influence outcomes in critically ill patients. Some of these outcomes have been linked to the contents of intravenous fluids, including colloid source and electrolyte compositions [1]. The chloride content of intravenous fluids has recently emerged as an area of interest in terms of acute kidney injury (AKI).

For example, a double-blind randomized controlled trial in healthy volunteers showed significantly better renal cortical tissue perfusion following a 2-l infusion of a low-chloride fluid (Plasma-Lyte®) compared with a high-chloride fluid (0.9 % saline) [2]. Similar effects were seen with the administration of hydroxyethyl starch (HES) in a low chloride solution compared to HES in saline [3]. These studies suggest that excess chloride administration may modulate renal perfusion in humans. However, the

clinical implications of reducing chloride administration remain poorly understood. We previously reported the findings of a before-and-after study of restrictive vs. liberal intravenous chloride administration in a tertiary intensive care unit (ICU). Although our study found a beneficial renal effect of restricting chloride administration [4], it was suggested that a Hawthorne effect induced by preparation and education for the before-and-after study may have accounted for these findings [5].

Accordingly, to mitigate the impact of such a putative Hawthorne effect, we extended the control and intervention periods of our study from 6 months to 1 year to include a longer control and intervention period, when the most common prescribers (ICU residents and fellows) had not received any specific training and simply rotated through the ICU when only low chloride fluids were available.

Materials and methods

Patient population and study design

This study was an extension of a prospective, open-label, before-and-after pilot study in the 22-bed multidisciplinary ICU of the Austin Hospital, a tertiary care hospital affiliated with the University of Melbourne. This extended study was approved by the local Human Research Ethics Committee (approval no. LNR/14/Austin/369). The design and outcomes of this study were described elsewhere in detail [4, 6]. To obtain a control period of similar duration and patient numbers, we prolonged the control period backward to include the preceding 6 months. This did not affect the study protocol as the control arm was a standard intravenous practice period without clinician awareness. All consecutive admissions during this 1-year period received intravenous fluids based on clinician preferences. These fluids included 0.9 % saline (chloride concentration 150 mmol/l) (Baxter Pty Ltd.), 4 % succinylated gelatin solution (chloride concentration 120 mmol/l) (Gelofusine, BBraun), and 4 % albumin in sodium chloride (chloride concentration 128 mmol/l) (4 % Albumex, CSL Bioplasma).

We similarly prolonged the intervention period by including the 6 months after the initial intervention. Thus, we maintained the chloride-restrictive intervention for an extra 6 months. For all consecutive admissions during this 1-year period, chloride-rich fluids (0.9 % saline, 4 % succinylated gelatin solution, or 4 % albumin solution) were only available after prescriptions by an intensive care specialist for specific conditions (e.g., hyponatremia, traumatic brain injury, and cerebral edema). Patients in the control group only received lactated crystalloid solution (chloride concentration 109 mmol/l) (Hartmann solution, Baxter Pty Ltd.), balanced buffered solution (chloride concentration 98 mmol/l) (Plasma-Lyte 148, Baxter Pty Ltd.), and 20 % albumin solution (chloride concentration 19 mmol/l) (20 % Albumex, CSL Bioplasma).

We collected key demographic data including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores, Simplified Acute Physiology Score II (SAPS II), and multiple clinical characteristics of each admission for all the additional patients enrolled. We similarly retrieved pre-ICU admission serum creatinine concentrations and daily morning creatinine concentrations during ICU admission from the computerized central laboratory database. Patients in this extended analysis had the same renal replacement therapy (RRT) initiation criteria as those of patients recruited into the Randomised Evaluation of Normal vs. Augmented Level (RENAL) replacement therapy in the ICU trial [7, 8].

The classification of a patient as requiring RRT excluded pre-existing end-stage kidney disease patients on long-term dialysis and patients treated with RRT for drug toxicity not associated with AKI.

The primary outcome for this extended study was the incidence of AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine definitions in keeping with the evolution [9]. Secondary outcomes included the need for RRT, length of stay in the ICU and hospital, and ICU and hospital survival. We defined baseline creatinine concentration as the lowest creatinine concentration available in the 1-month period prior to ICU admission; when a measurement was not available, we estimated the creatinine concentration using the Modification of Diet in Renal Disease (MDRD) equation (assuming a lower limit of normal baseline GFR of 75 ml/min) [10].

Statistical analysis

With 2,994 patients this study had >80 % power (two-sided P value of 0.01) to detect a difference in the proportion of patients with AKI of 5 % (20 vs. 15 %) and a difference in the proportion of patients requiring RRT of 3.5 % (10 vs. 6.5 %). Differences of this magnitude are perceived to be of clinical importance.

All statistical analysis was performed using Stata version 11 (StataCorp) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). We performed baseline comparisons using chi-square tests for equal proportion with results reported as numbers, percentages, and 95 % confidence intervals. Continuously normally distributed variables were compared using Student's t tests and presented as means (95 % CI) whilst non-normally distributed data were compared using Wilcoxon rank sum tests and presented as medians (interquartile range). Multivariate analysis of AKI (defined by KDIGO 2 or 3) and the need for RRT was determined using Cox proportional hazards regression, adjusting for the predefined covariates of sex, APACHE III score, diagnosis, operative status, diagnostic group, source of ICU admission, use of mechanical ventilation, admission type (elective or

emergency), and season. Results have been presented as cumulative incidence graphs with a corresponding comparison of groups performed using Gray's test [11].

We performed further sensitivity analysis by comparing outcomes during each 6-month period of this extended study: the original control, extended control, original intervention, and extended intervention periods. We compared the incidence of KDIGO-defined AKI stages 2 and 3 and the need for RRT among these four groups also adjusting for the above variables. To further determine if the treatment effect was consistent across periods, an interaction was fitted between treatment (intervention vs. control) and period (original vs. extended).

To reduce the chance of a type I error and increase the robustness of our findings, a two-sided P value of <0.01 was used to indicate statistical significance.

Results

We studied 2,994 patients: 1,476 during the control period and 1,518 during the intervention period. The baseline characteristics of the patients during the control and intervention periods are shown in Table 1. The two groups were similar with regard to age, sex, baseline creatinine concentration, APACHE scores, SAPS II, comorbidities, and types of admission but also differed for several variables including diagnostic grouping, source of ICU admission, and use of mechanical ventilation.

Table 2 shows the detailed composition of the study fluids. The intervention resulted in significant changes in fluid therapy. Saline prescription decreased from 4,700 to 139 l (97 % reduction; 3.2 vs. 0.09 l/patient; $P < 0.001$)

Table 1 Baseline characteristics of the patients during the control and intervention periods

	No. (%) [95 % CI] of patients[a]		*P*
	Control period (mid-August 2007 to 2008) (n = 1,476)	Intervention period (mid-August 2008 to 2009) (n = 1,518)	
Male sex	893 (61) [58–63]	947 (62) [60–65]	0.29
Mechanical ventilation	936 (63) [61–66]	1018 (67) [65–69]	0.04
Admission after elective surgery	467 (32) [29–34]	441 (29) [27–31]	0.12
Postoperative admission	755 (51) [49–54]	747 (49) [47–52]	0.29
Admission from			
Emergency department	326 (22) [20–24]	354 (23) [21–26]	0.42
Ward	245 (17) [15–19]	214 (14) [12–16]	0.06
Admission from other ICU	150 (10) [9–12]	203 (13) [12–15]	0.006
Diagnosis[b]			
Cardiovascular	541 (37) [34–39]	532 (35) [33–38]	0.36
Gastrointestinal	273 (18) [17–21]	255 (17) [15–19]	0.22
Metabolic	88 (6) [5–7]	78 (5) [4–6]	0.32
Neurological	93 (6) [5–8]	136 (9) [8–10]	0.006
Renal or genitourinary	53 (4) [3–5]	48 (3) [2–4]	0.52
Respiratory	204 (14) [12–16]	220 (14) [13–16]	0.60
Comorbidities[b]			
Severe sepsis or septic shock	113 (8) [6–9]	139 (9) [8–11]	0.14
Chronic lung disease	35 (2) [1–3]	35 (2) [1–3]	0.91
Chronic cardiovascular disease	42 (3) [2–4]	49 (3) [2–4]	0.54
Chronic liver disease	89 (6) [5–7]	81 (5) [4–7]	0.41
Chronic renal failure	59 (4) [3–5]	61 (4) [3–5]	0.98
Imunosuppression	52 (4) [3–5]	48 (3) [2–4]	0.58
Lymphoma	10 (1) [0–1]	14 (1) [0–2]	0.45
Metastatic cancer	48 (3) [2–4]	50 (3) [2–4]	0.95
Leukemia or myeloma	9 (1) [0–1]	18 (1) [1–2]	0.10
Mean (95 % CI)			
Age	61 (60–62)	61 (60–62)	0.91
APACHE II score (range 0–71)[c]	16 (15–16)	16 (16–16)	0.76
APACHE III score (range 0–300)[c]	58 (57–60)	57 (56–59)	0.44
SAPS II (range 0–163)[c]	33 (32–33)	33 (32–33)	0.90
Baseline creatinine level, μmol/l	119 (113–125)	112 (106–118)	0.08

APACHE Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *SAPS* Simplified Acute Physiology Score
SI conversion factor to convert creatinine to mg/dl, divide by 88.4

[a] The control period was from 18 August 2007 through 17 August 2008, and the intervention period was from 18 February 18 2009 through 17 February 2010

[b] According to the APACHE classification

[c] Higher scores indicate greater illness severity

Table 2 Composition of study fluids

	Saline	Hartmann	4 % Gelatin	Plasma-Lyte 148	4 % Albumin	20 % Albumin
Sodium	150	129	154	140	140	48–100
Potassium	0	5	0	5	0	0
Chloride	150	109	120	98	128	19
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

All concentrations in mmol/l

Table 3 Incidence of acute kidney injury stratified by the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria

	No. (%) [95 % CI] of patients[a]		*P* value
	Control period ($n = 1{,}476$)	Intervention period ($n = 1{,}518$)	
KDIGO classification			
Stage 1	253 (17.1) [15.3–19.1]	208 (13.7) [12.1–15.5]	0.009
Stage 2	87 (5.9) [4.8–7.2]	66 (4.3) [3.4–5.5]	0.05
Stage 3	215 (14.6) [12.9–16.5]	172 (11.3) [9.8–13.0]	0.008
Stages 2 and 3	302 (20.5) [18.5–22.6]	238 (15.7) [13.9–17.6]	<0.001
RRT	144 (9.8) [8.3–11.4]	103 (6.8) [5.6–8.2]	0.003

Values are number (%) [95 % CI]

[a] The control period was from 18 August 2007 through 17 August 2008, and the intervention period was from 18 February 2009 through 17 February 2010

and 4 % gelatin solution from 1,021 to 0 l (0.7 vs. 0 l/patient; $P < 0.001$). Conversely, Hartmann's solution prescription increased from 969 to 6,221 l (0.7 vs. 4.1 l/patient; $P < 0.001$) and Plasma-Lyte® prescription from 125 to 326 l (0.08 vs. 0.2 l/patient; $P < 0.01$). Finally, 4 % albumin use decreased from 688 to 146 l (0.5 vs. 0.1 l/patient; $P < 0.001$) and chloride-poor 20 % albumin use increased from 218 to 568 l (0.1 vs. 0.4 l/patient; $P < 0.001$).

The above changes in fluid therapy translated into a decrease in fluid-related chloride administration by a total of 263,660 mmol, from 694 to 501 mmol/patient over the 12-month period. Similarly, sodium administration decreased from 751 to 623 mmol/patient. In contrast, study fluid-related potassium administration increased from 3.7 to 21.6 mmol/patient and lactate administration from 19 to 119 mmol per patient. The incidence of severe hyperchloremia in both control and intervention periods is presented in eTable 1.

Over 12 months, the chloride-restrictive strategy was associated with a significantly lower incidence of moderate-to-severe (stages 2 and 3) KDIGO-defined AKI and a decrease in RRT use (Table 3). Cumulative incidence plots of both outcomes are presented in Figs. 1 and 2.

Compared with intervention, after adjusting for gender, APACHE III score, diagnosis, operative status, baseline serum creatinine concentration, diagnosis, source of admission, mechanical ventilation, admission type (elective or emergency), and season, the overall risk of stages 2 and 3 of KDIGO-defined AKI remained significantly greater [hazard ratio 1.32 (95 % CI 1.11–1.58); $P = 0.002$] during the control period as did RRT use [hazard ratio 1.44 (95 % CI 1.10–1.88); $P = 0.006$].

Sensitivity analyses after exclusion of patients who had baseline creatinine estimated with the MDRD equation and after exclusion of patients who had AKI on ICU admission are shown in eTable 2. Neither analysis altered our findings of a greater risk of AKI and RRT use.

eTable 3A shows the unadjusted incidence of KDIGO-defined AKI stages 2 and 3 and RRT use during the four 6-month periods of the extended study. eTable 3B shows the results of multivariate analysis for the risk of stages 2 and 3 of KDIGO-defined AKI and use of RRT for these four periods. There was a greater risk of KDIGO stages 2 and 3 AKI during the extended 6-month control period compared with the original 6-month control period but also during the 6-month extended intervention period compared with the original 6-month intervention period. These findings were confirmed by a significant interaction between treatment and period ($p = 0.01$) on multivariable analysis.

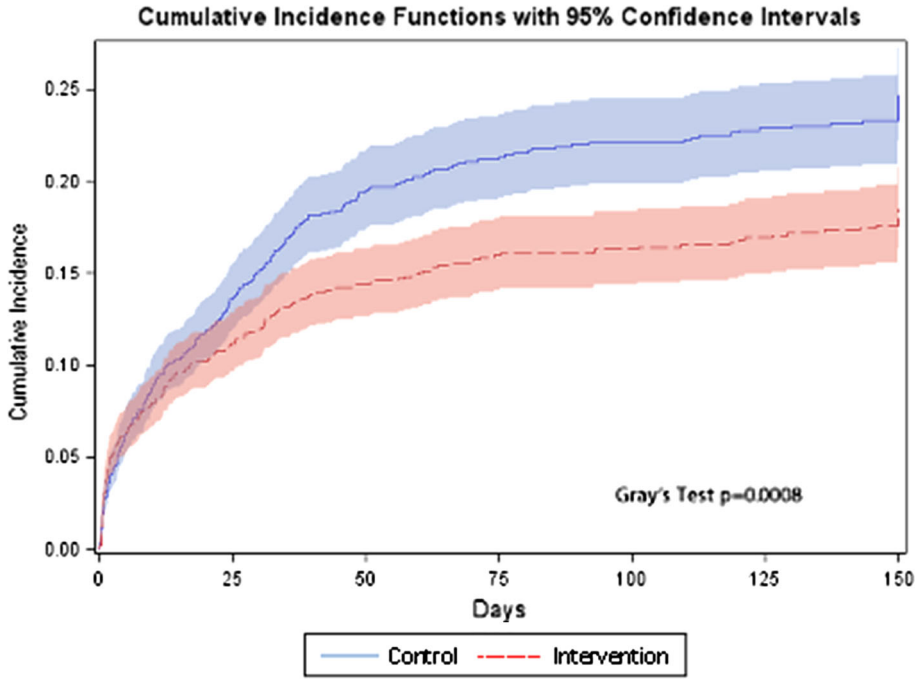

Fig. 1 Cumulative incidence of KDIGO-defined acute kidney injury stages 2 and 3

Mortality and length of stay

ICU mortality was 126 patients (9 %; 95 % CI 7–10 %) during the control period compared with 107 patients (7 %; 95 % CI 6–9 %) during the intervention period ($P = 0.13$). Hospital mortality was 220 patients (15 %; 95 % CI 13–17 %) during the control period vs. 193 patients (13 %; 95 % CI 11–15 %) during the intervention period ($P = 0.08$). Median ICU length of stay was 43 h (IQR 20–91 h) vs. 43 h (IQR 22–85 h), respectively ($P = 0.46$); median hospital length of stay was 11 days (IQR 7–21 days) vs. 11 days (IQR 7–21 days) ($P = 0.52$). There were no significant differences when comparing each 6-month extended and original control period and intervention periods with or without adjustment for the same key variables used in the multivariable model of KDIGO-AKI and use of RRT.

Discussion

Key findings

We aimed to test the robustness of the findings of a previous prospective, 6-month, open-label, sequential period pilot study where we found that restricting intravenous chloride in ICU patients decreased the incidence of acute kidney injury (AKI) and to assess for a possible seasonal or Hawthorne effect to explain them.

Accordingly, we extended our analysis to a 1-year period. We found that, even over a period of 1 year of continued chloride restriction, there was a persistent decrease in the incidence of AKI and RRT requirement. However, we also found evidence to suggest that other unidentified confounders may have also contributed to fluctuations in the incidence of AKI.

Comparison with previous studies

Our overall results confirm those of our previous study [4]. They are consistent with a number of studies showing better physiological renal outcomes with low-chloride fluids, albeit in different settings [2, 3]. They are also consistent with studies showing better clinical outcomes with low-chloride fluids. A large cohort study using an electronic administrative database of open abdominal surgery patients demonstrated a significantly lower requirement for dialysis after propensity-matching of 926 patients who received Plasma-Lyte® to 2,778 patients receiving saline [12].

A recent large retrospective observational study involving a data set of 22,851 surgical patients [13] detected a 22 % incidence of postoperative hyperchloremia, defined as serum chloride >110 mmol/l. In this study, 85 % of the patients with postoperative hyperchloremia were propensity-matched with patients who had normal postoperative serum chloride. The postoperative hyperchloremic group was found to have significantly higher risk of mortality at 30 days postoperatively, longer hospital stay, and postoperative renal dysfunction. Logistic regression analysis of the variables in the study also showed that hyperchloremia remained an independent predictor of 30-day mortality.

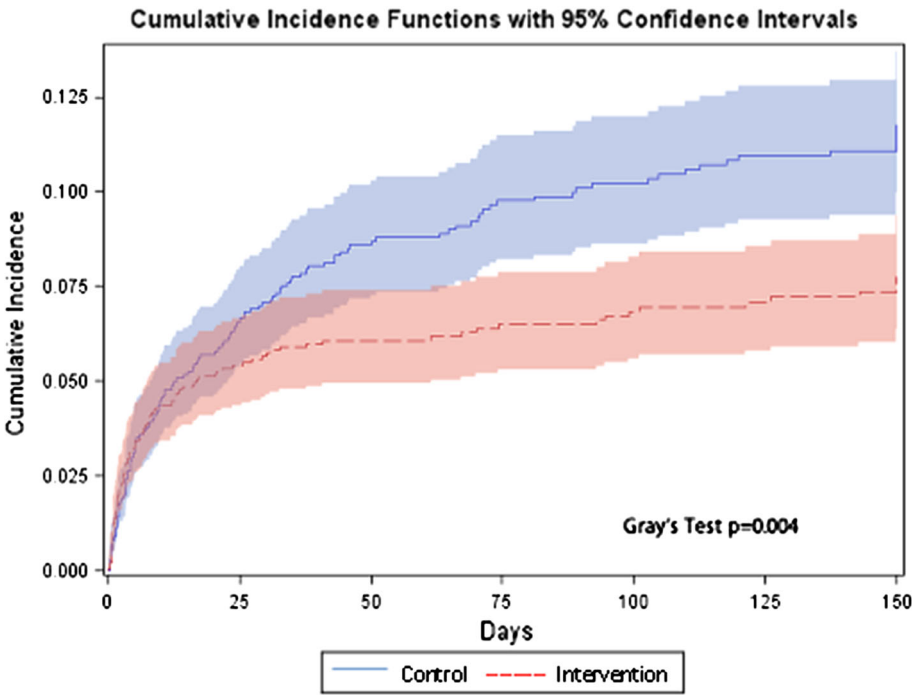

Fig. 2 Cumulative incidence of renal replacement therapy (RRT)

More recent studies have focused on the effect of sodium chloride-rich fluids on renal blood flow [14], their contribution to a positive fluid balance [15–17], and the increased risk of death associated with either the use of saline compared with balanced solutions in adults with severe sepsis [18] or higher intravenous chloride load during resuscitation in adults with SIRS [19].

Significance of the study findings

Our extended analysis shows that the positive renal outcomes resulting from the practice of restricting chloride-rich fluids in the ICU persisted even after doubling the observation period, suggesting a degree of robustness. However, they also show significant fluctuations over each 6-month period in the incidence of the outcomes of interest. The explanations for these findings may relate to unidentified confounders in patient characteristics and/or junior clinician expertise. They may also relate to a Hawthorne effect during the first 6 months of the intervention generated among nursing and medical staff by the knowledge that a novel nonblinded intervention was being applied to patient care. Finally, a combination of the above effects and/or other unidentified confounders may explain such 6-monthly fluctuations.

Strengths and limitations

This is an extension of a previous study to compare renal outcome changes associated with treatment using a chloride-restrictive approach vs. a chloride-liberal approach throughout the entire ICU stay. The changes in practice and separation in chloride therapy were clear with decreased overall chloride administration by more than a quarter million millimoles and a decrease in saline administration of 97 %.

We used the most recent consensus KDIGO criteria in analyzing incidence of AKI, and we continued to show significant differences in AKI severity when the control and intervention periods were extended from 6 to 12 months. The clinical relevance of this difference in AKI incidence was further supported by a decrease in the use of RRT.

The main limitation of our extended study is that, like the initial report, it represented an intervention that was neither randomized nor blinded. The complexity of blinding a bundle of care involving six different types of fluids in four different containers (bags and bottles) made blinding logistically impossible. Moreover, the non-blinded nature of our study is similar to that of other studies involving complex care in acutely ill patients [20, 21].

A further limitation of our study is its single-center, Australian academic tertiary care design that may not be generalizable to wider ICU practice. This study was further limited by the fact that patient follow-up was censored at hospital discharge, so our results pertaining to AKI and the need for renal replacement therapy cannot extend beyond the hospital stay.

We also did not collect information on the administration of chloride-rich fluid before or after ICU treatment. However, this study aimed to test whether a

chloride-restrictive policy in the ICU was associated with changes in renal function in the ICU. There are potential risks associated with restricting chloride-rich fluids and using isotonic fluids in patients with hyponatremia, alkalemia, cerebral edema, or traumatic brain injury. These considerations are acknowledged and are the reasons why some saline was prescribed during the intervention period to selected patients.

Adequate assessment of baseline creatinine is a known issue in the analysis of AKI [22]. In some patients, such information was absent, and we calculated the premorbid creatinine concentrations using the MDRD equation. This method has limitations. However, inaccuracies arising from its use are unlikely to have biased our results as they applied to both periods. In addition, the outcomes were objective and dependent on laboratory tests, which were not amenable to ascertainment bias or manipulation.

We are unable to identify the mechanisms responsible for the seasonal changes in renal outcomes demonstrated in the 6-monthly analysis. We can only speculate that there may have been unplanned and protocol-independent changes in the process of care, which altered such outcomes, or that undetected seasonal changes in patient characteristics or doctor characteristics may have occurred to explain such variation. Finally, the above factors or other factors that we cannot identify may, together, explain the observed changes in renal outcomes.

Conclusion

We conducted an extended assessment of the effects of restricting the use of chloride-rich fluids in a tertiary ICU and confirmed an overall decreased incidence of AKI and RRT requirement over a 1-year period. However, we also found that unidentified confounders or a Hawthorne effect may have contributed to some of our findings. Our observations continue to support the notion that chloride restriction is feasible and safe and that excess chloride administration may adversely affect renal function. However, they add uncertainty about the robustness of the observed benefits and provide a strong case in favor of conducting randomized controlled trials.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Myburgh JA, Mythen MG (2013) Resuscitation fluids. N Engl J Med 369:1243–1251
2. Chowdhury AH, Cox EF, Francis ST, Lobo DN (2012) A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9 % saline and Plasma-Lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 256:18–24
3. Chowdhury AH, Cox EF, Francis ST, Lobo DN (2014) A randomized, controlled, double-blind crossover study on the effects of 1-L infusions of 6 % hydroxyethyl starch suspended in 0.9 % saline (Voluven) and a balanced solution (Plasma Volume Redibag) on blood volume, renal blood flow velocity, and renal cortical tissue perfusion in healthy volunteers. Ann Surg 259:881–887
4. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M (2012) Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 308:1566–1572
5. Waikar SS, Winkelmayer WC (2012) Saving the kidneys by sparing intravenous chloride? JAMA 308:1583–1585
6. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK (2011) The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med 39:2419–2424
7. RENAL Study Investigators (2008) Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc 10:225–230
8. Bellomo R, Cass A, Cole L, Cass A, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S, RENAL Replacement Therapy Study Investigators (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627–1638
9. The KDIGO Acute Kidney Injury Work Group (2012) KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int 2(Suppl):1–138
10. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, Bellomo R, Kellum JA, AKI6 investigators (2010) A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transpl 25:3911–3918
11. Gray R (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141–1154
12. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA (2012) Major complications, mortality, and resource utilization after open abdominal surgery: 0.9 % saline compared to Plasma-Lyte. Ann Surg 255:821–829
13. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS (2013) Hyperchloremia after non-cardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg 117:412–421

14. Ke L, Calzavacca P, Bailey M, May CN, Li WQ, Bertolin J, Bellomo R (2014) Systemic and hemodynamic effects of fluid bolus therapy: sodium chloride versus sodium octanoate. Crit Care Resusc 16(1):29–33
15. Bihari S, Peake SL, Seppelt I, Wiliams P, Wilkins B, Bersten A (2013) Sodium administration in critically ill patients in Australia and New Zealand: a multicentre point prevalence study. Crit Care Resusc 15:294–300
16. Bihari S, Festa M, Peake SL, Seppelt I, Wiliams P, Wilkins B, Bersten A (2014) Sodium administration in critically ill paediatric patients in Australia and New Zealand: a multicentre point prevalence study. Crit Care Resusc 16:112–118
17. Gattas D, Saxena MK (2013) Is maintenance fluid therapy in need of maintenance? Crit Care Resusc 15:255–256
18. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK (2014) Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 42:1585–1591
19. Shaw AD, Raghunathan A, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR (2014) Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med 40:1897–1905
20. Sharek PJ, Parast LM, Leong K, Coombs J, Earnest K, Sullivan J, Frankel LR, Roth SJ (2007) Effect of a rapid response team on hospital-wide mortality and code rates outside the ICU in a children's hospital. JAMA 298:2267–2274
21. Chan PS, Khalid A, Longmore LS, Berg RA, Kosiborod M, Spertus JA (2008) Hospital-wide code rates and mortality before and after implementation of a rapid response team. JAMA 300:2506–2513
22. Cruz DN, Ricci Z, Ronco C (2009) Clinical review: RIFLE and AKIN—time for reappraisal. Crit Care 13(3):211