EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2017) doi: 10.1111/1742-6723.12821

ORIGINAL RESEARCH

Renal effects of an emergency department chloride-restrictive intravenous fluid strategy in patients admitted to hospital for more than 48 hours

Nor'azim Mohd YUNOS,[1,2] Rinaldo BELLOMO,[1,3,4] David McD TAYLOR,[4,5] Simon JUDKINS,[5] Fergus KERR,[5] Harvey SUTCLIFFE,[6] Colin HEGARTY[6] and Michael BAILEY[3]

[1]Department of Intensive Care, Austin Hospital, Melbourne, Victoria, Australia, [2]Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru, Malaysia, [3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [4]School of Medicine, The University of Melbourne, Melbourne, Victoria, Australia, [5]Emergency Department, Austin Hospital, Melbourne, Victoria, Australia, and [6]Department of Pathology, Austin Hospital, Melbourne, Victoria, Australia

Abstract

Objective: Patients commonly receive i.v. fluids in the ED. It is still unclear whether the choice of i.v. fluids in this setting influences renal or patient outcomes. We aimed to assess the effects of restricting i.v. chloride administration in the ED on the incidence of acute kidney injury (AKI).

Methods: We conducted a before-and-after trial with 5008 consecutive ED-treated hospital admissions in the control period and 5146 consecutive admissions in the intervention period. During the control period (18 February 2008 to 17 August 2008), patients received standard i.v. fluids. During the intervention period (18 February 2009 to 17 August 2009), we restricted all chloride-rich fluids. We used the Kidney Disease: Improving Global Outcomes (KDIGO) staging to define AKI.

Results: Stage 3 of KDIGO-defined AKI decreased from 54 (1.1%; 95% confidence interval [CI] 0.8–1.4) to 30 (0.6%; 95% CI 0.4–0.8) (P = 0.006). The rate of renal replacement therapy did not change, from 13 (0.3%; 95% CI 0.2–0.4) to 8 (0.2%; 95% CI 0.1–0.3) (P = 0.25). After adjustment for relevant covariates, liberal chloride therapy remained associated with a greater risk of KDIGO stage 3 (hazard ratio 1.82; 95% CI 1.13–2.95; P = 0.01). On sensitivity assessment after removing repeat admissions, KDIGO stage 3 remained significantly lower in the intervention period compared with the control period (P = 0.01).

Conclusion: In a before-and-after trial, a chloride-restrictive strategy in an ED was associated with a significant decrease in the incidence of stage 3 of KDIGO-defined AKI.

Key words: *acute kidney injury, chloride, emergency department, saline.*

Key findings

- A chloride-restrictive fluid strategy was successfully implemented in the ED of a university hospital.
- Such a chloride-restrictive fluid strategy in an ED was associated with a decrease in stage 3 KDIGO-defined AKI in patients admitted to the hospital for more than 48 h.
- Such a chloride-restrictive fluid strategy was not associated with changes in the need for renal replacement therapy.

Introduction

Intravenous fluids are commonly prescribed for the treatment of hospital patients, including ED patients. However, which i.v. crystalloid fluids should be used for such therapy remains controversial and is the subject of ongoing research.[1–4]

Most of the studies in this area have focused on surgical and critically ill patients.[5–7] Such studies have suggested that using balanced solutions and avoiding chloride-rich solutions may protect the kidneys from additional injury[5] or may reduce in-hospital mortality.[6,7] In this regard, a before-and-after study of restrictive *versus* liberal i.v. chloride fluid administration in a tertiary ICU,[8,9] showed an increased incidence of acute kidney injury (AKI) in the liberal i.v. chloride group. In contrast, a recent four-centre cluster randomised controlled trial showed no difference in AKI outcomes between chloride-liberal 0.9% saline and chloride-restrictive Plasma-Lyte 148 groups of critically ill patients.[10]

However, the above studies were affected either by marked confounding changes in the use of artificial colloids[8,9] or by the limited statistical power associated with a cluster trial

Correspondence: Dr Nor'azim Mohd Yunos, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 80100 Johor Bahru, Malaysia. Email: nor.azim@monash.edu

Nor'azim Mohd Yunos, MD, Intensivist; Rinaldo Bellomo, MD, FCICM, Intensivist, Director of Intensive Care Research; David McD Taylor, FACEM, Emergency Physician, Director of Emergency Medicine Research; Simon Judkins, FACEM, Emergency Physician; Fergus Kerr, FACEM, Emergency Physician; Harvey Sutcliffe, BSc, Systems Administrator; Colin Hegarty, BSc, Systems Administrator; Michael Bailey, PhD, Statistician.

Accepted 12 May 2017

design.[10] More relevant to this investigation, neither study addressed the impact of chloride restriction during fluid therapy for ED patients, another important cohort of patients who are exposed to significant fluid administration.

We hypothesised that a chloride-restrictive i.v. fluid strategy implemented in the ED might also be associated with decreased severity of AKI during hospital admission and conducted a before-and-after study to test this hypothesis.

Methods

Study design and setting

We conducted a prospective, open-label, before-and-after study in the ED of the Austin Hospital, a tertiary care hospital affiliated with the University of Melbourne. The local Human Research Ethics Committee approved the study and waived the need for informed consent (Reference: H2008/03445).

Study population

We included all consecutive adult admissions to the hospital through the ED during a 6 month control period (18 February 2008 to 17 August 2008) and a 6 month intervention period (18 February 2009 to 17 August 2009). Using the Austin Hospital Inpatient Separation Episodes Database, we excluded patients who had hospital admissions of less than 48 h, patients with either pre-existing end-stage kidney disease receiving chronic dialysis or pre-existing AKI at ED presentation (defined as Kidney Disease: Improving Global Outcomes [KDIGO] 2 or 3 on first serum creatinine reading in ED). We also excluded patients who were lost to follow up, that is patients with missing creatinine values. There were 468 such patients (7.7% of the original number) in the control group and 485 (7.8%) in the intervention group.

Study protocol

During the 6 month control period, the choice of i.v. fluids for all patients seen in the ED was based on clinician preferences. None of the clinicians was aware of the plan to subsequently restrict i.v. fluids to low chloride solutions. The types of fluids available included 0.9% saline (chloride concentration: 150 mmol/L) (Baxter, Old Toongabbie, NSW, Australia), lactated crystalloid solution (chloride concentration: 109 mmol/L) (Hartmann's solution, Baxter), balanced buffered solution (chloride concentration: 98 mmol/L) (Plasma-Lyte 148, Baxter) and succinylated gelatin solution (chloride concentration: 120 mmol/L) (Gelofusine, B. Braun, Melsungen, Germany).

We used the next 6 months as a 'washout period'. During this period, we announced the decision to remove chloride-rich fluids from ED practice and educated all ED staff on the shift in i.v. fluid practice to a chloride-restrictive approach.

During the 6 month intervention period, we then restricted the i.v. fluids used in the ED to low chloride solutions only. All patients seen in ED received either lactated crystalloid solution (chloride concentration: 109 mmol/L) (Hartmann's solution, Baxter) or balanced buffered solution (chloride concentration: 98 mmol/L) (Plasma-Lyte 148, Baxter).

During this period, chloride-rich fluids were now available only for specific conditions such as severe hyponatremia and traumatic brain injury and under prescription by an ED specialist.

The choice of i.v. fluids on the general hospital wards, following admission through the ED, was not modified and was left to clinician preferences.

Measurements and outcomes

We collected key demographic data including age, sex and admitting diagnosis of all the enrolled admissions. We retrieved pre-hospital admission serum creatinine concentrations and daily morning creatinine concentrations during hospital admission from the computerised central laboratory database.

The primary outcome was the incidence of AKI according to the KDIGO creatinine definitions during the hospital admission.[11] Secondary outcomes included the need for renal replacement therapy (RRT), length of stay in hospital and hospital survival. We defined baseline creatinine concentration as the lowest creatinine concentration available prior to hospital admission; when a measurement was not available, we estimated creatinine concentration using the Modification of Diet in Renal Disease (MDRD) equation (assuming a lower limit of normal baseline glomerular filtration rate of 75 mL/min).[12]

Data analyses

As sample size was determined by the number of patients admitted during two 6 month periods, the following power calculations have been performed retrospectively. With more than 4300 patients admitted to ED per 6 months, this study had an 87% power (two-sided *P*-value of 0.01) to detect a difference in the absolute proportion of patients with AKI of 1% (1% *vs* 2%) and a 90% power to detect an absolute difference in the proportion of patients requiring RRT of 0.7% (0.3% *vs* 1.0%). Differences of these magnitudes were judged to be both possible and of clinical importance.

All statistical analyses were performed using STATA version 11 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). We performed baseline comparisons using χ^2 tests for equal proportion with results reported as numbers, percentages and 95% confidence intervals (CIs). Continuous normally distributed variables were compared using Student's *t*-tests and presented as means (95% CI), while non-normally distributed data was compared using Wilcoxon signed-rank sum tests and presented as medians (interquartile range [IQR]). Outcomes were compared using Cox-proportional hazards regression for time to event analysis, logistic regression for binomial outcomes and linear regression for log-transformed lengths of stay, with results presented as hazard ratios (95% CI), odds ratios (95% CI) and geometric means (95% CI),

respectively. To account for competing risk, survival times are presented as cumulative incidence graphs with a corresponding comparison of groups performed using Gray's test.[13] Multivariable models were constructed adjusting for the pre-defined covariates; sex, age, diagnosis, surgical status, admission number per patient and baseline creatinine. To further account for repeat admissions, additional sensitivity analysis was conducted considering each patient's first admission only. Proportional hazard assumptions were assessed using log-log plots, while goodness of fit and model discrimination for logistic regression models were reported using Hosmer-Lemeshow test and area under receiver operating characteristic curve (95% CI), respectively. To increase the robustness of our findings, a two-sided *P*-value of 0.01 was used to indicate statistical significance.

TABLE 1. *Baseline characteristics of the patient admissions during the control and intervention periods*†

	Number (%) [95% CI] of admissions‡	
	Control period (n = 5008)	Intervention period (n = 5146)
Male	2692 (54) [52–55]	2754 (54) [52–55]
Surgical status§	1187 (23) [22–24]	1167 (24) [23–25]
Repeat admission	709 (14) [13–15]	807 (16) [15–17]
Diagnostic group		
Cardiology	412 (8.2) [7.5–9.0]	360 (7) [6–8]
Colorectal	161 (3.2) [2.8–3.7]	174 (3.4) [2.9–3.9]
Emergency	530 (10.6) [9.8–11.5]	546 (10.6) [9.8–11.5]
Endocrinology	50 (1) [0.8–1.3]	51 (1) [0.8–1.3]
General medicine	1244 (25) [24–26]	1198 (23) [22–24]
Haematology	71 (1.4) [1.1–1.8]	90 (1.7) [1.4–2.1]
Hepatobiliary	281 (5.6) [5.0–6.3]	305 (5.9) [5.3–6.6]
Infectious disease	54 (1.1) [0.8–1.4]	78 (1.5) [1.2–1.9]
Liver	90 (1.8) [1.5–2.2]	73 (1.4) [1.1–1.8]
Neurology	134 (2.7) [2.3–3.2]	136 (2.6) [2.2–3.1]
Neurosurgery	56 (1.1) [0.9–1.5]	66 (1.3) [1.0–1.6]
Oncology	249 (5) [4.4–5.6]	259 (5) [4.5–5.7]
Orthopaedics	267 (5.3) [4.7–6.0]	297 (5.8) [5.2–6.4]
Plastic surgery	128 (2.6) [2.2–3.0]	83 (1.6) [1.3–2.0]
Respiratory	221 (4.4) [3.9–5.0]	265 (5.1) [4.6–5.8]
Spinal	61 (1.2) [0.9–1.6]	63 (1.2) [1.0–1.6]
Stroke	239 (4.8) [4.2–5.4]	276 (5.4) [4.8–6.0]
Upper gastrointestinal	246 (4.9) [4.4–5.6]	289 (5.6) [5.0–6.3]
Urology	91 (1.8) [1.5–2.2]	83 (1.6) [1.3–2.0]
	Mean (95% CI)	
Age in years	63.9 (63.3–64.5)	63.2 (62.6–63.8)
Baseline creatinine (μmol/L)	86.5 (85.8–87.2)	86.0 (85.3–86.7)

†International System of Units conversion factor: to convert creatinine to mg/dL, divided by 88.4. ‡The control period was from 18 February 2008 to 17 August 2008, and the intervention period was from 18 February 2009 to 17 August 2009. §Had surgery during the admission. CI, confidence interval.

Results

Characteristics of study subjects

We studied 8638 patients experiencing 10 154 ED admissions: 4299 patients experiencing 5008 admissions during the control period and 4339 patients experiencing 5146 admissions during the intervention period. The baseline characteristics of the patients during the control and the intervention periods are shown in Table 1. The two groups were similar with regard to age, sex, admission diagnosis and baseline creatinine concentration. During the control period, 3216 admissions (64.2%; 95% CI 62.9–65.5) did not have a baseline creatinine level available and had the level estimated with the MDRD equation compared with 3294 admissions (64%; 95% CI 62.7–65.3) during the intervention period (P = 0.83).

Table 2 shows the composition of the study fluids. The intervention resulted in significant changes in i.v. fluid therapy in the ED. Overall, 0.9% saline prescription decreased from 7200 to 79 L (99% reduction; 1.4 *vs* 0.02 L/admission; P < 0.001) and 4% gelatin solution from 112 to 1.5 L (99% reduction, 0.02 *vs* 0.003 L/admission; P < 0.001). Conversely, Hartmann's solution prescription increased from 870 to 8217 L (89% increase, 0.2 *vs* 1.6 L/admission; P < 0.001) and Plasma-Lyte prescription from 49 to 230 L (79% increase, 0.001 *vs* 0.04 L/admission; P < 0.01), with an overall saving of AUD2143.4.

The above changes in fluid therapy translated into a decrease in fluid-related chloride administration by a total of 262 984 mmol, or from 238 to 181 mmol/admission over the 6 month period. Similarly, sodium administration decreased from 243 to 215 mmol/admission. In contrast, study fluid-related potassium

TABLE 2. *Composition and prices of study fluids*†

	0.9% Saline	Hartmann's solution	4% Gelatin	Plasma-Lyte 148
Sodium	150	129	154	140
Potassium	0	5	0	5
Chloride	150	109	120	98
Calcium	0	2	0	0
Magnesium	0	0	0	1.5
Lactate	0	29	0	0
Acetate	0	0	0	27
Gluconate	0	0	0	23
Octanoate	0	0	0	0
Price‡	$1.09/L	$1.06/L	$23/L	$2.15/L

†All concentrations in mmol/L. ‡All prices in AUD.

TABLE 3. *KDIGO definition and staging of AKI*[11]†

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥26.5 μmol/L increase within 48 h	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR increase in serum creatinine to ≥353.6 μmol/L OR initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria ≥12 h

†AKI is defined as any of the following: increase in serum creatinine by ≥26.5 μmol/L within 48 h; or increase in serum creatinine ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 h. AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio.

administration increased from 2.4 to 9 mmol/patient and lactate administration from 5 to 46 mmol/patient.

Primary outcomes

Table 3 shows the KDIGO definition and the staging of AKI.[11] The patients who were admitted to the ward for more than 48 h after receiving a chloride-restrictive fluid strategy in the ED had a statistically significant lower incidence of stage 3 KDIGO-defined AKI and a non-significant decrease in RRT use (Table 4). Cumulative incidence plots of both outcomes are presented in Figures 1 and 2.

Compared with the intervention period, the risk of stage 3 of KDIGO-defined AKI remained significantly greater during the chloride-rich control phase for both crude (hazard ratio 1.83; 95% CI 1.16–2.89; $P = 0.01$) and adjusted (hazard ratio 1.74; 95% CI 1.10–2.76; $P = 0.01$) levels. These findings were confirmed when analysed using logistic regression with crude odds ratio 1.86 (95% CI 1.19–2.91; $P = 0.01$) and adjusted odds ratio 1.81 (95% CI 1.14–2.85; $P = 0.01$). These findings remained significant when considering only first admissions to ED (Tables S1 and S2). Table S3 shows the simplified baseline characteristics of the stage 3 of KDIGO-defined AKI subgroup of patients, and the time to the stage 3 KDIGO-defined AKI event.

Secondary outcomes

A total of 210 patients died in hospital (4.9%; 95% CI 4.3–5.5) during the control period compared with 192 patients (4.4%; 95% CI 3.8–5.2) during the intervention period ($P = 0.31$). Median hospital length of stay was 4 days (IQR: 2–9 days) *versus* 4 days (IQR: 2–8 days), respectively ($P = 0.14$). Table S4 shows the secondary outcomes of the stage 3 of KDIGO-defined AKI subgroup of patients.

Discussion

Key findings

In a before-and-after study involving more than 8000 patients admitted to hospital through the ED of a tertiary hospital, we found that a chloride-restrictive fluid management approach was associated with a significant decrease in KDIGO stage 3 AKI.

Comparison with previous studies

To our knowledge, no interventional studies have assessed the renal effects of a chloride-restrictive i.v. fluid strategy for ED patients. The closest relevant study is a recent large retrospective cohort investigation that studied the initial fluid choice in the first two hospital days among more than 60 000 patients diagnosed with sepsis.[14] However, this study focused on in-hospital mortality instead of renal outcomes and found a significant association between a chloride-liberal initial fluid choice and higher mortality.

The reduced incidence of stage 3 KDIGO seen in our study is consistent with controlled double-blinded human studies that reported better renal cortical tissue perfusion

TABLE 4. *Incidence of acute kidney injury stratified by Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria*

KDIGO classification	Number (%) [95% CI] of events†		*P*-value
	Control period (*n* = 5008)	Intervention period (*n* = 5146)	
Stage 1	626 (12.5) [11.6–13.4]	703 (13.7) [12.8–14.6]	0.08
Stage 2	97 (1.9) [1.6–2.4]	99 (1.9) [1.6–2.3]	0.96
Stage 3	54 (1.1) [0.8–1.4]	30 (0.6) [0.4–0.8]	0.006
RRT	13 (0.3) [0.2–0.4]	8 (0.2) [0.1–0.3]	0.25

†The control period was from 18 February 2008 to 17 August 2008, and the intervention period was from 18 February 2009 to 17 August 2009. CI, confidence interval; RRT, renal replacement therapy.

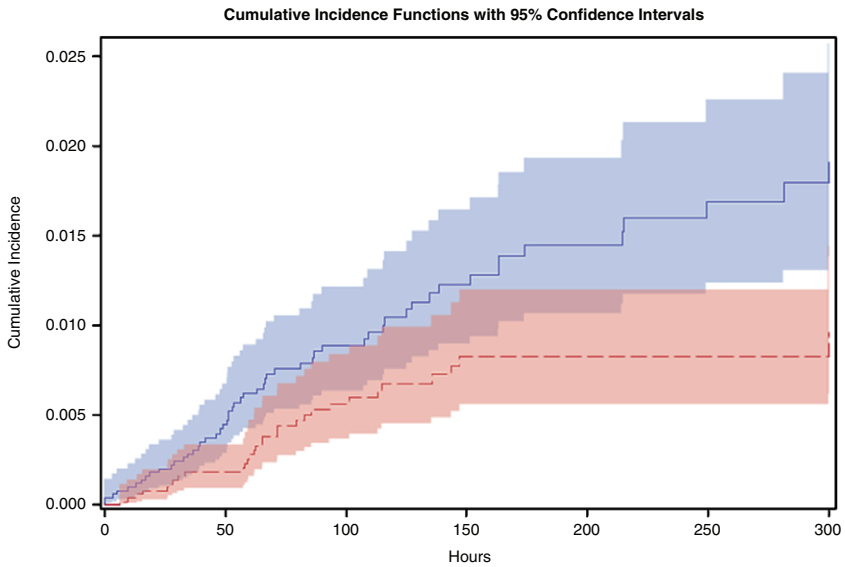

Figure 1. *Cumulative incidence of Kidney Disease: Improving Global Outcomes (KDIGO)-defined stage 3. Cumulative risk is low, <0.1%. Gray's test* P = *0.007. (—), Control; (- - -), intervention.*

with lower chloride fluids compared with saline.[15,16] It is also consistent with several previous observational clinical studies linking excessive chloride administration and chloride levels with increased risk of renal dysfunction or mortality.[5–9]

Significance of study findings

Our before-and-after study provides evidence to suggest that the initial fluid choice in the treatment of ED patients may have an impact on subsequent renal outcomes during their hospital stay. As such, it implies that ED implementation of a chloride-restrictive strategy may reduce the incidence of severe AKI (KDIGO stage 3). This observation adds to existing concerns with the use of 0.9% saline[17–20] and to the long list of studies that have highlighted worse outcomes[5–9,21] with 0.9% saline instead of balanced crystalloids. Our findings indirectly support the avoidance of chloride-rich gelatin solutions, also separately linked with unfavourable renal outcomes,[22] and, given the equivalent cost of lactated solutions, imply that there is no cost benefit of giving saline to ED patients. Thus, from a renal point view and a healthcare cost point of view, our study implies that there is no logical reason to administer saline to ED patients outside of specific indications.

Strengths of study

To our knowledge, this is the first study to compare the changes in renal outcomes associated with an i.v. fluid therapy strategy based on a chloride-restrictive approach *versus* a chloride-liberal approach in the ED setting. Moreover, the study population was large and the outcome difference remained significant after correction for baseline characteristics. Finally, the changes in i.v. fluid practice and the separation in the amount of chloride given were clear with decreased chloride administration by more than a quarter million millimoles and a decrease in saline administration of 99%.

Limitations

Our study had a number of important limitations. Our intervention was not a randomised controlled trial and was not blinded. However, there were no significant practice changes implanted in the ED of our institution during this before-and-after study and the baseline characteristics of our patients did not differ between the two groups. Furthermore, lack of blinding would not have biased the measurement of serum creatinine during the subsequent hospital stay.

A further limitation of our study was its single-centre design, which might have reduced its external validity. However, our ED has all the typical features of a tertiary hospital ED in the developed world, making our findings likely relevant to similar institutions. Our study also did not include the larger group of ED patients – those discharged on the same day or short hospital stay of less than 48 h – limiting its generalisability to all patients seen in ED.

We did not collect information on individual i.v. fluid administration

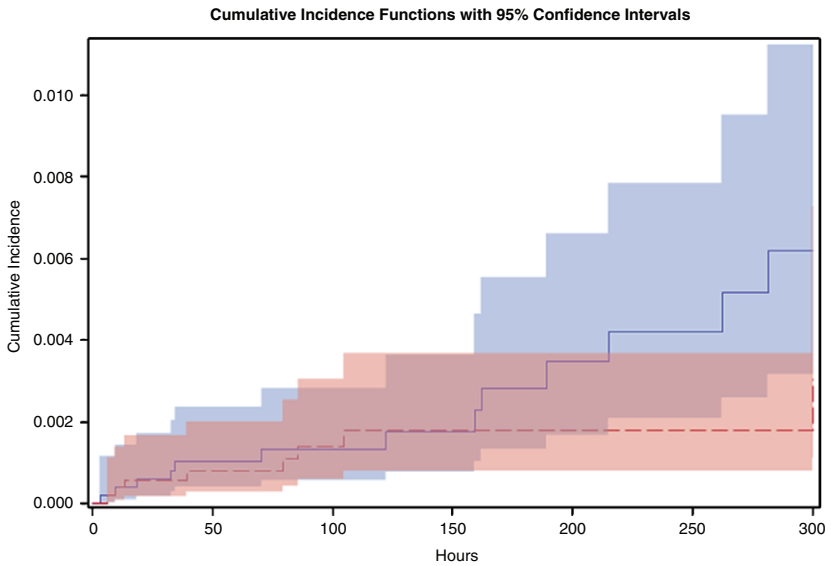

Figure 2. *Cumulative incidence of renal replacement therapy (RRT). Cumulative risk is low, <0.1%. Gray's test* P = *0.28. (—), Control; (- - -), intervention.*

and cannot exclude the potential confounding effects of succinylated gelatin solution on renal outcomes.[22–26] However, the change in gelatin use in our study represented only a total of 110.5 L (average decrease of approximately 22 mL/patient) and was much less than the >7100 L decrease in saline administration (average decrease of approximately 1.4 L/patient).

We did not collect information on i.v. fluids use after the transfer from ED to the ward. However, the present study aimed to test the hypothesis that even an early ED application of chloride-restrictive policy could result in changes in renal outcomes during hospital stay. Moreover, no general wards were notified of the study or requested to continue ED fluids as prescribed. We hope future studies will extend the analysis into the potential larger volume of fluids received during the hospital admissions.

The assessment of baseline creatinine is a recognised issue in the analysis of AKI.[27] In patients for whom such information was absent, we estimated the pre-morbid 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.

Conclusions

We conducted a before-and-after study comparing the renal effects of a chloride-restrictive *versus* a chloride-liberal i.v. fluid strategy in the ED setting. We found that, in ED patients admitted to the hospital for more than 48 h, a chloride-restrictive fluid strategy in ED was associated with a statistically significant decrease in the incidence of stage 3 KDIGO-defined AKI. However, we did not find any significant effect on need for RRT or mortality. Our observations from this large study of thousands of ED patients support ongoing concern about the renal safety of excessive i.v. chloride-rich fluid administration.

Acknowledgements

We acknowledge the Pathology Department for their kind assistance in obtaining the creatinine results required for this study and the Pharmacy Department for study fluid delivery, monitoring and reconciliation.

Author contributions

NMY co-designed the study, collected the data, analysed and interpreted the data, assisted with statistical analysis and wrote the manuscript. RB co-designed the study, analysed and interpreted the data, assisted with statistical analysis and edited the manuscript for content. DMT co-designed the study, provided administrative and technical support and edited the manuscript for content. SJ co-designed the study and provided administrative and technical support. FK co-designed the study and provided administrative and technical support. HS collected the data. CH collected the data. MB performed the statistical analysis and edited the manuscript for content.

Competing interests

RB has received consultancy fees from Baxter and B. Braun and grant money from Baxter. Both Baxter and B. Braun have also paid for RB's travel and accommodation, and meeting expenses.

References

1. Young P. Saline is the solution for crystalloid resuscitation. *Crit. Care Med.* 2016; **44**: 1538–40.
2. Semler MW, Rice TW. Saline is not the first choice for crystalloid resuscitation fluids. *Crit. Care Med.* 2016; **44**: 1541–4.
3. Reddy SK, Young PJ, Beasley RW *et al.* Overview of the study protocols and statistical analysis plan for the Saline versus Plasma-Lyte 148 for Intravenous Fluid Therapy (SPLIT) research program. *Crit. Care Resusc.* 2015; **17**: 29–36.
4. Glassford NJ, French CJ, Bailey M, Mårtensson J, Eastwood GM, Bellomo R. Changes in intravenous fluid use patterns in Australia and New Zealand: evidence of research translating into practice. *Crit. Care Resusc.* 2016; **18**: 78–88.
5. Shaw AD, Bagshaw SM, Goldstein SL *et al.* Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to

Plasma-Lyte. *Ann. Surg.* 2012; **255**: 821–9.
6. Raghunathan K, Shaw A, Nathanson B *et al.* Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. *Crit. Care Med.* 2014; **42**: 1585–91.
7. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. *Intensive Care Med.* 2014; **40**: 1897–905.
8. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566–72.
9. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. -chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med.* 2015; **41**: 257–64.
10. Young P, Bailey M, Beasley R *et al.* Effect of a buffered crystalloid solution vs. saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA* 2015; **314**: 1701–10.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int.* 2012; 2 (Suppl 1): 19–36.
12. Závada J, Hoste E, Cartin-Ceba R *et al.* A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol. Dial. Transplant.* 2010; **25**: 3911–8.
13. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann. Stat.* 1988; **16**: 1141–54.
14. Raghunathan K, Bonavia A, Nathanson BH *et al.* Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. *Anesthesiology* 2015; **123**: 1385–93.
15. Chowdhury AH, Cox EF, Francis ST, Lobo DN. 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.* 2012; **256**: 18–24.
16. Chowdhury AH, Cox EF, Francis ST, Lobo DN. 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.* 2014; **259**: 881–7.
17. Wakim KG. 'Normal' 0.9 percent salt solution is neither 'normal' nor physiological. *JAMA* 1970; **214**: 1710.
18. Yunos NM, Kim IB, Bellomo R *et al.* The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit. Care Med.* 2011; **39**: 2419–24.
19. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999; **90**: 1265–70.
20. Verma B, Luethi N, Cioccari L *et al.* A multicentre randomised controlled pilot study of fluid resuscitation with saline or Plasma-Lyte 148 in critically ill patients. *Crit. Care Resusc.* 2016; **18**: 205–12.
21. Rochwerg B, Alhazzani W, Sindi A *et al.* Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann. Intern. Med.* 2014; **161**: 347–55.
22. Pisano A, Landoni G, Bellomo R. The risk of infusing gelatin? Die-hard misconceptions and forgotten (or ignored) truths. *Minerva Anestesiol.* 2016; **82**: 1107–14.
23. Schick MA, Isbary TJ, Schlegel N *et al.* The impact of crystalloid and colloid infusion on the kidney in rodent sepsis. *Intensive Care Med.* 2010; **36**: 541–8.
24. Simon TP, Schuerholz T, Hüter L *et al.* Impairment of renal function using hyperoncotic colloids in a two hit model of shock: a prospective randomized study. *Crit. Care* 2012; **16**: R16.
25. Bayer O, Schwarzkopf D, Doenst T *et al.* Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – a prospective sequential analysis. *Crit. Care Med.* 2013; **41**: 2532–42.
26. Bayer O, Reinhart K, Kohl M *et al.* Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance and patient outcomes in patients with severe sepsis: a prospective sequential analysis. *Crit. Care Med.* 2012; **40**: 2543–51.
27. Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN – time for reappraisal. *Crit. Care* 2009; **13**: 211.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1. Cox-Proportional Hazards regression analysis of stage 3 of KDIGO-defined AKI and use of RRT after exclusion of repeat admissions (adjusted for sex, age, diagnosis, surgical status, admission number per patient and baseline creatinine).
Table S2. Logistic regression analysis of stage 3 of KDIGO-defined AKI and use of RRT after exclusion of repeat admissions (adjusted for sex, age, diagnosis, surgical status, admission number per patient and baseline creatinine).
Table S3. Simplified baseline characteristics and time to event of the stage 3 KDIGO-defined AKI patients.
Table S4. Secondary outcomes of the stage 3 KDIGO-defined AKI patients.