Addressing the inadvertent sodium and chloride burden in critically ill patients: a prospective before-and-after study in a tertiary mixed intensive care unit population

Shailesh Bihari, Shivesh Prakash, Simon Potts, Elisha Matheson and Andrew D Bersten

ABSTRACT

Background: Inadvertent fluid loading — and resultant sodium and chloride — is common in critically ill patients. Sources such as fluid used as vehicles for drug infusions and boluses (fluid creep) and maintenance fluid are a common cause. We hypothesised that total sodium and chloride loading can be safely reduced in critically ill patients both by the use of 5% glucose as a diluent for infusions and boluses, when possible, and by its use as a maintenance fluid.

Methods: This was a prospective before-and-after study design in a single centre tertiary mixed intensive care unit (ICU). Comprehensive data about patient demographics, sources of fluid, feeds, intravenous drugs, fluid balance and electrolyte levels were collected for 4 weeks before and after the intervention (2016 and 2017). The amount of administered sodium was estimated from these sources.

Results: There were 146 patients (643 study days) and 133 patients (684 study days) examined in 2016 and 2017 respectively. The change of practice lead to an increase in the use of 5% glucose as the maintenance fluid and as a diluent, which resulted in a decrease in the total daily administered sodium from a median of 197 mmol (interquartile range [IQR], 155–328 mmol) to a median of 109 mmol (IQR, 77–288 mmol) ($P = 0.0001$). It also resulted in decrease in daily fluid balance, plasma chloride and ICU-acquired hypernatraemia.

Conclusions: It is safely possible to decrease the total sodium and chloride loading to ICU patients by intervening on fluid creep and on maintenance fluid types. This intervention was accompanied by favourable changes in serum electrolyte and fluid balance.

Crit Care Resusc 2018; 20 (4): 285-293

Inadvertent fluid and resultant sodium and chloride loading is common in critically ill patients.[1-3] The sources are often unintended and include fluids used as a diluent for drug infusions and boluses (fluid creep) and fluids used for maintenance and replacement purposes. These sources also account for more than half of the daily administered fluid volume in critically ill patients.[1]

Almost universally, the common fluid used as a diluent for drug infusions and boluses is 0.9% saline.[2] Similarly, 0.9% saline and other isotonic fluids are the most commonly used maintenance fluid.[4] These sources contribute to a high daily sodium and chloride load.[1-3] Much of the research done in the past couple of decades has focused on resuscitation fluid types and regimens;[5-7] however, their overall contribution to the total administered fluid and fluid balance is relatively small.[1,8,9]

These often obscure and inadvertent sources lead to a high sodium and chloride load and resultant positive balance in critically ill patients, which has been associated with respiratory[8,10] and electrolyte dysbalances such as increases in serum sodium[11] and chloride.[12,13] Isotonic fluid usage, such as 0.9% saline, as a maintenance fluid is often used due to the concern of hyponatraemia in paediatric patients.[14-16] This concern has been extrapolated to the routine use of isotonic fluids in the adult setting.[17] Moreover, there are other justifiable reasons, such as drug compatibility, but there are also reasons with little scientific rationale, such as availability in convenient packaging and historical practice.

We hypothesised that total sodium loading can be safely reduced in critically ill patients by the use of 5% glucose as a diluent for infusions and boluses, when possible, and its use as a maintenance fluid.

We designed a before-and-after study to examine the total fluid and sodium load, fluid balance and the resultant effect on serum electrolytes in a single centre tertiary level intensive care unit (ICU). The proposed intervention was introduced as a practice change in the ICU.

Methods

We conducted a prospective before-and-after study with measurements made before and after practice change at a single centre tertiary ICU with a mixed population. The study was approved by the Southern Adelaide clinical human research ethics committee (approval no. 475.14). The data were recorded over 4 consecutive weeks in March 2016 (before phase) and in June 2017 (after phase).

During these time periods, we recorded daily data from all patients in the ICU, which included sources of fluid administration such as boluses, maintenance and

replacement fluid, fluid used as a diluent for boluses or infusions, and fluid used as flush for catheter-based intravascular devices, details of all intravenous drugs, details of total enteral and parenteral nutrition and whether patients were allowed oral intake. Daily highest sodium, chloride and bicarbonate levels were recorded. Daily data were collected about total fluid administered, urine output and fluid balance in these patients. Finally, demographic data — including type of admission, admission severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II and III), admission renal function, requirement for interventions such as invasive mechanical ventilations and renal replacement therapy (on the study day), and all ICU and hospital-based outcomes — were recorded.

As we also wanted to examine the safety of this intervention, we specifically examined the effects on electrolyte levels, as the use of hypotonic fluids has been observed to cause hyponatraemia in a paediatric population.[14-16] To study the safety of this intervention, we separately examined the total use of insulin (to examine the effect on blood sugar levels), vasopressors usage and dosage (to examine the effect on shock, as the use of isotonic fluids has shown to affect aldosterone levels),[18] and use of diuretics (to examine its role in fluid balance and dyselectrolytaemia).

Sodium values from various sources were individually calculated from previously published values.[3] These sources were separated as boluses, maintenance fluid, infusions and boluses, antibiotics, flushes and feeds (both enteral and parenteral) as done previously.[2,3,19]

Implementation of the practice change was a challenging aspect of this study. Intensive and repeated teaching and in-service education were completed for ICU doctors and nurses both for the use of diluent (for drug infusions and boluses) and of the default maintenance fluid. One hurdle that we faced was the non-availability of a licenced 5% glucose in 10 mL plastic vial in Australia, unlike 0.9% saline vials, which are available in 10 mL plastic vials, providing for a convenient diluent. To overcome this problem, we used 500 mL bags of 5% glucose. These were hung at each

Table 1. Demographic profile, admission biochemistry, study intervention and patient-related outcomes during the study period in 2016 and 2017

Variables	2016	2017	*P*
Patient number	146	133	
Study days	643	684	
Age (years), median (IQR)	62.0 (51.0–73.3)	60.0 (49.0–71.8)	0.71
Weight (kg), median (IQR)	80 (70–90)	80 (70–90)	0.51
Male	87 (60%)	72 (54%)	0.39
Medical admission	87 (60%)	93 (70%)	0.08
Surgical admission	59 (40%)	40 (30%)	
APACHE II, median (IQR)	18 (14–23)	17 (13–21)	0.46
APACHE II ROD, median (IQR)	0.21 (0.09–0.42)	0.21 (0.11–0.37)	0.99
APACHE III, median (IQR)	66 (48–77)	60 (46–76)	0.90
APACHE III ROD, median (IQR)	0.15 (0.05–0.27)	0.16 (0.05–0.32)	0.31
Biochemistry and interventions			
Serum albumin on admission (g/L), median (IQR)	28 (24–31)	27 (23–30)	0.34
Serum urea on admission (mmol/L), median (IQR)	8 (5–12)	7 (5–10)	0.56
Serum creatinine on admission (μmol/L)	103 (68–177)	98 (65–171)	0.87
IMV on study day	328 (51%)	363 (53%)	0.47
RRT on study day	90 (14%)	89 (13%)	0.63
Patient outcome			
ICU LOS (hours), median (IQR)	90 (55–187)	92 (43–207)	0.72
Alive at ICU discharge	137 (94%)	125 (94%)	0.79
Hospital LOS (hours), median (IQR)	404 (222–601)	321 (165–592)	0.18
Alive at hospital discharge	120 (82%)	114 (86%)	0.45

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IMV = invasive mechanical ventilation. IQR = interquartile range. LOS = length of stay. ROD = risk of death. RRT = renal replacement therapy.

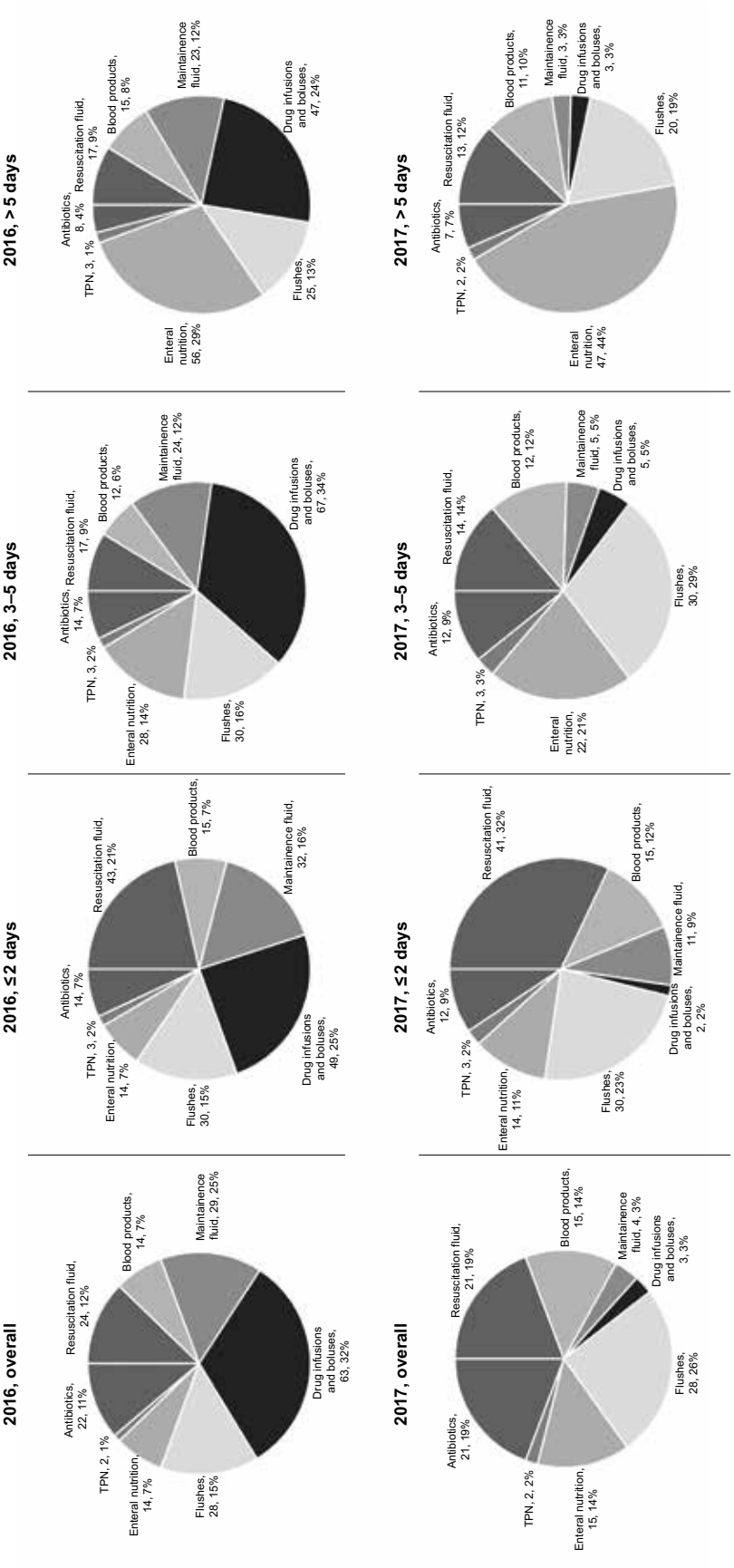
bedside and accessed by a nurse via a one-way chemical and microbiological valve (61-CS-15 CLAVE connector). Any time a diluent for drug infusion or bolus or a flush was required and when compatibility permitted, the valve was accessed by nurse following standard aseptic techniques. These bags were changed every 8 hours. For the convenience of the nursing staff, with the help of the ICU pharmacist and with drug compatibility data, we also used bedside signage and a poster detailing what commonly used drugs are compatible with 5% glucose. This information was double checked on two independent references.[20,21] The notable exceptions were phenytoin and insulin, for which, although physically compatible, a therapeutic incompatibility exists (Appendix, online at cicm.org.au/Resources/Publications/Journal). Rarely, if the drug compatibility was not known, then the use of the diluent that was considered safe or routine was allowed in consultation with the ICU pharmacist. Finally, all the doctors had separate training sessions about the

Table 2. Daily administered fluid, urine output, fluid balance, fluid types and amount, and specific details of the use of insulin, noradrenaline and frusemide between the study years

Variable	2016	2017	*P*
Study days	643	684	
Total daily administered fluid (mL), median (IQR)	2183 (1591–2793)	2138 (1692–2680)	0.87
Daily urine output (mL), median (IQR)	1705 (1080–2495)	1893 (1216–2675)	0.02
Daily fluid balance (mL), median (IQR)	393 (–560 to 1217)	201 (–588 to 956)	0.04
Resuscitation fluid	298 (46%)	301 (44%)	0.41
Amount (mL), median (IQR)	500 (200–750)	500 (200–700)	0.65
Type of resuscitation fluid			
4% albumin	174 (58%)	171 (57%)	0.74
20% albumin	71 (24%)	96 (32%)	0.03
CSL	13 (4%)	21 (7%)	0.21
0.9% saline	13 (4%)	7 (2%)	0.18
Blood products	84 (13%)	82 (12%)	0.56
Maintenance fluid	365 (57%)	376 (55%)	0.58
Amount (mL), median (IQR)	1140 (660–1440)	1110 (655–1450)	0.68
Type of maintenance fluid			
5% glucose	25 (7%)	321 (85%)	< 0.001
4% glucose + 0.18 saline	285 (78%)	8 (2%)	< 0.001
CSL	12 (3%)	30 (8%)	0.006
0.9% saline	38 (10%)	8 (2%)	< 0.001
Oral feed on study day	206 (32%)	212 (31%)	0.72
Enteral feeding	199 (31%)	219 (32%)	0.68
Amount (mL), median (IQR)	1120 (685–1440)	1200 (675–1480)	0.58
Parenteral feeding	32 (5%)	27 (4%)	0.42
Amount (mL), median (IQR)	1230 (959–1512)	1280 (923–1414)	0.26
Arterial line	624 (97%)	657 (96%)	0.37
Central line	559 (87%)	609 (89%)	0.27
IV infusion and bolus	630 (98%)	670 (98%)	1.00
Amount (mL), median (IQR)	422 (217–700)	415 (206–697)	0.22
Insulin (50 U/50 mL)	225 (35%)	226 (33%)	0.48
Amount (mL), median (IQR)	24 (16–40)	23 (12–48)	0.65
Noradrenaline (6 mg/100 mL)	244 (38%)	233 (34%)	0.15
Amount (mL), median (IQR)	83 (32–206)	84 (33–170)	0.18
Frusemide	116 (18%)	185 (27%)	< 0.001

CSL = compound sodium lactate (Hartmann's solution). IQR = interquartile range. IV = intravenous.

Figure 1: Contribution to daily sodium loading from sources of sodium from bolus fluid, maintenance fluids, fluids used as drug boluses and infusions, antibiotics, flushes, and enteral and parenteral nutrition*



* There was a decrease in the amount of sodium administered as maintenance fluid and as drug infusions and boluses, resulting in a significant reduction in the total amount of sodium administered from 2016 to 2017. Each source is presented as the average daily amount of sodium administered (mmol) and its contribution to the daily amount (%).

change of practice and the use of 5% glucose as the default maintenance fluid instead of 4% glucose and 0.18% saline, which was the routine practice at that time (2016), unless contraindicated by a specific patient condition, such as traumatic brain injury, diabetic ketoacidosis, or severe electrolyte imbalances, or in the opinion of the clinician, it was not in the best interest of the patient.

Statistical analysis

This was a prospective before-and-after study design. Data are presented as mean (standard deviation [SD]), median (interquartile range [IQR]) or as a percentage, as appropriate for the data type. Data were log-transformed when necessary. Comparison was made through the use of standard parametric and non-parametric statistical methods. $P < 0.05$ was considered significant.

Results

There were 146 patients examined in 2016 and 133 patients in 2017, contributing to 643 and 684 study days in 2016 and 2017, respectively. There was no difference in baseline demographics, admission biochemistry, severity of illness, or requirement for intervention on the study day between the two patient groups (Table 1). Overall, patient-related outcomes were similar between the groups. Complete 24-hour data were not available in 116 (18%) and 115 (17%) study days in 2016 and 2017, respectively. On these days, data were available for a median of 19 h (IQR, 16–22 h) and 20 h (IQR, 16–23 h), respectively.

The daily administered fluid volume was similar between the years, but there was an increase in urine output and a resultant less positive fluid balance in 2017. This was accompanied by an increase in the use of diuretics in 2017 (Table 2). There was no difference between the fluid bolus volumes or in the number of patients it was administered, with 4% albumin being the most commonly used fluid, but in 2017 there was a small increase in the use of 20% albumin (Table 2). There was no difference between the number and the volume of maintenance fluid used between the time periods. However, there was a significant increase in the use of 5% glucose in 2017 and a simultaneous decrease in the use of 4% glucose and 0.18% saline (Table 2), whereas the use of other fluids, such 0.9% saline and Hartmann's solution, was relatively low in both groups.

The amount of fluid used daily as a diluent (vehicle) for infusions and boluses (fluid creep) was more than 400 mL in both time periods (Table 2), but there was increased use of 5% glucose (95%) as the vehicle in 2017, instead of 0.9% saline (99%) in 2016. Finally, there was no difference in the amount of vasopressors and insulin used between the study periods.

There was a significant decrease in the amount of total administered sodium in 2017 by around 100 mmol per day (Table 3). This reduction was even more significant when patients who were not having oral feeds were examined separately. The decrease was a result of less contribution of sodium from sources such as the vehicle used for infusion and boluses (63 mmol [32%] to 3 mmol [3%]) and from maintenance fluid (29 mmol [15%] to 4 mmol [3%]) (Figure 1). The contribution of sodium from resuscitation fluid was relatively small in both years (Figure 1). This difference was maintained throughout the stay in the ICU (Figure 1).

Overall, there was no significant decrease in plasma sodium levels between 2016 and 2017 (Table 3). Similarly, there was no difference either in the rate or level of hyponatraemia (< 135 mmol/L) between the years (Table 3). The rate of severe hyponatraemia was relatively small with plasma sodium < 130 mmol/L (11 episodes in 2016 and 13 in 2017) and < 125 mmol/L (four episodes in 2016 and one in 2017) in both time periods. While examining hypernatraemia, there was no difference between the number of patients between the years; however, there was a trend towards a lower value in patients who developed it in 2017 (Table 3).

There was a significant reduction in plasma chloride level in 2017 compared with 2016 (Table 3), and this was accompanied by a reduction both in the number and level of hyperchloraemia in 2017. There was also an increase in plasma bicarbonate level in 2017 (Table 3).

We also examined the data on day of stay in ICU as early (≤ 2days), medium (3–5 days) and long stay (> 5 days) (Table 4). Although there was no difference in the amount of fluid administered during these study time periods, there was a difference in the urine output and fluid balance between 2016 and 2017 in patients who stayed in the ICU for more than 5 days (Table 4). The amount of administered sodium was lower in 2017 across all time periods (Table 4). There was also a difference in the plasma concentration of sodium (decrease in plasma concentration with long stay in the ICU), chloride (decrease in plasma concentration across all time periods) and bicarbonate levels (increase in plasma concentration with medium and long stay) between 2016 and 2017 (Table 4).

Discussion

In a prospective before-and-after study design, we showed a decrease in the amount of administered sodium in critically ill ICU patients. This was accompanied by an increase in urine output, a decrease in positive fluid balance and an increase in the use of diuretics. Despite an increase in the use of diuretics, there was a decrease in ICU-acquired hypernatraemia, hyperchloraemia and increase in serum bicarbonate levels.

We showed that this practice change of using 5% glucose, both as the routine maintenance fluid and as a vehicle of drug infusion and boluses, can result in a

sustained decrease in the total amount of administered sodium in critically ill ICU patients without any observed adverse associations. Though not directly measured, this result will also be accompanied by a reduction of daily administered chloride.

The rationale of this study was the knowledge that critically ill ICU patients receive more than 200 mmol of sodium daily,[1-3] the major source of which was not resuscitation fluid but inadvertent sources such as vehicle for infusions and boluses (fluid creep), with a contribution from maintenance fluids. These sources also contribute to a high daily chloride burden in critically ill patients.[1] Changing the unit practice to the default use of 5% glucose led to a significant reduction in the total daily administered sodium values. In addition, an increase in the use of salt-poor albumin in 2017 could have also contributed, though the total contribution from the bolus fluids was similar between the years.

Our study also underscores the safety of the use of 5% glucose for fluid creep and maintenance fluid, as it did not cause hyponatraemia. Similar findings have been reported in fasting adult volunteers receiving hypotonic fluids.[18] Likewise, there was no difference in the use of vasopressors or insulin with the practice change. Increases in plasma sodium[22-25] and chloride,[26-30] particularly during ICU stay,[22-25] have been associated with worse clinical outcomes. Mitigation of these changes could lead to better patient-centred outcomes and this should be measured in future studies.

Positive fluid balance has been associated with poor outcomes in critically ill patients,[31-33] and this change of practice was associated with reduced positive fluid balance and an increase in urine output in ICU patients, especially in the long-stay ones. There could be multiple possible reasons for this finding. First, there was a greater use of diuretics in 2017. Relatively smaller increments in serum sodium in 2017 may have allowed for safer use of diuretics, which is otherwise limited due to development of hypernatraemia.[34] Second, isotonic fluids are excreted more slowly than an equal amount of hypotonic fluid,[18,35-37] leading to an increase in fluid balance. Finally, a decrease in serum chloride could have a beneficial effect on renal function [27-30] and urine output, with resultant less positive fluid balance.

A decrease in the amount of administered sodium and a decrease in positive fluid balance (increase in urine output) could have resulted in a decreased positive sodium balance. Previously, we observed that in mechanically ventilated, critically ill ICU patients, by Day 3, sodium balance exceeded 700 mmol, which had associations with adverse respiratory function and tissue oedema.[8] Positive pressure ventilation initiates complex neurohormonal changes that lead to sodium and water retention.[38] The effect of sodium restriction on sodium balance should be examined in future studies in this cohort of patients. This study highlights the

Table 3. Daily administered sodium, serum sodium (including hyponatraemia and hypernatraemia), chloride (hyperchloraemia and hypochloraemia) and bicarbonate levels during the study period in 2016 and 2017

Variable	2016	2017	*P*
Sodium administration			
Sodium administered in 24 h (mmol), median (IQR)	197 (155–328)	109 (77–288)	0.0001
Sodium administered in patients not having oral feeds (mmol), median (IQR)	232 (177–356)	125 (101–254)	0.0001
Plasma electrolytes			
Plasma sodium (mmol/L),* median (IQR)	141 (137–144)	140 (137–144)	0.70
▸ Plasma sodium < 135 mmol/L	68 (11%)	79 (12%)	0.59
▸ Plasma sodium < 135 mmol/L, median (IQR)	132 (129–133)	132 (131–133)	0.26
▸ Plasma sodium > 145 mmol/L	99 (16%)	112 (17%)	0.65
▸ Plasma sodium > 145 mmol/L, median (IQR)	148 (146–150)	147 (146–149)	0.08
Plasma chloride (mmol/L),† median (IQR)	105 (101–109)	100 (97–104)	0.0001
▸ Plasma chloride < 96 mmol/L	49 (8%)	73 (11%)	0.07
▸ Plasma chloride < 96 mmol/L, median (IQR)	94 (90–95)	93 (91–94)	0.22
▸ Plasma chloride > 106 mmol/L	222 (36%)	95 (14%)	0.0001
▸ Plasma chloride > 106 mmol/L, median (IQR)	110 (108–112)	110 (107–112)	0.36
Plasma bicarbonate (mmol/L),‡ median (IQR)	25 (23–28)	26 (24–29)	0.008

IQR = interquartile range. * Values available for 618/643 study days (96%) in 2016 and 660/684 study days (96%) for 2017. † Values available for 618/643 study days (96%) in 2016 and 660/684 study days (96%) for 2017. ‡ Values available for 618/643 study days (96%) in 2016 and 659/684 study days (96%) for 2017

Table 4: Daily administered fluid, urine output, fluid balance, administered sodium and serum electrolytes divided in duration of stay as early (≤ 2 days), medium (2–5 days) and long (> 5 days) in the intensive care unit in 2016 and 2017

Days of stay	≤ 2 days			3–5 days			> 5 days		
	2016	**2017**	***P***	**2016**	**2017**	***P***	**2016**	**2017**	***P***
Study days	236	228		156	172		251	284	
Daily administered fluid (mL), median (IQR)	2180 (1453–2839)	2049 (1399–2624)	0.28	2253 (1669–2751)	2217 (1757–2743)	0.57	2023 (1807–2625)	2124 (1844–2651)	0.59
Daily urine output (mL), median (IQR)	1570 (1021–2303)	1350 (866–2421)	0.76	2015 (1190–3139)	1980 (1264–2874)	0.63	1975 (1456–2590)	2340 (1547–2996)	0.01
Daily fluid balance (mL), median (IQR)	645 (–278 to 1332)	502 (–310 to 1253)	0.58	215 (–834 to 934)	203 (–638 to 903)	0.47	222 (–856 to 674)	49 (–902 to 535)	0.02
Daily administered sodium (mmol/L), median (IQR)	200 (163–340)	128 (88–296)	< 0.01	195 (152–320)	102 (70–276)	< 0.01	194 (141–308)	106 (64–256)	< 0.01
Serum sodium (mmol/L), median (IQR)	140 (136–144)	140 (137–142)	0.89	140 (137–145)	140 (136–144)	0.33	143 (138–148)	141 (137–145)	0.04
Serum chloride (mmol/L), median (IQR)	103 (99–108)	102 (98–106)	0.09	105 (101–108)	100 (96–104)	< 0.01	108 (103–110)	100 (97–104)	< 0.01
Serum bicarbonate (mmol/L), median (IQR)	25 (22–27)	24 (21–27)	0.92	25 (23–28)	26 (23–29)	0.02	25 (23–30)	27 (24–31)	0.01

IQR = interquartile range.

relatively small contribution of total resuscitation fluid, sodium and possibly chloride levels in critically ill patients, especially those with a prolonged ICU stay.[1]

Although this is the first study designed to demonstrate feasibility and safety of limiting sodium creep in ICU, there are certain limitations. First, the data are collected from a single centre with the use of a prospective before-and-after study design. Due to this design, a complete 24-hour record was not available in some patients; however, similar study designs have been used in the past to examine conservative oxygen therapy, which has led to larger clinical trials.[39] A large proportion of patients were on dialysis on the study day and an accurate assessment of administered sodium is difficult in these patients, as there is sodium and chloride loading as a result of dialysis itself in these patients.[40] In addition, despite our best efforts to meticulously record all the sources of administered sodium, it might still be an under-representation of the total amount administered. In 2016, our ICU used predominantly a hypotonic fluid (4% glucose + 0.18% saline) as the routine maintenance fluid; hence, changing it to 5% glucose only offers a small magnitude of difference in the administered sodium. However, as most centres across Australia and New Zealand use isotonic fluid, usually 0.9% saline, the change of practice in these centres will have a larger impact on the amount of administered sodium.

Despite our efforts to decrease the amount of administered sodium in critically ill patients, the total administered level is still high (> 100 mmol per day) and exceeds the recommendation for a healthy person.[41] Further areas of interventions that can be explored in the future are the use of low sodium in enteral and parenteral feeds, hypotonic fluid use as a flush for flush-based intravascular devices, and increased used of salt-poor albumin for resuscitation.

Conclusion

This is the first study to intervene on fluid creep composition, maintenance fluid types, and the resultant inadvertent sodium and chloride loading in critically ill ICU patients. We have shown that it is feasible and safe to decrease the total sodium loading in ICU patients, with a change in unit policy with regards to the use of 5% glucose. This was accompanied by favourable changes in serum electrolyte and fluid balance. The long term patient related outcomes with this intervention should be examined in future studies.

Acknowledgements: We thank the ICU nurses Kate Norman, Kate Schwartz, Tapaswi Shrestha and Xia Jin for their help with the data collection.

Competing interests

None declared.

Author details

Shailesh Bihari[1,2]

Shivesh Prakash[1,2]

Simon Potts[1,2]

Elisha Matheson[1]

Andrew D Bersten[1,2]

1. Department of Intensive and Critical Care Unit, Flinders Medical Centre, Bedford Park South Australia 5042
2. Department of Critical Care Medicine, Flinders University, Bedford Park South Australia 5042

***Correspondence*:** biharishailesh@gmail.com

References

1 Van Regenmortel N, Verbrugghe W, Roelant E, et al. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med* 2018; 44: 409-17.

2 Bihari S, Peake SL, Seppelt I, et al. Sodium administration in critically ill patients in Australia and New Zealand: a multicentre point prevalence study. *Crit Care Resusc* 2013; 15: 294-300.

3 Bihari S, Ou J, Holt AW, Bersten AD. Inadvertent sodium loading in critically ill patients. *Crit Care Resusc* 2012; 14: 33-7.

4 Bihari S, Watts NR, Seppelt I, et al. Maintenance fluid practices in intensive care units in Australia and New Zealand. *Crit Care Resusc* 2016; 18: 89-94.

5 Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247-56.

6 Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-11.

7 PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock — a patient-level meta-analysis. *N Engl J Med* 2017; 376: 2223-34.

8 Bihari S, Peake SL, Prakash S, et al. Sodium balance, not fluid balance, is associated with respiratory dysfunction in mechanically ventilated patients: a prospective, multicentre study. *Crit Care Resusc* 2015; 17: 23-8.

9 Hammond NE, Taylor C, Finfer S, et al. Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: an international cross-sectional study. *PLoS ONE* 2017; 12: e0176292.

10 Bihari S, Baldwin CE, Bersten AD. Fluid balance does not predict estimated sodium balance in critically ill mechanically ventilated patients. *Crit Care Resusc* 2013; 15: 89-96.

11 Choo W-P, Groeneveld AB, Driessen RH, Swart EL. Normal saline to dilute parenteral drugs and to keep catheters open is a major and preventable source of hypernatremia acquired in the intensive care unit. *J Crit Care* 2014; 29: 390-4.

12 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.

13 Bihari S, Wiersema UF, Schembri D, et al. Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes interstitial pulmonary edema in healthy subjects. *J Appl Physiol* 2015; 119: 783-92.

14 Friedman JN, Beck CE, DeGroot J, et al. Comparison of isotonic and hypotonic intravenous maintenance fluids: a randomized clinical trial. *JAMA Pediatr* 2015; 169: 445-51.

15 McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. *Lancet* 2015; 385: 1190-7.

16 Holliday MA, Friedman AL, Segar WE, et al. Acute hospital-induced hyponatremia in children: a physiologic approach. *J Pediatr* 2004; 145: 584-7.

17 Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med* 2015; 373: 1350-60.

18 Van Regenmortel N, De Weerdt T, Van Craenenbroeck AH, et al. Effect of isotonic versus hypotonic maintenance fluid therapy on urine output, fluid balance, and electrolyte homeostasis: a crossover study in fasting adult volunteers. *Br J Anaesth* 2017; 118: 892-900.

19 Bihari S, Festa M, Peake SL, et al. Sodium administration in critically ill paediatric patients in Australia and New Zealand: a multicentre point prevalence study. *Crit Care Resusc* 2014; 16: 112-8.

20 Society of Hospital Pharmacists of Australia. Australian Injectable Drugs Handbook (AIDH) — 7th edition. Melbourne: SHPA; 2018. https://www.shpa.org.au/australian-injectable-drugs-handbook-aidh-7th-edition (viewed May 2018).

21 King Guide Publications. King Guide to Parenteral Admixtures [online]. Napa, CA: King Guide Publications; 2014. https://www.kingguide.com/trademark.html (viewed May 2018).

22 Darmon M, Diconne E, Souweine B, et al. Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. *Crit Care* 2013; 17: R12.

23 Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. *Ann Intern Med* 1996; 124: 197-203.

24 Lindner G, Funk GC, Schwarz C, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis* 2007; 50: 952-7.

25 Funk GC, Lindner G, Druml W, et al. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med* 2010; 36: 304-11.

26 Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; 308: 1566-72.

27 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.

28 Van Regenmortel N, Verbrugghe W, Van den Wyngaert T, Jorens PG. Impact of chloride and strong ion difference on ICU and hospital mortality in a mixed intensive care population. *Ann Intensive Care* 2016; 6: 91.

29 Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent "pre-renal" acute kidney injury?: con. *Kidney Int* 2014; 86: 1096-105.

30 de Vasconcellos K, Skinner DL. Hyperchloraemia is associated with acute kidney injury and mortality in the critically ill: a retrospective observational study in a multidisciplinary intensive care unit. *J Crit Care* 2018; 45: 45-51.

31 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564-75.

32 Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39: 259-65.

33 Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; 76: 422-7.

34 Bihari S, Holt AW, Prakash S, Bersten AD. Addition of indapamide to frusemide increases natriuresis and creatinine clearance, but not diuresis, in fluid overloaded ICU patients. *J Crit Care* 2016; 33: 200-6.

35 Lobo DN, Stanga Z, Simpson JA, et al. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clin Sci* 2001; 101: 173-9.

36 Hahn RG, Isacson MN, Fagerström T, et al. Isotonic saline in elderly men: an open-labelled controlled infusion study of electrolyte balance, urine flow and kidney function. *Anaesthesia* 2016; 71: 155-62.

37 Reid F, Lobo DN, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)* 2003; 104: 17-24.

38 Frazier SK. Neurohormonal responses during positive pressure mechanical ventilation. *Heart Lung* 1999; 28: 149-65; quiz 166-7.

39 Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. *Crit Care Med* 2014; 42: 1414-22.

40 Bihari S, Taylor S, Bersten AD. Inadvertent sodium loading with renal replacement therapy in critically ill patients. *J Nephrol* 2014; 27: 439-44.

41 National Health and Medical Research Council, Australian Government Department of Health and Ageing, New Zealand Ministry of Health. Nutrient reference values for Australia and New Zealand — including recommended dietary intakes. Canberra: NHMRC; 2006. www.nhmrc.gov.au/_files_nhmrc/file/your_health/healthy/nutrition/17599_nhmrc_nrv_update-dietary_intakes_0.pdf (viewed May 2018).