A multicentre, randomised controlled pilot study of fluid resuscitation with saline or Plasma-Lyte 148 in critically ill patients

Brij Verma, Nora Luethi, Luca Cioccari, Patryck Lloyd-Donald, Marco Crisman, Glenn Eastwood, Neil Orford, Craig French, Rinaldo Bellomo and Johan Martensson

Crystalloid solutions are used universally to resuscitate critically ill patients in the intensive care unit, and sodium chloride (saline) is the most commonly used crystalloid solution in the world.[1] However, "normal" saline (NS) is neither normal nor physiological,[2] as it has about 1.5 times as much chloride than normal plasma (95–110 mmol/L). Thus, its use may contribute to hyperchloraemia and metabolic acidosis.[3]

Pre-clinical and early clinical data suggest that administration of NS may also give rise to adverse effects including immune dysfunction,[4] gastrointestinal dysfunction,[5] and decreased renal cortical perfusion and renal blood flow.[6] Recent data have also raised concerns about the safety of NS in critically ill patients.[7-11] In a single-centre, prospective, open-label, sequential-period pilot study of about 1500 critically ill patients, the implementation of a chloride-restrictive strategy that included avoiding NS was associated with a significant decrease in the incidence of acute kidney injury (AKI) and the use of renal replacement therapy (RRT).[7] Extended analysis of almost 3000 patients over a 1-year period showed that the overall beneficial impact on AKI of restricting chloride-rich fluids remained.[8] Another recent prospective, single-centre, observational study (a substudy of the Finnish Acute Kidney Injury [FINNAKI] study), which included 445 patients and analysed chloride values measured during the ICU stay, showed higher time-weighted mean chloride levels that were independently associated with an increased risk of AKI.[12]

More relevant to our study is a large, retrospective, observational investigation of about 32 000 adults undergoing major open abdominal surgery. This study suggested that, compared with NS, the use of Plasma-Lyte 148 (PL-148) was associated with a decreased risk of major complications, in that patients were 4.8 times less likely to develop AKI requiring dialysis.[9]

ABSTRACT

Background: Normal saline (NS) is the most commonly used crystalloid solution worldwide but contains an excess of chloride and may cause metabolic acidosis and hyperchloraemia. Such abnormalities may be attenuated by the use of a balanced solution such as Plasma-Lyte 148 (PL-148).

Objective: To assess the feasibility, safety and biochemical and physiological effects of resuscitation with NS versus PL-148 in critically ill patients.

Design, setting and participants: An exploratory, multicentre, double-blind, randomised controlled trial involving patients aged ≥ 18 years who were prescribed crystalloid fluid resuscitation by the treating clinician between 16 July and 22 October 2015, in three multidisciplinary intensive care units in Melbourne, Victoria, Australia.

Methods: Random allocation of NS or PL-148 was concealed, and all fluids were delivered in indistinguishable bags.

Intervention: NS or PL-148 was administered for all fluid resuscitation and for all subsequent crystalloid fluid therapy until Day 4 of ICU admission. The treating intensivist determined the rate and frequency of fluid administration.

Main outcome measures: Primary outcome was daily base excess (BE). Relevant secondary outcomes included the incidence of acute kidney injury (AKI), change in serum creatinine and serum chloride levels, and mortality.

Results: Seventy patients were recruited, with 34 in the NS group and 33 in the PL-148 group available for analysis. Baseline characteristics of study patients were well balanced; the mean ages were 64 and 62 years, respectively, and nearly two-thirds of the patients in each group were men. The median Acute Physiology and Chronic Health Evaluation III scores were 64 for the NS group (interquartile range [IQR], 48–73) and 55 for the PL-148 group (IQR, 44–81). After treatment, there was no significant difference in the worst (most negative) median BE between the NS and PL-148 groups (–4 mEq/L [IQR, –7 to –2 mEq/L] v –3 mEq/L [IQR, –7 to 2 mEq/L]; $P = 0.42$). Chloride levels were significantly higher with NS therapy (median, 111 mmol/L [IQR, 108–116 mmol/L] v 108 mmol/L [IQR, 106–110 mmol/L]; $P = 0.01$). There was no significant difference in the incidence of AKI ($P = 0.48$), peak creatinine levels ($P = 0.92$) or ICU or hospital mortality between the two groups.

Conclusions: In our exploratory, double-blind, randomised controlled trial, when compared with NS, PL-148 did not significantly increase BE values in critically ill patients requiring fluid resuscitation, but decreased peak chloride concentrations.

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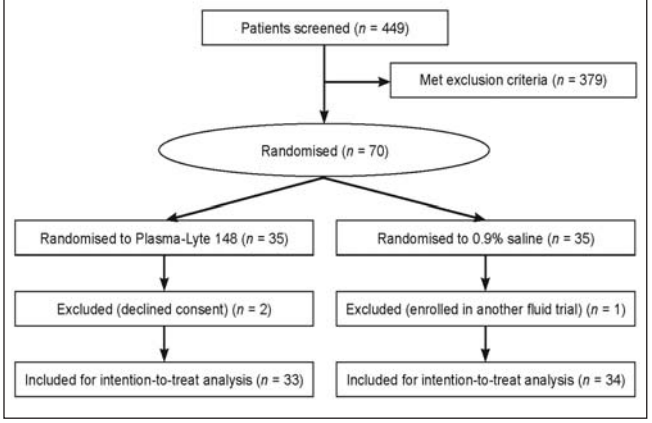
Figure 1. Flow of patients through study



PL-148 is a low-chloride crystalloid solution which has a more physiological concentration of chloride (98 mmol/L) than Hartmann's solution (109 mmol/L). Because it does not contain calcium, it is compatible with blood products, which are preserved in citrate-based anticoagulation solutions.[3] Recently, a multicentre, double-blind, clustered, double-crossover trial compared NS with PL-148 and did not find any differences in the incidence of AKI, use of RRT and in-hospital mortality. However, this study did not use individual randomisation and did not report on the effect of PL-148 on chloride levels.[13]

We conducted a pilot study which was a multicentre, double-blinded, randomised controlled trial to assess the feasibility, safety and biochemical and physiological effects of fluid resuscitation with NS or PL-148. We used the worst (most negative) base excess (BE) levels during the first 4 days (when most fluid administration takes place) in the ICU as the primary outcome measure. We assessed chloride concentration, incidence of AKI and changes in serum creatinine level as secondary clinical outcomes.

Methods

The 0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy (SPLIT) study was an exploratory, multicentre, prospective, double-blinded, randomised controlled trial conducted in three multidisciplinary ICUs in Victoria, Australia.

We designed our pilot trial (which preceded the SPLIT trial) and registered it on the Australian New Zealand Clinical Trials Registry (ANZCTRN 12615000158561). Our study protocol was approved by the Human Research Ethics Committee at the Austin Hospital and by each participating institution. We obtained written, informed consent before randomisation, or delayed consent, from each patient or their legal surrogate. Statistical analyses were conducted with blinding to study allocation and with all data de-identified before assessment.

Patients

We included all ICU patients who were 18 years or older and judged by the treating clinician to require crystalloid fluid resuscitation. Patients who were transferred from another hospital to a study ICU in order to receive RRT for AKI were excluded, as were patients admitted to the ICU after cardiac surgery or for consideration of organ donation.

We designed our study to compare the use of NS with the use of PL-148 as primary fluid therapy. The volumes of study fluid and other fluids were recorded. Randomisation was in permuted blocks, conducted using a computer-based randomisation program and sealed envelopes. Blinding of study fluids was done by Baxter Healthcare. Study fluid bags were indistinguishable 1 L Viaflex bags, and each bag was labelled with a unique participant number to ensure complete blinding. The principal investigators at each site did not have access to the randomisation key, which was only available to the research coordinators in each study centre.

Once the treating clinician had decided that fluid resuscitation was needed, a sealed envelope was opened and the treatment fluid number was made available to the treating team. The team then obtained the bag of blinded study fluid with the corresponding number from a 10 L batch of fluid with the same study number. All fluid resuscitation and all crystalloid fluid therapy was performed with that fluid until discharge from the ICU. If more than 10 L of fluid was given, the patient was allocated by the research coordinator to a second batch of fluid containing the same type of fluid as the first batch, thus maintaining blinding of treating doctors, nurses and patients.

Outcome measures

The primary outcome measure was the maximum BE in the first 4 days. Secondary outcomes included peak serum chloride levels, peak creatinine level in the ICU, the incidence of AKI in the first 4 days in the ICU, the need for RRT during the hospital stay, ICU and hospital lengths of stay, and ICU and in-hospital mortality rates.

Data collection and management

Data relating to demographic information, illness severity and outcomes were collected by trained ICU staff for quality assurance purposes.[14] All other data were collected as part of routine daily care. Data management and statistical analysis were performed with blinding to study fluid allocation, and all data used for analysis were de-identified before statistical assessment.

Statistical analysis

We performed statistical analyses using Stata, version 11.2 (StataCorp). Continuous variables are expressed as medians and interquartile ranges (IQRs), and categorical variables as

Table 1. Baseline characteristics of study patients

Characteristic	Normal saline (*n* = 34)	Plasma-Lyte 148 (*n* = 33)	*P*
Demographic data			
Median age, years (IQR)	64 (46–72)	62 (45–70)	0.72
Women, *n* (%)	13 (38.2%)	12 (36.4%)	0.87
Clinical data, median (IQR)			
Body weight, kg	73 (61–87)	74 (65–87)	0.72
APACHE III score	64 (48–73)	55 (44–81)	0.96
Creatinine, μmol/L	90 (60–121)	85 (58–134)	0.67
Heart rate, bpm	88 (72–103)	88 (75–105)	0.74
MAP, mmHg	71 (60–82)	77 (69–84)	0.11
CVP, mmHg	6 (4–7) (*n* = 15)	8 (5–14) (*n* = 18)	0.08
Lactate, mmol/L	1.4 (1.0–2.3)	1.4 (0.9–2.8)	0.65
First study bolus, mL	500 (250–500)	500 (250–500)	0.97
Sepsis diagnosed, *n* (%)	14 (41.2%)	15 (45.5%)	0.72
Clinical support, *n* (%)			
Mechanical ventilation	19 (55.9%)	19 (57.6%)	0.89
CRRT	2 (5.9%)	0	–
Vasopressors	11 (32.4%)	15 (45.5%)	0.27
Admission source, *n* (%)			
Operating theatre	16 (47.1%)	9 (27.3%)	0.24
Emergency department	9 (26.5%)	15 (45.5%)	–
Ward	5 (14.7%)	3 (9.1%)	–
Other hospital	4 (11.8%)	6 (18.2%)	–
Non-operative admission diagnosis, *n* (%)			
Cardiovascular	0/34	2/33 (6.1%)	0.31
Respiratory	6/34 (17.6%)	3/33 (9.1%)	–
Gastrointestinal	2/34 (5.9%)	5/33 (15.2%)	–
Neurological	3/34 (8.9%)	2/33 (6.1%)	–
Sepsis	3/34 (8.9%)	4/33 (12.1%)	–
Trauma	1/34 (2.9%)	1/33 (3.0%)	–
Metabolic	1/34 (2.9%)	1/33 (3.0%)	–
Haematological	0/34	1/33 (3.0%)	–
Other	1/34 (2.9%)	0/33	–
Operative admission diagnosis, *n* (%)			
Cardiovascular	2/34 (5.9%)	2/33 (6.1%)	–
Respiratory	1/34 (2.9%)	6/33 (18.2%)	–
Gastrointestinal	12/34 (35.3%)	5/33 (15.2%)	–
Trauma	1/34 (2.9%)	1/33 (3.0%)	–
Orthopaedic	1/34 (3.0%)	0/33	–

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. bpm = beats per minute. MAP = mean arterial pressure. CVP = central venous pressure. CRRT = continuous renal replacement therapy.

frequencies and percentages. We used the Mann–Whitney *U* test for comparison between continuous variables, and the χ^2 test or Fisher exact test for comparisons between categorical variables. Differences in biochemical variables between the NS group and the PL-148 group during the 4-day assessment period were explored using repeated-measures analysis of variance (ANOVA) after including an interaction variable between group and time in the ANOVA model. A two-sided $P < 0.05$ was considered statistically significant.

Results

From 16 July 2015 to 22 October 2015, we screened 449 patients and randomised 70 patients to the study (Figure 1). In the NS group, one patient was incorrectly enrolled into a competing fluid trial, so was excluded, and, in the PL-148 group, two patients withdrew consent, leaving a total of 67 patients participating (34 in the NS group and 33 in the PL-148 group).

The baseline characteristics of the study patients are shown in Table 1. The two groups of patients were well balanced. The median age was 64 years for the NS group and 62 years for the PL-148 group, and just over one-third were women in both groups. The sources of admission were similar between the two groups, as were the Acute Physiology and Chronic Health Evaluation (APACHE) III scores, the proportions of patients admitted with sepsis and the proportions of patients requiring vasopressor or mechanical ventilator support.

Process of care

After randomisation, both groups received similar volumes of study fluid and non-study fluids (eg, blood products and nutritional therapy) (Table 2). The overall volume of study fluid administered by Day 3 was about 3.4 L for the NS group and about 2.9 L for the PL-148 group (Table 2). In comparison, non-study fluid volumes administered were about 1.1 L for the NS group and about 1.7 L for the PL-148 group. There were no differences in the use of blood, blood products or colloid solutions between the two groups.

Outcomes

There was no significant difference in the most negative BE between NS and PL-148 groups (Table 3). Similarly, there were no differences in AKI, peak serum creatinine levels, RRT, vasopressor therapy or mechanical ventilation. On direct overall comparison, however, peak chloride levels were lower in the PL-148 group ($P = 0.01$). On repeated-measures ANOVA analysis, chloride levels were significantly and consistently

Table 2. Fluids, vasoactive agents, blood products and nutrition given during study period, by group

Therapy	Normal saline (*n* = 34)	Plasma-Lyte 148 (*n* = 33)	*P*
Median study fluid volume, mL (IQR)			
Day 0	1168 (565–1750)	1080 (575–1720)	0.91
Day 1	1275 (435–2243)	1090 (620–2500)	0.95
Day 2	800 (205–1403)	443 (205–880)	0.22
Day 3	200 (0–450)	320 (240–500)	0.13
Median non-study fluid volume, mL (IQR)			
Day 0	290 (65–515)	366 (86–536)	0.61
Day 1	312 (146–753)	457 (125–1227)	0.27
Day 2	288 (20–716)	508 (205–1093)	0.15
Day 3	200 (0–460)	412 (250–1009)	0.03
Red blood cell transfusion, *n* (%)			
Day 0	2/34 (5.9%)	3/33 (12.1%)	0.43
Day 1	0/32	1/27 (3.7%)	–
Day 2	0/24	2/22 (9.1%)	–
Day 3	0/19	2/15 (13.3%)	–
Fresh frozen plasma transfusion, *n* (%)			
Day 0	1/34 (2.9%)	2/33 (6.1%)	0.61
Day 1	0/32	1/27 (3.7%)	–
Day 2	0/24	0/22	–
Day 3	0/19	0/15	–
Cryoprecipitate transfusion, *n* (%)			
Day 0	0	0	–
Day 1	0	0	–
Day 2	0	0	–
Day 3	0	0	–
Platelet transfusion, *n* (%)			
Day 0	1/34 (2.9%)	2/33 (6.1%)	0.61
Day 1	0	0	–
Day 2	0	0	–
Day 3	0	0	–
4% human albumin infusion,* *n* (%)			
Day 0	1/34 (2.9%)	0/33	–
Day 1	1/32 (3.1%)	1/27 (3.7%)	1.0
Day 2	1/24 (4.2%)	1/22 (4.5%)	1.0
Day 3	0	0	–
20% human albumin infusion,* *n* (%)			
Day 0	1/34 (2.9%)	3/33 (9.1%)	0.36
Day 1	2/32 (6.3%)	3/27 (11.1%)	0.65
Day 2	1/24 (4.2%)	2/22 (9.1%)	0.60
Day 3	0/19	1/15 (6.7%)	–
Total parenteral nutrition, *n* (%)			
Day 0	1/34 (2.9%)	1/33 (3.0%)	1.0
Day 1	1/32 (3.1%)	4/27 (14.8%)	0.17
Day 2	0/24	4/22 (18.2%)	–
Day 3	1/19 (5.3%)	3/15 (20.0%)	0.30
Enteral nutrition, *n* (%)			
Day 0	15/34 (44.1%)	16/33 (48.5%)	0.72
Day 1	18/32 (56.3%)	14/27 (51.9%)	0.74
Day 2	14/24 (58.3%)	13/22 (59.1%)	0.96
Day 3	14/19 (73.7%)	11/15 (73.3%)	0.98
Vasopressor infusion, *n* (%)			
Day 0	19/34 (55.9%)	16/33 (48.5%)	0.54
Day 1	14/32 (43.8%)	12/27 (44.4%)	0.96
Day 2	8/24 (33.3%)	9/22 (40.9%)	0.60
Day 3	4/19 (21.1%)	6/15 (40.0%)	0.28

IQR = interquartile rage. * Albumex (CSL).

Table 3. Study outcomes, by group

Outcome	Normal saline (*n* = 34)	Plasma-Lyte 148 (*n* = 33)	*P*
Median most negative base excess, mmol/L (IQR)	–4 (–7 to –2)	–3 (–7 to 2)	0.42
Acute kidney injury, *n* (%)	6/33 (18.2%)	9/32 (28.1%)	0.34
Median peak creatinine, µmol/L (IQR)	96 (69–164)	92 (68–186)	0.92
Worst AKI or RIFLE stage, *n* (%)			
No AKI	27/33 (81.8%)	23/32 (71.9%)	0.72
R	3/33 (9.1%)	4/32 (12.5%)	–
I	1/33 (3.0%)	3/32 (9.4%)	–
F	2/33 (6.1%)	2/32 (6.3%)	–
Renal replacement therapy, *n* (%)	3/34 (8.8%)	5/33 (15.2%)	0.48
Median duration of mechanical ventilation, hours (IQR)	16 (0–32)	12 (0–50)	0.80
Median duration of vasopressor infusion, hours (IQR)	5 (0–27)	6 (0–32)	0.59
Median peak chloride, mmol/L (IQR)	111 (108–116)	108 (106–110)	0.01
Median lowest pH (IQR)	7.3 (7.2–7.4)	7.3 (7.3–7.4)	0.51
Median ICU length of stay, days (IQR)	2.5 (1.2–3.8)	3.2 (1.5–5.0)	0.21
Median hospital length of stay, days (IQR)	10 (6.6–17)	11 (4.0–16)	0.94
Discharged alive from ICU, *n* (%)	32/34 (94.1%)	30/33 (90.9%)	0.67
Discharged alive from hospital, *n* (%)	32/34 (94.1%)	28/33 (84.8%)	0.26

IQR = interquartile range. AKI = acute kidney injury. RIFLE = risk (R), injury (I), failure (F), loss of kidney function and end-stage kidney disease. ICU = intensive care unit.

lower over time with PL-148 therapy (P = 0.008) (Figure 2A). When analysed by repeated-measures ANOVA, such changes were not associated with differences in sodium level (Figure 2B) or BE (Figure 2D) over time, but did result in an increased strong ion difference (P = 0.049) (Figure 2C). Finally, there were no significant group differences in ICU and hospital lengths of stay, or in ICU and hospital survival between the two groups (Table 3).

Discussion

Key findings

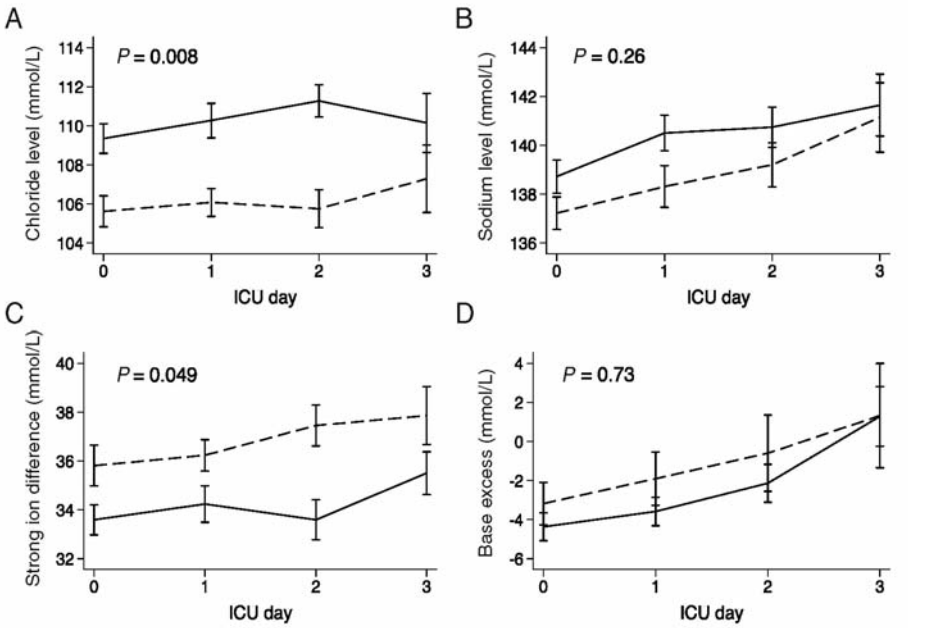
In our prospective, multicentre, randomised, double-blind pilot study, we found that patients randomised to receive NS did not develop a greater negative peak BE value compared with patients randomised to PL-148. In addition, there were no differences in serum creatinine levels, incidence of AKI, duration of vasopressor or mechanical ventilation support, or ICU length of stay and survival. However, compared with NS treatment, PL-148 was associated with lower serum chloride levels and increased strong ion difference.

Relationship to previous studies

Our findings are consistent with previous studies comparing NS with PL-148 in peri-operative patients,[15-18] patients undergoing resuscitation after trauma[19] and patients with diabetic ketoacidosis,[20] and with studies comparing NS with other balanced solutions.[16,21-23] In patients with sepsis, Park and colleagues showed that 2000 mL (± 300 mL) of 0.9% saline infusion resulted in a disproportionate elevation of serum chloride level compared with the sodium concentration.[24] Our study showed a non-significant trend towards greater negative BE in the NS group, with the ability to detect significance partly affected by the limited resolution of the BE system, which allowed for no decimal places. Our findings are also consistent with most randomised studies comparing NS with balanced solutions in peri-operative patients.[15-18,23,25]

Multiple previous randomised studies comparing NS with balanced solutions in peri-operative patients and dehydrated patients in the emergency department, and in resuscitation of trauma patients, showed significantly lower pH in the NS groups.[18,19,23,25-27] However, they typically focused on the immediate post-infusion period, the immediate peri-operative period and the administration of substantial volumes of fluids over a short time, thus maximising the chance of a positive observation. Our study is the first double-blind, individual randomisation trial in an environment where only about 3 L of study fluids were given over 4 days, and only morning blood pH measurements were used for analysis. In this setting and within its limited power, it did not show a significant difference in pH between the NS and PL-148 groups. Our results are also consistent with a recent multicentre, cluster-randomised trial comparing NS and buffered crystalloid solution in patients in the ICU, which did not show an increased risk of AKI or increased need for RRT with NS use.[13]

Figure 2. Electrolyte measurements in first 4 days of study, in patients treated with saline and Plasma-Lyte 148



A = peak chloride. B = peak sodium. C = strong ion difference. D = most negative base excess. —— = saline. ---- = Plasma-Lyte 148. *P* values are for overall differences between groups, measured with repeated-measures analysis of variance.

Study implications

Our study, using a double-blind, randomised controlled design, confirmed that, in the ICU setting, fluid resuscitation with PL-148 reduces the extent of hyperchloraemia compared with NS, thus increasing the strong ion difference and attenuating plasma acidification. These findings imply that PL-148 can be an alternative crystalloid solution to NS for patients at high risk of or with pre-resuscitation hyperchloraemia, or for patients in whom significant acidosis already exists or is developing.

Strengths and limitations

Our study has several strengths. First, ours is the only multicentre, double-blind, individual randomisation study of heterogeneous ICU patients comparing PL-148 with NS, thus minimising the confounding effects of selection or allocation bias. It also provides a more detailed assessment of acid–base balance changes associated with these interventions, in contrast with previous studies in the ICU. Second, our study assessed acid–base and serum chloride levels for longer periods than previously studied to estimate physiological separation between the groups over time. Third, our study included medical and surgical ICU patients, which would be expected to improve the generalisability of the study findings. Fourth, it established the safety of giving PL-148 not only as resuscitation fluid but also as maintenance infusion fluid, when warranted, after the first episode of fluid resuscitation.

Our study also carries several limitations. First, the sample size was small, which increased the chance of a type II error. This problem is inherent in all pilot feasibility studies, and when differences were present (as was the case with chloride levels), they could be identified. Second, the volumes of study fluid administered were small, which decreased the chance of a biochemical impact. However, the amounts administered were similar to those reported in a recent cluster-randomised controlled trial[13] and consistent with other fluid resuscitation studies.[28] Third, the timing of blood sampling was not coupled with administration of fluid boluses, so we could have missed short-lived differential effects of PL-148 on the acid–base balance or pH. Our focus was on the overall average acid–base and electrolyte status over each 24-hour period, rather than on momentary fluctuations in acid–base physiology. Fourth, we cannot rule out the possibility of ascertainment bias, because treating clinicians had access to blood test results and they might have restricted study fluid infusion in response to hyperchloraemia. However, even under these circumstances, the effect on the chloride levels was clear. Our study patients were only moderately ill, as evidenced by their median APACHE III scores, low ICU mortality, low incidence of AKI, low RRT requirement and short length of ICU stay. Thus, our study results may not apply to more severely ill, high-risk patients requiring larger volumes of fluid. Our study helps establish the need for a population of greater illness severity to be studied in definitive comparative trials.

Conclusions

In our pilot, multicentre, double-blind, randomised controlled study comparing NS with PL-148, PL-148 resuscitation and therapy did not alter the value of the most negative base excess or improve clinical outcomes. However, PL-148 treatment attenuated the extent of hyperchloraemia and the reduction in strong ion difference associated with NS. This information may help clinicians choose a crystalloid fluid therapy in specific high-risk situations, and informs the design of future Phase III trials.

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Competing interests

None declared.

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