Effect of saline 0.9% or Plasma-Lyte 148 therapy on feeding intolerance in patients receiving nasogastric enteral nutrition

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The administration of intravenous fluid is one of the most common interventions in critically unwell patients. Saline 0.9% (saline) is the most frequently prescribed intravenous fluid.[1,2] It contains a supraphysiological concentration of chloride (see Table 1) and when administered in appreciable volumes can lead to hyperchloraemic metabolic acidosis.[3,4] Observational, pre-clinical and animal studies have shown that hyperchloraemia may be associated with decreased renal artery blood flow velocity, impaired immune function and impaired gastrointestinal (GI) function.[5-9]

GI feeding intolerance is the most frequent reason for unwanted cessation of enteral nutrition in patients in the intensive care unit.[10-12] Observational data suggest that GI feeding intolerance in ICU patients is associated with decreased nutrient intake and adverse clinical outcomes.[13,14] It is biologically plausible that using saline may increase the incidence of GI dysfunction through altered GI perfusion, impaired GI motility or submucosal intestinal oedema.[6,15]

We conducted a pilot cohort study to provide preliminary data on the comparative effectiveness of Plasma-Lyte (PL)-148 and saline for intravenous fluid therapy in a select group of mechanically ventilated ICU patients receiving enteral nutrition, with a particular focus on GI feeding intolerance. Our hypothesis was that PL-148 would reduce GI intolerance, compared with saline.

Methods

Study design

This was a single-centre pilot study nested within the 0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy (SPLIT) trial.[16] The SPLIT trial was an investigator-initiated, multicentre, prospective, double-blind, cluster-randomised, double-crossover study conducted in four tertiary ICUs in New Zealand.

Our study protocol was approved by the New Zealand Northern B Health and Disability Ethics Committee (12/NTB/57). It compared the effectiveness of two standard treatment approaches, with an opt-out consent process. The details of the SPLIT trial and the statistical analysis plan for this study have been reported previously.[17] The study fluid was supplied and distributed by Baxter Healthcare.

ABSTRACT

Objective: To compare the effect of Plasma-Lyte (PL)-148 and saline 0.9% (saline) on gastrointestinal (GI) feeding intolerance in mechanically ventilated patients receiving nasogastric (NG) feeding in an intensive care unit.

Design and setting: A single-centre pilot study, nested within a multicentre, double-blind, cluster-randomised, double-crossover trial, performed in a mixed medical and surgical ICU.

Participants: All adult patients who required crystalloid fluid therapy as part of the 0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy (SPLIT) trial, were expected to need mechanical ventilation for more than 48 hours and were receiving enteral nutrition exclusively by NG tube were eligible. We enrolled 69 patients and assigned 35 to PL-148 and 34 to saline.

Interventions: We randomly allocated saline or PL-148 for four alternating 7-week blocks, with staff blinded to the solution.

Main outcome measures: The primary outcome was the proportion of patients with GI feeding intolerance, defined as high gastric residual volume (GRV), diarrhoea or vomiting while receiving NG feeding in the ICU. The proportions of patients with each of high GRV, diarrhoea and vomiting were secondary outcomes.

Results: In the PL-148 group, 21 of 35 patients (60.0%) developed GI feeding intolerance, compared with 22 of 34 patients (64.7%) in the saline group (odds ratio [OR], 0.82; 95% CI, 0.31–2.17; *P* = 0.69). A high GRV was seen in four of 35 patients (11.4%) in the PL-148 group, and in 11 of 34 patients (32.4%) in the saline group (OR, 0.27; 95% CI, 0.08–0.96; *P* = 0.04).

Conclusion: Among mechanically ventilated patients receiving NG feeding, the use of PL-148, compared with saline, did not reduce the proportion of patients developing GI feeding intolerance, but was associated with a decreased incidence of high GRV.

Table 1. Characteristics of human plasma, saline 0.9% and Plasma-Lyte 148*

Parameter	Plasma	Saline 0.9%	Plasma-Lyte 148
Sodium (mmol/L)	136–145	154	140
Potassium (mmol/L)	3.5–5.0	–	5
Magnesium (mmol/L)	0.8–1.0	–	1.5
Calcium (mmol/L)	2.2–2.6	–	–
Chloride (mmol/L)	98–106	154	98
Acetate (mmol/L)	–	–	27
Gluconate (mmol/L)	–	–	23
Lactate (mmol/L)	–	–	–
Malate (mmol/L)	–	–	–
eSID (mEq/L)	42	0	50
Theoretical osmolarity (mOsmol/L)	291	308	295
Actual/measured osmolarity (mOsmol/kg H2O)	287	286	271
pH	7.35–7.45	4.5–7	4–8

eSID = effective strong ion difference. * Acetate and gluconate buffered solution; manufactured by Baxter Healthcare.

Patients

Patients enrolled in the SPLIT trial at the Wellington ICU were assessed for eligibility for this study. Eligibility criteria included patients who were aged 18 years or older, were expected to require mechanical ventilation for more than 48 hours and were receiving enteral nutrition exclusively by nasogastric (NG) tube.

As in the main SPLIT trial, patients were excluded if they were usually receiving dialysis for end-stage renal failure, were currently receiving renal replacement therapy or expected to require renal replacement therapy within 6 hours, were admitted to the ICU solely for consideration of organ donation or for palliative care, or were previously enrolled in the SPLIT study. All baseline data were collected from the patients' medical records at the time of study enrolment.

In the study ICU, we had a standardised approach to nutritional support and NG feeding. Enteral nutrition was started as early as clinically possible, with the aim of achieving the nutritional goal rate within 48 hours. NG feeding was the preferred feeding method for mechanically ventilated patients and, whenever possible, patients were nursed in a semi-recumbent position (30°–45°, head up). Once the intragastric position of the NG tube was radiographically verified, feeds of 1.28 kcal/mL were started at a rate of 30 mL/h and increased by a rate of 30 mL/h every 4 hours, until the goal rate was achieved. The initial goal rate was prescribed by the treating clinician and was subsequently adjusted in collaboration with the ICU dietitian,

if necessary. Measurement of gastric residual volume (GRV) was performed at 4-hourly intervals via syringe aspiration through the NG tube, and volumes below 500 mL were returned to the patient. Once the goal feeding rate was tolerated for 24 hours, the frequency of NG aspiration was decreased to 12-hourly. The size of the NG tube inserted, changes to type of NG feed used, and use of prokinetic agents were at the discretion of the treating clinicians.

Randomisation and treatment

Within the SPLIT trial, participating ICUs were allocated to use saline or PL-148 alternately for four 7-week blocks. The order of allocation within the study ICU was: first 7-week block, PL-148; second 7-week block, saline; third 7-week block, PL-148; fourth 7-week block, saline. During the 28 weeks of the study, two crossovers occurred, so that the study ICU used each fluid type twice. Staff were blinded to which fluid was used; study fluids were labelled "Fluid A" or "Fluid B" in otherwise indistinguishable 1000 mL bags. Any patient who remained in the ICU through a crossover or was readmitted to the ICU continued to receive the study fluid to which they were originally assigned, for up to 90 days.

The frequency, rate and volume of the study fluid given to patients were determined by the treating clinician. Fluid administration outside the ICU (eg, during surgical procedures) was not formally controlled but, whenever possible, the use of the allocated study fluid was encouraged. Both open-labelled PL-148 and saline were available for when the treating clinician believed there was a specific indication for one fluid or the other.

We recorded the proportion of patients in each treatment group who received prokinetic drugs (metoclopramide or erythromycin), opiates or catecholamines after randomisation, because we considered these to be an important co-intervention.

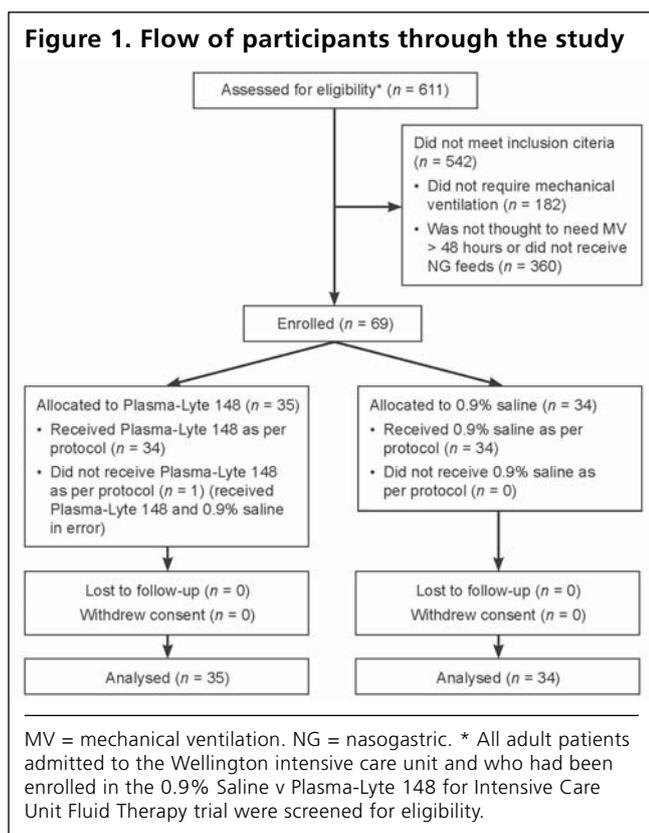### Outcome measures

Primary outcomes
Our primary outcome was the proportion of patients with GI feeding intolerance, defined as having any of the following while receiving NG feeding in the ICU:

- high GRV (a single NG aspirate volume > 500 mL)[10]
- diarrhoea (three or more loose or liquid stools per day)[11]
- vomiting (enteral formula ejected from mouth, irrespective of amount).[11]

Secondary outcomes
Secondary outcomes within the 90-day follow-up period were:

- proportion of patients with each of high GRV, diarrhoea and vomiting

Figure 1. Flow of participants through the study

MV = mechanical ventilation. NG = nasogastric. * All adult patients admitted to the Wellington intensive care unit and who had been enrolled in the 0.9% Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy trial were screened for eligibility.

- diet:volume ratio (administered volume of diet/ prescribed volume of diet) at 48 hours after study enrolment
- durations of NG feeding and mechanical ventilation
- reason for cessation of NG feeding
- ICU and hospital lengths of stay from first receiving study fluid.

Statistical analysis

To our knowledge, no previous clinical trial has compared the effect of use of saline with a buffered crystalloid solution on GI feeding intolerance. We did not perform a prospective sample size calculation for this exploratory study. All analysis was on an intention-to-treat basis and there was no imputation for missing values.

We assessed all continuous variables for normality, and log-transformed them when appropriate. We compared groups using χ^2 tests for equal proportion, the Student t test for normally distributed variables, or the Wilcoxon rank-sum test otherwise. We report results as frequencies with percentages, means with standard deviations, or medians with interquartile ranges (IQRs), respectively. We analysed binomial outcome variables using logistic regression, and report them as odds ratios (ORs) with 95% confidence intervals.

We conducted additional multivariate sensitivity analyses considering the baseline characteristics that

Table 2. Characteristics of patients at baseline

Characteristic	Colloid received*	
	Plasma-Lyte 148 (*n* = 35)	Saline 0.9% (*n* = 34)
Mean age, years (SD)	55.2 (16.7)	51.4 (18.5)
Male, *n* (%)	20 (57%)	27 (79%)
Median body mass index (IQR)	27.54 (24.5–30.2)	26.02 (24.2–32.0)
Ethnicity, *n* (%)		
New Zealand–European	26 (74%)	22 (65%)
Maori	3 (9%)	6 (18%)
Pacific Islands	3 (9%)	3 (9%)
Other	3 (9%)	3 (9%)
Diagnosis type at admission, *n* (%)		
Medical	14 (40%)	9 (27%)
Surgical	15 (43%)	13 (39%)
Trauma	6 (17%)	12 (35%)
APACHE II score ≥25, *n* (%)	6 (17%)	3 (9%)
Mean APACHE II[†] score (SD)	17.9 (6.1)	16.9 (5.6)
Median time from ICU admission to first study fluid, hours (IQR)	2.3 (1.0–16.8)	2.1 (0.5–6.8)
Median time from ICU admission to starting NG feeding, hours (IQR)	13.8 (5.3–30.7)	19.3 (14.2–32.2)
Mean pre-randomisation BGL, mmol/L (SD)[‡]	8.9 (4.1)	8.0 (3.4)
Received opiates in 24 hours before randomisation, *n* (%)[‡]	35 (100%)	33 (97%)
Received catecholamines in 24 hours before randomisation, *n* (%)[‡]	27 (77%)	23 (68%)

SD = standard deviation. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. NG = nasogastric. BGL = blood glucose level. * There were no significant differences between groups for any baseline characteristic. † APACHE II scores range from 0 to 71; higher scores indicate increased risk of death. ‡ Additional baseline characteristics included after peer review

were imbalanced between groups (sex, trauma admission diagnosis and time until NG feeding commencement), as given by $P < 0.10$. We performed all analyses using SPSS, version 22.0 (IBM).

Results

Patients

From April 2014 to October 2014, 69 patients were enrolled and analysed, with 35 assigned to receive PL-148 and 34 to receive saline (Figure 1). Demographic and outcome data were available for all patients. There were no significant between-group differences in baseline characteristics or

Table 3. Study outcomes, by fluid type

Outcome	Fluid type		OR or GMR (95% CI)	P
	Plasma-Lyte 148 (n = 35)	Saline 0.9% (n = 34)		
Gastrointestinal feeding intolerance, n (%)	21 (60.0%)	22 (64.7%)	OR, 0.82 (0.31–2.17)	0.69
High gastric residual volume, n (%)	4 (11.4%)	11 (32.4%)	OR, 0.27 (0.08–0.96)	0.04
Vomiting, n (%)	9 (25.7%)	6 (17.6%)	OR, 1.62 (0.51–5.12)	0.42
Diarrhoea, n (%)	16 (45.7%)	15 (44.1%)	OR, 1.07 (0.41–2.76)	0.89
Mean diet:volume ratio (SE)	0.86 (0.03)	0.93 (0.04)	–	0.10
Mean duration of nasogastric feeding, days (SE)	8.4 (1.3)	10.1 (1.2)	–	0.23
Mean duration of mechanical ventilation, days (SE)	7.8 (1.2)	8.5 (1.1)	–	0.36
Reason for cessation of nasogastric feeding, n (%)				
Commencement of oral diet	13 (37.1%)	8 (23.5%)	OR, 1.92 (0.67–5.48)	0.22
Gastrointestinal complication	4 (11.4%)	0 (0)	–	0.99
Other complication	0 (0)	1 (2.9%)	–	0.99
ICU discharge	12 (34.3%)	16 (47.1%)	OR, 0.59 (0.22–1.55)	0.28
ICU death	6 (17.1%)	9 (26.5%)	OR, 0.58 (0.18–1.84)	0.35
Median time in ICU, days (IQR)*	8.1 (6.5–9.8)	10.0 (8.1–12.4)	GMR, 0.80 (0.60–1.08)	0.24
Median time in hospital, days (IQR)*	13.1 (10.4–16.6)	14.0 (11.0–17.8)	GMR, 0.54 (0.67–1.31)	0.71

OR = odds ratio. GMR = geometric means ratio. ICU = intensive care unit. IQR = interquartile range. *TIme in ICU and hospital calculated from time patient first received study fluid in ICU, until ICU and hospital discharge.

diagnostic admission categories of the patients (Table 2). Relatively few patients had baseline comorbidities. In the saline group, there was one patient with cirrhosis and one patient with leukaemia and receiving immunosuppression therapy. In the PL-148 group, there was one patient who had chronic respiratory disease. The mean age of enrolled patients was 53 years (SD, 17.6 years). The mean APACHE II illness severity score for the PL-148 group was 17.9 (SD, 6.1), and for the saline group was 16.9 (SD, 5.6).

Fluid therapy and co-interventions

There was no significant difference in the volumes received or the proportion of patients receiving crystalloid or colloid solutions or blood products 24 hours before randomisation. The median total volume of study fluid given in the PL-148 group was 2500 mL (IQR, 1000–5200 mL), compared with 3155 mL in the saline group (IQR, 2154–5266 mL), but the difference was not significant (P = 0.21). Most of the study fluid was given over the first 2 days after study enrolment, and there was also no difference in the volumes of study fluid, non-study fluid and blood products administered per day to patients while in the ICU (see Tables S1A and S1B in the Appendix online at cicm.org.au/Resources/Publications/Journal). One patient in the PL-148 group had received a 500 mL bolus of saline study fluid in error during the study.

There were no significant differences between groups in the proportions of patients requiring prokinetics (metoclopramide

and erythromycin), opiates or catecholamines while in the ICU (see Table S3 in the Appendix).

Outcomes

In the PL-148 group, 21 of 35 patients (60.0%) developed GI feeding intolerance (OR, 0.82; 95% CI, 0.31–2.17; P = 0.69), compared with 22 of 34 patients (64.7%) in the saline group (Table 3). A GRV of > 500 mL was seen in four of 35 patients (11.4%) in the PL-148 group, and in 11 of 34 patients (32.4%) in the saline group (OR, 0.27; 95% CI, 0.08–0.96; P = 0.04). This result remained significant after multivariate sensitivity analysis (see Table S2 in the Appendix).

After peer review of our initial manuscript, we performed additional analysis on the total daily GRV and biochemical data. There was a significantly lower median GRV on Day 7 in the PL-148 group (see Table S4 in the Appendix). We found no significant differences between groups in the mean lowest and mean highest levels of blood pH, CO_2, bicarbonate, glucose, sodium or potassium on Day 0, Day 1, Day 2 or Day 3 (see Table S5 in the Appendix). There were no significant differences between groups in reasons for cessation of NG feeding, ratio of diet:volume received, duration of NG feeds, duration of mechanical ventilation, days in ICU or days in hospital (Table 3).There were no reported serious events that were judged to be potentially related to study treatment.

Discussion

Key findings

In our single-centre, nested-cohort study of a population of mechanically ventilated patients receiving NG feeding and receiving PL-148 compared with saline for crystalloid fluid therapy, there was no difference in our primary outcome of proportion of patients developing GI feeding intolerance. However, our secondary endpoint of high GRV in isolation occurred in a significantly higher proportion of patients assigned to saline. This difference remained after adjustment for baseline imbalance.

Significance of findings

To our knowledge, no previous clinical trials have assessed the GI effects of different crystalloid fluids in critically ill patients. Prospective studies that have investigated the influence of different crystalloid fluids on GI symptoms have largely been performed in selective surgical populations. A recent propensity-matched, observational study of patients undergoing major abdominal surgery reported that the odds of having a minor GI complication (defined as nausea, vomiting or ileus) were significantly higher in patients who had received exclusively PL-148 or Plasma-Lyte A, compared with patients who had exclusively received saline (OR, 1.45; $P < 0.05$).[2]

High GRV and vomiting are considered valid surrogate markers for upper GI feeding intolerance.[13] The stomach is under complex intrinsic neurohormonal control, and normal function has been reported to be sensitive to external influences. Several agents commonly used in the ICU, such as opiates, sedatives and vasopressors, are thought to significantly affect gastric emptying and feeding tolerance.[18] Significant differences in intraoperative gastric tonometry CO_2 gradient (a surrogate measure for gastric mucosal perfusion), as well as significantly lower rates of hyperchloraemia and metabolic acidosis, have been seen with the use of buffered fluids compared with saline in elective surgical patients.[6] Our finding of no significant metabolic differences between groups shows that intravenous fluid may impair upper GI function by an alternative mechanism to acid–base disturbance. It has been reported that, in rat models, crystalloid fluid resuscitation can cause acute hydrostatic gut oedema and delayed intestinal transit time.[15] In healthy volunteers, a 2 L infusion of saline has been shown to cause significantly increased extracellular fluid expansion when compared with a 2 L infusion of PL-148.[5] These findings raise the possibility that increased interstitial oedema caused by intravenous fluid administration may have some effect on upper GI motility. Our findings are consistent with this possibility.

Strengths and limitations

Our pilot study was an opportunistic, pragmatic study that allowed for co-enrolment and concurrent investigation of the impact on GI function of a ubiquitous intervention used in the ICU, in a high-risk, previously unstudied population. We minimised our risk of bias with allocation concealment, blinding of study groups and publication of a pre-specified statistical analysis plan.[17]

The main limitations of our study are the small sample size and that it was not possible to perform prospective sample size calculations. This was for two reasons. First, as recruitment of our study was dependent on enrolment into the SPLIT study, which was set to run for a specific duration, the final recruitment number for our study was unknown at its start. Second, no previous studies had been performed in this population that would allow for appropriate power calculations. Based on the results from our study, we estimate that 1665 patients per group would need to be enrolled for a study to have 80% power to detect a proportion of patients with GI feeding intolerance of 60.0% in the PL-148 group, and 64.7% in the saline group, at an overall two-sided alpha of 0.05.

We did not account for multiple comparisons in our analysis plan, so the observed difference in GRV between treatment groups may represent a type 1 error and should be regarded as hypothesis-generating. The numerically higher proportion of patients given prokinetics in the saline group may partly explain the lower proportion of patients in the saline group with vomiting, but a significantly higher proportion of these patients had high GRV.

Our primary outcome was a composite one of clinical signs and symptoms indicating GI feeding intolerance.[10,11] We acknowledge that definitions in this field are varied and largely based on expert opinion. Our definitions for diarrhoea and vomiting were based on the European Society of Intensive Care Medicine recommendations.[11] There is controversy about the use of GRV monitoring, and marked variation in GRV measurement technique, frequency and cut-off value. We chose 500 mL as our cut-off value, as this was in line with our established NG enteral feeding protocol, and we contend that most intensivists would regard a single GRV of > 500 mL as abnormal.[10,19]

We did not conduct any physiological test of GI function, as this was cost-prohibitive, there are no accurate markers to assess GI function in daily clinical practice and there is no validated system for grading of severity of GI dysfunction.[11,19,20]

Our study had several strengths. Because 99.7% of all eligible patients were included and analysed in the SPLIT trial, and all these patients were screened for eligibility and, if eligible, were included in our study, our data were not subject to selection bias.[16] The use of a specific feeding

protocol allowed for a standardised approach to enteral feeding that may have reduced the risk of bias.

Conclusion

We conducted a single-centre study nested within a randomised, double-blind, double-crossover study, comparing the effects on the GI system of PL-148 versus saline for crystalloid fluid therapy in a population of NG-fed, mechanically ventilated patients in a multidisciplinary, tertiary ICU. We found no difference in the combined proportion of patients with GI feeding intolerance, but a higher proportion of patients in the saline group developed high GRV. Our findings support the need for further clinical investigation in this area.

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Table S1A: **Volume of study fluid administered (mL) and proportion of patients receiving fluid.***

Fluid - mls	Plamsa-Lyte 148 (n=35)	0.9% saline (n=34)
Proportion of patients receiving fluid		
Plasma-Lyte 148 (study fluid)		
Day 0 - median [IQR]	1000 [0-2000] 35/35	0[0-0]
no./total no. (%)	(100)	0/34 (0)
Day 1 - median [IQR]	220 [0-1080]	0[0-0]
no./total no. (%)	21/35 (60)	0/34 (0)
Day 2 - median [IQR]		0[0-0]
no./total no. (%)	0[0-500] 14/35 (40)	0/34 (0)
Day 3 - median [IQR]	0 [0-0]	0[0-0]
no./total no. (%)	6/35 (17)	0/34 (0)
Day 4 to 90 - median [IQR]	0 [0-1200]	0[0-0]
no./total no. (%)	12/35 (34)	0/34 (0)
0.9% saline (study fluid)		
Day 0 - median [IQR]	0[0-0]	1020 [0-2673]
no./total no. (%)	0/35 (0)	34/34 (100)
Day 1 - median [IQR]	0[0-0]	500 [0-1670]
no./total no. (%)	0/35 (0)	22/34 (65)
Day 2 - median [IQR]	0[0-0]	0[0-620]
no./total no. (%)	0/35 (0)	13/34 (38)
Day 3 - median [IQR]	0[0-0]	0 [0-0]
no./total no. (%)	0/35 (0)	5/34 (15)
Day 4 to 90 - median [IQR]	0[0-0]	0 [0-1000]
no./total no. (%)	1/35 (3)	15/34 (44)

*There were no significant differences in between the groups for the volume of study fluid received. P value for comparison of volume of fluid administered by treatment group calculated using Wilcoxon Rank Sum test.

Table S1B. Non- Study fluids and blood products administered

	Plasma-Lyte 148 (n=35)	0.9% saline (n=34)
Plasma-Lyte 148 (open label)		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 2/35 (6)	0[0-0] 1/34 (3)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 2/34 (6)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 1/34 (3)
Day 4 to 90 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 2/34 (6)
0.9% saline (open label)		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 3/34 (9)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 2/35 (6)	0[0-0] 2/34 (6)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 4 to 90 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 2/34 (6)
5% Dextrose		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 4/35 (11)	0[0-0] (12)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 5/34 (15)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 5/35 (14)	0[0-0] 3/34 (9)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 2/35 (6)	0[0-0] 0/34 (0)
4% Albumin		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
20% Albumin		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 0/34 (0)
Gelofusine		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Voluven or Volulyte		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Other colloids		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Packed red blood cells		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 1/34 (3)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 6/35 (17)	0[0-0] 2/34 (6)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 2/34 (6)
Fresh frozen plasma		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 3/35 (9)	0[0-0] 2/34 (6)

	Plasma-Lyte 148	0.9% saline
Day 1 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 1/34 (3)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 1/34 (3)
Platelets		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 2/35 (6)	0[0-0] 1/34 (3)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 2/34 (6)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Cryoprecipitate		
Day 0 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 0/34 (0)
Day 1 - median [IQR] no./total no. (%)	0[0-0] 1/35 (3)	0[0-0] 0/34 (0)
Day 2 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)
Day 3 - median [IQR] no./total no. (%)	0[0-0] 0/35 (0)	0[0-0] 0/34 (0)

*There were no significant differences in between the groups for the volume of study fluid received. P value for comparison of volume of fluid administered by treatment group calculated using Wilcoxon Rank Sum test.

Table S2. **Unadjusted and adjusted analysis of the primary outcome and key secondary outcomes.**

Outcome	Plamsa-Lyte 148, n/N (%)	0.9% saline, n/N (%)	OR 95%CI (unadjusted)	P-value	OR 95%CI (adjusted)*	P-Value
Total number of patients with a GI complication	21/35 (60.0)	22/34 (64.7)	0.82 (0.31, 2.17)	0.69	1.00 (0.35, 2.89)	0.994
Patients with high GRV	4/35 (11.4)	11/34 (32.4)	0.27 (0.08, 0.96)	0.04	0.26 (0.07, 0.99)	0.049
Patients with vomiting	9/35 (25.7)	6/34 (17.6)	1.62 (0.51, 5.12)	0.42	2.92 (0.71, 12.09)	0.137
Patients with diarrhoea	16/35 (45.7)	15/34 (44.1)	1.07 (0.41, 2.76)	0.89	1.13 (0.41, 3.15)	0.811

* Adjusted analyses performed using logistic regression. Variables that were included are sex, trauma admission diagnosis and time until nasogastric feeding commencement.

Table S3. **Co-intervention use.**

Co-intervention	Plasma-Lyte 148	0.9% saline	P-value
Metoclopramide- no./total no. (%)	8/35 (22.9)	15/34 (44.1)	0.06
Erythromycin- no./total no. (%)	1/35 (2.9)	4/34 (11.8)	0.15
Opiates- no./total no. (%)	25/35 (100)	33/34 (97.1)	0.3
Catecholamines- no./total no. (%)	29/35 (82.9)	28/34 (82.4)	0.96

Table S4. **Daily total gastric residual volumes (mL) day 0 to day 7.**

Gastric residual volume	Plasma-Lyte 148	0.9% saline	P-Value
Day 0 - median [IQR] no./total no. (%)	140 [5 - 285] 35/35	68 [0 - 328] 34/34	0.48
Day 1 - median [IQR] no./total no. (%)	340 [41 - 530] 35/35	281 [83 - 1085] 34/34	0.27
Day 2 - median [IQR] no./total no. (%)	185 [49 - 500] 35/35	300 [59 - 564] 34/34	0.32
Day 3 - median [IQR] no./total no. (%)	100 [25 - 434] 34/35	167 [43 - 450] 31/34	0.57
Day 4 - median [IQR] no./total no. (%)	43 [14 - 268] 26/35	238 [28 - 603] 26/34	0.06
Day 5 - median [IQR] no./total no. (%)	43 [6 - 256] 20/35	138 [24 - 375] 24/34	0.36
Day 6 - median [IQR] no./total no. (%)	35 [11 - 188] 14/35	138 [19 - 315] 21/34	0.18
Day 7 - median [IQR] no./total no. (%)	15 [1 - 46] 12/35	50 [15 - 870] 21/34	0.049

Table S5. **Biochemical data from day 0 to day 3.**

	Plasma-Lyte 148	0.9% saline	P-value
Lowest bicarbonate			
• Day 0	21.9 (0.8)	21.0 (0.8)	0.40
• Day 1	22.6 (0.7)	22.1 (0.7)	0.64
• Day 2	24.2 (0.7)	24.6 (0.8)	0.71
• Day 3	24.66 (0.6)	24.3 (0.8)	0.73
Highest bicarbonate			
• Day 0	24.2 (0.8)	23.4 (0.8)	0.50
• Day 1	25.5 (0.5)	24.9 (0.7)	0.53
• Day 2	26.8 (0.7)	26.5 (0.7)	0.75
• Day 3	27.2 (0.7)	26.2 (0.7)	0.29
Lowest potassium			
• Day 0	3.7 (0.1)	3.8 (0.1)	0.75
• Day 1	3.7 (0.1)	3.7 (0.1)	0.60
• Day 2	3.7 (0.1)	3.7 (0.8)	0.66
• Day 3	3.7 (0.1)	3.6 (0.1)	0.47
Highest potassium			
• Day 0	4.3 (0.1)	4.4 (0.1)	0.57
• Day 1	4.6 (0.1)	4.4 (0.1)	0.40
• Day 2	4.3 (0.1)	4.2 (0.1)	0.64
• Day 3	4.2 (0.1)	4.1 (0.1)	0.48
Lowest sodium			
• Day 0	138.5 (1.0)	138.6 (0.7)	0.93
• Day 1	138.2 (0.9)	138.6 (0.6)	0.72
• Day 2	3.7 (0.1)	3.7 (0.1)	0.66
• Day 3	3.7 (0.1)	3.6 (0.1)	0.47
Highest sodium			
• Day 0	142.1 (1.1)	141.7 (0.7)	0.77
• Day 1	142.4 (0.9)	142.3 (0.6)	0.89
• Day 2	142.5 (0.8)	143.5 (0.9)	0.42
• Day 3	143.0 (0.9)	144.3 (1.1)	0.38
Lowest glucose			
• Day 0	7.4 (0.4)	7.2 (0.3)	0.66
• Day 1	7.2 (0.2)	6.9 (0.3)	0.40
• Day 2	7.3 (0.2)	7.4 (0.4)	0.90
• Day 3	7.3 (0.2)	7.0 (0.3)	0.36
Highest glucose			
• Day 0	9.7 (0.6)	9.4 (0.4)	0.62
• Day 1	10.6 (0.7)	9.1 (0.3)	0.07
• Day 2	10.0 (0.4)	9.2 (0.4)	0.14
• Day 3	9.7 (0.4)	9.1 (0.4)	0.32
Lowest pH			
• Day 0	7.31 (0.02)	7.31 (0.02)	0.94

• Day 1	7.34 (0.02)	7.35 (0.01)	0.60
• Day 2	7.37 (0.01)	7.38 (0.01)	0.25
• Day 3	7.41 (0.01)	7.39 (0.01)	0.24
Highest pH			
• Day 0	7.38 (0.02)	7.39 (0.01)	0.83
• Day 1	7.42 (0.01)	7.43 (0.01)	0.39
• Day 2	7.45 (0.01)	7.44 (0.01)	0.20
• Day 3	7.46 (0.01)	7.45 (0.01)	0.30
Lowest carbon dioxide			
• Day 0	49.1 (3.0)	46.5 (2.3)	0.50
• Day 1	45.7 (1.3)	43.9 (1.4)	0.34
• Day 2	46.0 (1.7)	43.0 (1.3)	0.17
• Day 3	42.6 (1.5)	42.7 (1.7)	0.97
Highest carbon dioxide			
• Day 0	38.5 (1.3)	37.5 (1.5)	0.61
• Day 1	37.0 (1.1)	34.8 (1.0)	0.12
• Day 2	37.2 (1.4)	36.7 (1.0)	0.78
• Day 3	36.5 (1.3)	36.2 (1.3)	0.87

Values followed by brackets are mean (Standard error).