Saline (0.9%) vs. PlasmaLyte® 148 Fluid Intervention Trial in Major Surgery Patients (The SPLIT- Major Surgery study): a single-centred randomised double-blind trial

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Background and Goals:

The administration of intravenous (IV) crystalloid fluid is a ubiquitous intervention in patients undergoing major surgery. We conducted a prospective Phase 4, single centre blinded study investigating the safety and efficacy of using Saline (0.9%) (Baxter Healthcare, Australia) or Plasmalyte 148 (Baxter Healthcare, Australia) as perioperative fluid therapy in adult patients undergoing major surgery. Exclusion criterion included: surgery less than 2 hours day, day surgery cases, raised intracranial pressure, patients undergoing liver or renal transplantation. **Primary outcome:** 1. Proportion of patients with either acute kidney (RIFLE-criteria). **Secondary outcomes:** 1. Development of metabolic acidosis (defined as a base deficit >2 mEq/L or a bicarbonate level <20 mmol/L) in the first 3 days after surgery; 2. Development of acidemia defined as a pH <7.3 in the first 3 days after surgery; 3. Postoperative complications (Clavien Dindo classification); 4. Hospital length of stay and mortality. Blinded study fluid was used for all intraoperative and postoperative crystalloid therapy until hospital discharge. Perioperative management including use of colloids, blood and other blood products were at the discretion of the attending anaesthesia and surgical teams. The study design is summarised in **Figure 1**.

Results:

1100 patients were recruited. The consort diagram is presented in **Figure 2**. Patients in both groups had similar baseline characteristics, including types of surgery, ASA scores, and comorbidities. In the Plasmalyte group the median (IQR) age was 62 (50:74) years and 56% of patients were male. In the Saline group the median age was 63 (48:74) years; 57% of patients were male. Intraoperatively there were no significant differences in the types of surgery. 1100 patients (100%) received intraoperative Trial fluid; 476 patients received Plasmalyte and 634 patients received Saline (0.9%). The median (IQR) amount Trial fluid received was greater in the Plasmalyte group: 2000ml (1000:2000) vs. 1925 ml (1000:2000) in the Saline group (p=0.007) (**Table 1**). Median (IQR) duration of surgery was 196 (150:282) minutes in the Plasmalyte group and 197 (153:283) minutes in the Saline group. Postoperatively, there were no differences in the incidence of AKI between the group: 52 (10.9%) patients in the Plasmalyte group developed a postoperative AKI compared to 59 (9.3%) patients in the saline group (p=0.41, 95%CI: 0.6 to 1.2) (**Table 2**). Patients who developed an AKI were older, had larger volumes of fluid both intraoperatively and on postoperative Day 1, and had greater fluid balances intraoperatively and on postoperative Day 1. Patients receiving Saline a developed a transient hyperchloreaemic metabolic acidosis on postoperative Day 1 compared to patients receiving Plasmalyte. There were no differences in the development of postoperative complications between the groups (**Table 3**). Median (IQR) length of stay was almost identical in both groups (Plasmalyte 5.0 days (2.77:8.98) vs. Saline 5.0 days (2.81:9.04)).

Figure 1. Study design

Figure 2. Consort diagram

Table 2. Primary outcome: Incidence of AKI (RIFLE Criteria)

RIFLE Criteria	Plasmalyte n = 476	Saline n = 634	p-value	Grand Total n = 1110
Risk	37 (7.8%)	45 (7.0%)	0.7	82 (7.3%)
Injury	12 (2.5%)	12 (1.9%)	0.53	24 (2.2%)
Failure	3 (0.6%)	1 (0.2%)	0.3	4 (0.4%)
Loss	0 (0%)	0 (0%)	-	0 (%)
Total AKI	52 (10.9%)	59 (9.3%)	0.41 (95%CI: 0.6 to 1.2)	111 (10%)

Table 1. Intraoperative fluid intervention

	Plasmalyte n = 476		Saline n = 634		P-value
	No of patients (%)	Median (IQR)	No of patients (%)	Median (IQR)	
Trial fluid (mL)	476 (100%)	2000 (1000-2000)	634 (100%)	1925 (1000-2000)	0.007*
Other fluids administered at discretion of anaesthetist					
Saline 0.9%	9 (2%)	520 (100-1000)	32 (5%)	500 (500-1000)	0.68
Plasmalyte	33 (7%)	1000 (1000-2000)	25 (4%)	1000 (1000-3000)	0.1
Hartmann's	4 (<1%)	1000 (1000-1750)	1 (<1%)	1000 (1000-2000)	0.82
Colloids & blood products (mL)					
4% Albumex	29 (6%)	500 (500-500)	25 (4%)	500 (500-500)	0.23
20% Albumex	48 (10%)	100 (100-2000)	44 (7%)	200 (200-400)	0.014*
Packed red blood cells	33 (7%)	500 (253-710)	38 (6%)	506 (290-720)	0.94
Fresh frozen plasma	9 (2%)	573 (500-600)	6 (1%)	521 (470-553)	0.33
Platelets	14 (3%)	400 (343-702)	19 (3%)	336 (300-582)	0.49
Cryoprecipitate	4 (1%)	165 (71-400)	6 (1%)	336 (296-544)	0.14
Other input (mL)	19 (4%)	300 (100-875)	25 (4%)	175 (100-285)	0.04*
Medications, drug infusions and drug flushes					
Urine	133 (28%)	530 (275-990)	127 (20%)	500 (240-820)	0.83
Accurate Blood loss	76 (16%)	800 (300-1150)	60 (10%)	500 (200-1000)	0.46
Other (nasogastric, faeces)	10 (2%)	250 (77-825)	6 (1%)	525 (200-1500)	0.46
Total input (mL)	476 (100%)	2000 (1000-2166)	634 (100%)	2000 (1000-2013)	0.036*
Total output (mL)	138 (29%)	600 (315-1100)	133 (21%)	532 (240-881)	0.53
Tot fluid balance (mL)	476 (100%)	1900 (1000-2000)	634 (100%)	1668 (1000-2000)	0.46

Table 3. Postoperative complications (Clavien Dindo classification)

	Plasmalyte n = 476	Saline n = 634	Total n = 1110
Nil complications	183 (38.4%)	241 (38.0%)	424 (38.2%)
At least 1 complication	293 (61.6%)	393 (62.0%)	686 (61.8%)
Clavien Dindo Grade of worst complication			
Grade 1	78 (16.3%)	135 (21.2%)	213 (19.1%)
Grade 2	85 (17.3%)	71 (11.2%)	156 (14.1%)
Grade 3a	15 (3.1%)	17 (2.7%)	32 (2.9%)
Grade 3b	3 (0.6%)	2 (0.3%)	5 (0.5%)
Grade 4a	80 (16.8%)	133 (20.9%)	213 (19.1%)
Grade 4b	28 (5.9%)	32 (5.0%)	60 (5.4)
Grade 5	4 (0.8%)	3 (0.5%)	7 (0.6%)

Conclusion:

In patients undergoing major surgery, there were no differences in the incidence of AKI or the development of postoperative complications in patients who received Plasmalyte or Saline for perioperative fluid intervention. Length of hospital stay was also similar between the groups. Patients who received Saline developed a transient hyperchloreaemic metabolic acidosis on postoperative Day 1.