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Postoperative outcomes based on crystalloid administration in pediatric patients with necrotizing enterocolitis undergoing laparotomy

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Abstract

Intravenous fluid prescription is an essential part of postoperative care and may play a causal role in postoperative complications. The objective of the present study was to evaluate the relationship between intraoperative fluid administration and postoperative outcomes in a large cohort of pediatric patients.

This analysis included a retrospective review of 172 patients who underwent gastroenterological surgery from January 2012 to September 2018 at an academic tertiary care hospital. Patients were evaluated based on the median amount of corrected crystalloids and subsequently dichotomized as low (<25.89 mL/kg h) versus high (>25.89 mL/kg h). The primary outcome measure was the postoperative length of hospital stay (pLOS). Secondary outcome measures included the postoperative time to restore gastroenterological functions and postoperative complications.

Patients who received larger amounts of crystalloids were more likely to have a lower intraoperative level of hemoglobin ($P=.78$) and an intraoperative blood transfusion ($P=.27$). There were trends toward lower incidence rates of hyperchloremic acidosis ($P=.375$) and metabolic acidosis ($P=.54$) in the high crystalloid administration cohort. The incidence of postoperative complications increased as the amount of administered fluid decreased ($P=.046$). The total length of hospital stay was shorter in patients who received high volumes of crystalloid fluid (19.5 [15.75–32.25] days) than in patients who received low volumes (22 [16–29.5] days, $P=.283$).

Significant and multifaceted variability in crystalloid administration was noted among pediatric patients undergoing major surgery. High fluid administration was associated with favorable postoperative outcomes; these findings could be applied to improve patient safety and facilitate better quality of care.

Abbreviations: AKI = acute kidney injury, ASA = American Society of Anesthesiologist, CI = confidence interval, CVP = central venous pressure, EBL = estimated blood loss, FO = fluid overload, GDT = goal-directed therapy, HR = heart rate, IVF = in vitro fertilization, LOS = length of stay, MAP = mean arterial blood pressure, NEC = necrotizing enterocolitis, NICU = newborn intensive care unit, OR = odds ratio, PRBC = packed red blood cell, RR = risk ratio.

Keywords: abdominal surgery, crystalloid administration, estimated blood loss, length of hospital stay

1. Introduction

Necrotizing enterocolitis (NEC) is among the most common and devastating diseases in neonates, and it is the major cause of death in neonates. It is common in preterm infants.[1,2] Approximately 15 million babies, 11.1% of all livebirths, are born preterm worldwide.[3] Approximately 7.8% of preterm births (gestational age <37 weeks) occur in China,[4] which means that there are >1 to 5 million preterm births per year in China.[5] Some neonates who suffer from necrotizing enterocolitis should undergo surgical treatment, especially critically ill infants.[6]

Children with NEC who undergo surgery are at high risk of fluid overload (FO). Hypervolemic fluid administration might improve delayed bowel function and postoperative ileus and may shorten hospitalization.[7] Furthermore, the high incidence of postoperative acute kidney injury (AKI) likely results from perioperative fluid overload, and this relationship has been extensively examined.[8–10] Adequate intraoperative fluid administration among infants undergoing intra-abdominal surgery is an especially crucial issue that can seriously affect postoperative organ function and outcomes.[7,11] Furthermore, it remains unclear whether the adverse outcomes mentioned are driven more by intraoperative events, patient characteristics, or true

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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differences in intraoperative fluid administration. Therefore, it is worthwhile to understand the spectrum of FO in children undergoing surgery and the associations between FO risk factors and outcomes to develop relevant interventions at the patient and provider levels.

In this retrospective analysis, we aimed to evaluate the role of intraoperative fluid administration in postoperative recovery in pediatric NEC patients who underwent surgical procedures. The goal of the present study was to assess the variability in crystalloid administration among pediatric patients undergoing major gastroenterological surgery at a large tertiary care hospital. We collected a sizeable number of infants to better compare the surgical treatment of patients and their clinical outcome between patients who received different levels of crystalloid administration.

2. Methods

2.1. Patients

We conducted this retrospective review of medical records among patients who underwent gastroenterological surgery in a newborn intensive care unit (NICU) or intensive care unit (ICU) from January 2012 to September 2018 at the Children's Hospital of Chongqing Medical University, with the approval of the institutional review board (2019–13). All the parents provided consent for the publication of their children's medical information. The patients who had been diagnosed with NEC using Bell's criteria as modified by Walsh and Kliegman[2] during the study period were considered eligible for inclusion in the study if they met the following inclusion criteria: stage III NEC requiring laparotomy; a gestational age of >31 weeks; and normal preoperative renal function. The surgical approach to patients included surgical resection of the perforated intestine and necrotic intestine, the creation of intestinal stomas, and/or peritoneal drainage. The exclusion criteria were spontaneous intestinal perforation, severe cardiac dysfunction, in vitro fertilization (IVF), acute pulmonary bacterial infection, and gastrointestinal anomalies (aproctia, intestinal atresia, or Hirschsprung disease); infants who died during acute NEC were also excluded. We compared all of the surgical features among the surgeons who performed these cases, and no differences were noted.

The electronic medical records of patients were reviewed, including preoperative data, operative data, and clinical outcomes, including demographic data, clinical and pathological details, pre-existing comorbidities, diagnosis and procedure information, American Society of Anesthesiologist (ASA) score, operative time, intraoperative estimated blood loss (EBL), transfusion, intraoperative hemoglobin levels, intraoperative crystalloid and colloid fluid administration, receipt of packed red blood cell (PRBC) transfusion, clinical management, laboratory data, mortality, postoperative length of stay (LOS), histopathology of the resected bowel segments, and discharge summaries. Additionally, administered crystalloids were reported as a corrected metric (mL of fluid per 1 kg weight, per 1 operative hour) to adjust for the confounding effects of body mass and operative time. The median amount of corrected crystalloids in this cohort was 25.89 mL/kg h. For the purpose of analysis, the patients were dichotomized based on the median amount of corrected crystalloids as low (<25.89 mL/kg h) versus high (>25.89 mL/kg h).

We computed the fluid balance according to the following formula: fluid balance = (crystalloid + 1.5 × [colloid + blood product]) (volume in) − (urine output + 3 × [estimated blood loss]) (volume out) − (operation duration [hrs] × [weight {kg}+40]) (maintenance). The calculated fluid balance was normalized the actual volume of resuscitation (volume in) relative to the expected amount of fluid requirement (volume out, maintenance requirement, and insensible loss), which accounted for physiologically relevant potential patient and procedural characteristics.[12] In some cases, biochemical parameters accounted for oxygen debt during surgery, such as serum lactate level, central venous oxygen saturation (ScvO2), arterial acid-base balance parameters, and intraoperative hemodynamic parameters, and any inotropes used were recorded and evaluated. The primary outcome measure was the postoperative LOS, defined from the calendar day of surgery to the day of discharge. Secondary outcome measures included postoperative morbidity, including infectious complications and other organ complications, until day 90 after surgery.

2.2. Statistical analysis

The data were subjected to statistical comparisons using the SPSS 22.0 software package (SPSS Inc., Chicago, IL). Categorical variables are expressed as frequencies with percentages and were compared with the chi-square test and/or Fisher exact statistic test, as appropriate. Continuous data with a normal distribution are presented as the means ± (standard deviations) and tested with paired or unpaired *t* tests. Continuous data that were non-normally distributed are presented as medians (interquartile ranges) and were compared with the Mann–Whitney *U* test and the Wilcoxon rank-sum test for unpaired and paired tests, respectively. The relative risks for postoperative variables were assessed using cross-tabulation (odds ratio [OR]) or multivariate logistic regression analysis (risk ratio [RR]). The statistical significance was evaluated using a two-tailed 95% confidence interval (CI) and a *P* value. A $P < .05$ was considered statistically significant for all tests.

3. Results

Between January 2012 and September 2018, a total of 172 patients who underwent laparotomy surgery following NEC diagnosis met the criteria for inclusion (Table 1). Fifteen patients who underwent simple drainage for NEC and 157 patients who underwent laparotomy for bowel resection and subsequent intestinal anastomosis or ostomy were identified. For the purpose of analysis, the corrected crystalloid volume was dichotomized as high or low based on the median amount of corrected crystalloids based on the median corrected crystalloid volume among the entire cohort was 25.89 mL/kg h (Table 2).

The baseline characteristics and clinical status of the high and low groups were similar, including maternal age, delivery mode, sex, APGAR scores (at 5 minutes), postnatal age at operation, history of enteral feeding, and other measures of perforated necrotizing enterocolitis disease severity. In the low crystalloid administration group, the patients' birth weight and weight at diagnosis were heavier ($P = .00$) than those in the high crystalloid administration group. Interestingly, the patients with longer gestational weeks were more often had low crystalloid administration ($P = .003$). In the high crystalloid administration group, a median of 153.00 mL of LR was administered

Table 1

Baseline demographics of eligible patient and preoperative variables.

	Total population		
	<25.89 mL/kg h (86)	**>25.89 mL/kg h (86)**	***P* values**
Age, d	11.96 (6.23–43.25)	10.98 (6.62–28.88)	.259
Male: female	49: 37	47: 39	.759
Weight at admission, kg	3.05 (2.38–3.76)	2.43 (1.99–2.94)	.000
Gestational age, wk	37.5 (34.93–39.29)	35.5 (33.40–38.43)	.003
Birth weight, kg	2.81 (2.19–3.35)	2.31 (1.79–2.86)	.000
Weight at diagnosis, kg	3.06 (2.40–3.70)	2.36 (1.99–2.95)	.000
History of enteral feeding, n (%)	81	78	.387
Probiotics, n (%)	72	78	.171
APGAR scores at 5 min	10 (9–10)	10 (9–10)	.888
Cesarean delivery, n (%)	55	62	.252
Maternal age, y	28 (24–32)	27 (25–31)	.290
SGA infant, n (%)	9	12	.485
Postnatal age at operation, d	21.74 (8.78∼53.38)	19.89 (8.02∼39.46)	.140
Congenital anomalies, n (%)	63	64	.862
Transfusion preoperation, n (%)	41	38	.646
Vasopressor use at enrollment, n (%)	6	10	.294
Respiratory support, n (%)	6	10	.294
First platelet count (onset of symptoms) (109/L)	300 (202–450.25)	260 (168.25–416.5)	.202
Hemoglobin, g/L	119 (93.75–138.75)	122 (92–144.5)	.688
First WBC (onset of symptoms) (109/L)	9.67 (5.59–13.04)	9.8 (6.38–16.26)	.525
First procalcitonin (onset of symptoms) (ng/mL, normal value: 0–0.5)	2.71 (0.35–10.54)	2.58 (0.31–10.91)	.990
First CRP (onset of symptoms) (mg/L, normal value: 0–10)	21 (8–49.5)	21.5 (8–49.25)	.615
Albumin (g/L, normal range, 35–50)	28.9 (25–32.55)	27.35 (24.5–30.2)	.131
Operative time, min	124.8 (104.55–150)	100.2 (87.45–126.15)	.000
Operative blood loss, mL	15 (10–20)	10 (7.25–21.25)	.392
Transfused patients, n (%)	70	64	.270
ASA classification			1.000
ASA1–2	5	5	
ASA3–4	81	81	
Bowel involvement, n (%)			
Distal ileum	40	57	
Distal ileum and colon	8	4	
Ascending colon	38	31	
Descending colon	32	13	
Extent of disease, n (%)			
Multifocal NEC	60	58	
Localized NEC	21	15	
Panintestinal NEC	5	14	

NEC = necrotizing enterocolitis.

intraoperatively compared with 111.25 mL in the low crystalloid administration group (Table 3).

No differences in mean arterial blood pressure (MAP), heart rate (HR), central venous pressure (CVP), or amount of diuresis between the groups were observed at the end of surgery, although significant decreases in MAP, relative to the baseline value, were found in both groups.

Table 2

Volume of crystalloid and fluids infused.

Intraoperative fluids	**<25.89 mL/kg h (86)**	**>25.89 mL/kg h (86)**	***P* values**
IV crystalloids, mL	111.25 (80–150)	153.00 (118.75–246.25)	.000
Colloid, n (%)	77 (89.53%)	67 (77.91%)	.039
IV colloids, mL	50 (50–62.5)	50.00 (13.75–50)	.004
Urine output, mL/kg h	20 (10–30)	20 (10–30)	.561
Balance	108.68 (56.74–164.43)	149.92 (86.32–215.82)	.001

Fluid Balance = (Crystalloid + 1.5 × [colloid + bloodproduct])(Volume In) − (UrineOutput + 3 × [estimatedbloodloss]) (VolumeOut) − (Operativeduration [hrs] × [weight {kg} + 40])(Maintenance).

3.1. Outcomes

According to established criteria, a comparison of the outcomes between the 2 groups is summarized in Table 3. There were no differences in the time to passage of the first stool or removal of the nasogastric tube between the study groups (Table 4).

Postoperative vomiting was reduced in patients with low-volume saline treatment compared with patients who received high-volume saline treatment, but this difference was not statistically significant ($P = .30$). Notably, patients receiving <25.89 mL/kg h were proportionally more likely to develop postoperative complications, including leakage, sepsis, infectious complications of pneumonia, and surgical site infections. Sixteen patients (55/86) in the low-volume saline group experienced at least 1 complication compared with 42 (42/86) in the high-volume saline group, which was significantly reduced in the high-

Table 3

Intraoperative laboratory variables according to the low and high crystalloids administration.

	<25.89 mL/kg h (86)	>25.89 mL/kg h (86)	*P* values
ScvO2	0.69 (0.59–0.81)	0.8 (0.62–0.84)	.245
Hypotensive events, n (%)	37 (43.0)	52 (60.5)	.02
Norepinephrine usage, n (%)	0 (0)	1 (1.2)	.32
Serum lactate, mmol/L	0.9 (0.7–1.6)	1.0 (0.7–1.65)	.448
Diuresis, n (%)	6 (7.0)	5 (5.8)	.755
Hyperchloremic acidosis, n (%)	14 (16.7)	10 (12.3)	.375
Serum potassium	3.55 (3.2–3.9)	3.4 (3.1–3.8)	.273
Serum bicarbonate, mmol/L	22.45 (21.1–25.55)	22.6 (20.6–24.6)	.576
pH	7.35 (7.3–7.41)	7.32 (7.27–7.40)	.111
Base excess	−2.5 (−4.8–0.33)	−3.1 (−5.75–0.95)	.22
BUN	6.69 (4.99–8.28)	6.5 (5.06–7.84)	.697
CR	41.1 (41.1–60.08)	46.5 (33.5–66.8)	.172
Serum sodium	137 (134–139)	136 (134.5–140)	.855
Serum osmolality	13.45 (11.68–15.28)	12.7 (11–14.6)	.218
Metabolic acidosis	41	37	.54
Hypokalemia	35	43	.142
Hyponatremia	4	8	.206
Acute kidney damage	37	36	.877
Intraoperative hemoglobin level	96 (81.5–106)	92 (83–106)	.784

volume fluid group (102 vs 59), with an OD of 0.538 (95% confidence interval [CI, 0.29–0.99]; *P* = .046) (Table 4).

The mean hospitalization time in the ICU or NICU (*P* = .002) was shorter in the group with drainage because most of the patients received continued treatment by their families for many reasons, so they had to be discharged in advance. Albumin was higher in the high-volume group than in the low-volume group within the in-hospital period (*P* = .01).

Usually, time spent on mechanical ventilation is utilized as a proxy for illness severity throughout the entire hospital stay, but the durations of mechanical ventilation were not significantly different between the 2 groups (*P* = .48); however, some patients were discharged in advance, which could have influenced the results. The overall mortality rate was higher in the high volume group (*P* = .005). Twenty-five infants died after the operation. The cause of death was primarily attributed to panintestinal NEC in 14 infants. The remaining deaths resulted from acute kidney failure (n = 4), severe infection (n = 1), hypotensive events (n = 2), and hypokalemia (n = 1), and 1 patient died of before discharge. No deaths occurred after stoma closure. There were obviously meaningful differences with respect to postoperative complications between the 2 groups (*P* = .046, Table 4). The most common complications were wound leakage (n = 65), septicemia (n = 59), and wound splitting (n = 27).

4. Discussion

This study demonstrates variation in the clinical outcome based on crystalloid fluid administration in patients undergoing pediatric elective major surgery. Perhaps of more importance, we found a large range of variability in crystalloid fluid administration, particularly in smaller babies in babies in

Table 4

Patient outcomes according to the crystalloid fluids utilization.

	<25.89 mL/kg h (86)	>25.89 mL/kg h (86)	*P* values	Odds ratio (95% CI)
First defecation, d	1 (1–2.5)	1 (1–2)	.696	
90 days parenteral nutrition depend, n (%)	6 (6.98)	18 (20.93)	.008	
Days to enteral feeds	7 (6–10)	7 (5–9)	.511	
NICU length of stay, d	2.16 (0.79–4.69)	1.70 (0.77–2.85)	.296	
Vomiting, N (%)	6 (6.98)	10 (11.63)	.294	
Mechanical ventilation, d	0.53 (0.21–1.63)	0.53 (0.21–1.09)	.476	
Albumin minimum (g/L, normal range, 35–50)	23.9 (19.9–26.5)	25.35 (22.43–28.65)	.01	
Mortality, n (%)	6 (6.98)	19 (22.09)	.005	
Removal nasogastric tube, d	5 (3–6.25)	5 (4–7.25)	.288	
Total number of complications, n (%)	102	59		
No. of patients with complications, n (%)	55 (12.0)	42 (19.6)	.046	0.538 (0.29–0.99)
Postoperation length of stay in hospital (d)	15 (11.75–20.25)	15 (11–21)	.616	0.73 (0.56–1.22)
Bacterial sepsis, n (%)	2 (2.33)	1 (1.16)	.56	
Short bowel syndrome, n (%)	1 (1.16)	1 (1.16)	1.0	
Total length of stay, d	22 (16–29.5)	19.5 (15.75–32.25)	.283	
Wound leakage, n (%)	33	32	.875	
Wound infectious, n (%)	12	15	.539	

unstable conditions, which might be determined by the surgeons and anesthesiologists. We noted that intraoperative administration of >25.89 mL/kg h of crystalloids was associated with significant improvements in metabolic and hemodynamic parameters and recovery measures, as well as a shortened hospital stay, among patients undergoing gastroenterological surgery. Furthermore, the amounts of norepinephrine and diuresis administered in the operating room were decreased in the low-volume patients, but the total number of complications was significantly increased in the low-volume group.

Intraoperative fluid administration is an integral and critical component of recovery protocols and may impact surgical outcomes.[12] FO has gained a significant amount of attention in recent ICU research as a risk factor for poor outcome.[13,14] Very little data have been published on the effect of FO as a risk factor for poor outcome in smaller babies and babies in unstable conditions who undergo gastroenterological surgery,[15] for whom perioperative fluid management plays a vital role and to our knowledge, this is the first study specifically examining FO.

It is critical for fluid management to reach a balance between insufficient fluid resuscitation with consequent hypovolemia and excessive fluid with resulting edema at certain risks including intestinal edema, pulmonary edema, latent wound healing, and postoperative ileus.[7] Several clinical trials have demonstrated improved outcomes with “goal-directed” fluid therapy, with less postoperative morbidity after major surgery.[16,17] A negative fluid balance was independently associated with weaning success in mechanically ventilated patients as well as improving survival.[18]

Furthermore, restricting intraoperative fluid administration can improve patient survival. However, it can also increase complications. The current study expanded previous work by examining the fluid administration status in pediatric patients undergoing major gastroenterological surgery, among whom the topic of crystalloid administration is particularly relevant. The association between increasing crystalloid administration and obtaining better clinical outcomes found in our study is not similar to findings from previous clinical studies conducted in adult patients with severe sepsis.[19]

The current study characterized and defined fluid administration patterns across a cohort of pediatric patients undergoing gastroenterological surgery. Previous reports covered a wide variety of serious conditions, ranging from major trauma to extensive surgery, focusing mainly on adult patients with different comorbidities and higher ASA scores, and postoperative gastroenterological recovery and complications might be different in terms of perioperative care. This difference is especially apparent when stratified by crystalloid administration.

As care standardization and pathway development have become increasingly important in operationalizing efficiency interventions, this residual variation is undesirable. Furthermore, the current research noted that these differences in fluid volume were absolutely correlated with hypotension events and operative time. Real opportunities exist to standardize behavior at the hospital level if best practices can be identified and codified. Furthermore, the wide range of fluids emphasizes the fact that giving a standard volume load is not appropriate when applied at the individual level. The results of the present study reiterate the need for individually indicated fluid support in relation to appropriately monitored hemodynamic changes.

Excess fluid administration might cause increased incidence rates of postoperative respiratory failure or pneumonia due to fluid accumulation or may prolong postoperative ileus due to gastrointestinal motility inhibition.[11,20,21,22] The occurrence of postoperative ileus is the most important driver of length of stay and has been associated with the volume of fluid administration during surgery. In addition, excess fluid may decrease tissue oxygenation, which has adverse implications for wound healing. Furthermore, coagulation may be enhanced with crystalloids, which may predispose patients to postoperative thrombosis.[23] A common element of modern enhanced recovery protocols is the limitation of excessive intravenous fluid, with a focus on the maintenance of normovolemia.[24]

The rate and number of postoperative complications in our study decreased as the amount of fluid administered increased. This reduction corresponds with many goal-directed therapy (GDT) trials, including the recently published study by Mayer et al,[25] where only 20% of GDT patients developed complications compared with 50% in the control group. GDT is generally associated with infusion of larger amounts of crystalloids and improvement in hemodynamic parameters at the end of surgery. However, we did not observe differences in relation to the recovery of gastrointestinal function between groups. In contrast to the lower incidence and number of complications, a limited impact on the length of stay in the ICU or hospital was found in our study. Hospital length of stay was only reduced in those patients whose optimization protocol was carried out. However, some factors may limit the generalization of these findings. Each institution usually has its own regimens and protocols of ICU and ward care, which can significantly impact the length of stay.

Discharge criteria were not predefined in our study, which can limit the interpretation of both the hospital and ICU length of stay parameters. Biochemical parameters of oxygen debt (serum lactate level, its normalization and low ScvO2 or low mixed venous oxygen saturation [SvO2]) could serve as these markers and are early indicators of unfavorable outcome in critically ill patients.[26–29] The course of ScvO2 values at different time points was similar in both groups, with a slight elevation during anesthesia and a decrease 24 hours after the operation. A difference in arterial serum lactate levels between patients with complications and those without complications was detected. The extent of disease was reported to impact mortality because survival was observed to be lower for infants with panintestinal involvement compared with those multifocal and isolated NEC.[30,31]

In the present study, the disease extent was greater in the patients who died, particularly when the rectum, jejunum, and ileum were involved. Furthermore, the average age of presentation was lowest for the panintestinal involvement group, so it does not appear that a delay in diagnosis contributed to worse outcomes. Necrotizing enterocolitis with panintestinal involvement also presents with a more widespread inflammatory process that can result in necrosis of the distal ileum and proximal colon. This raises the question of whether it is possible that the greater PRISM (pediatric risk of mortality) score and greater numbers of patients with shock in the high crystalloid group signified much sicker patients, which may have led to increased mortality rather than mortality being directly related to crystalloid fluid administration. Because this is a retrospective study, it is not possible to distinguish whether high crystalloid administration was simply a marker of illness severity or a causative factor of outcome. Taken together with previous reports, data from the current study serve to highlight the need for implementing evidence-based best practices for fluid resuscitation therapy to reduce unwanted variations within the health care system and to promote safer and higher quality patient care.[22] In fact, we are beginning to develop and implement an enhanced recovery pathway using tangible hemodynamic end points for the resuscitation of pediatric patients undergoing major surgery.

Several potential weaknesses of our study should be considered when interpreting the data. First, the relatively small sample of heterogeneous patients from one institution may limit the generalizability of the results. Furthermore, the data were collected retrospectively over a very long study time period, and many care practice changes led to different clinical treatment algorithms have resulted in an inherent risk of selection bias between study patients.

Routines of perioperative care at our institution, such as the use of prophylactic antibiotics, deep vein thrombosis prophylaxis, dispensed nutritional support, and early postoperative mobilization, did not change over the period of the study. Moreover, the routine use of nasogastric tubes had been abandoned before the study commenced, and early postoperative feeding has been routinely implemented in our hospital since 2002. Given the retrospective nature of this single-center study, selection bias was a possibility. Furthermore, there was a number of infants withdrawing from support, making it difficult to interpret the survival data. There may be residual confounders that have potentially impacted the variability in fluid administration. It is possible that the exclusion of patients who stayed in the PICU for <72 hours could have significantly weakened the power of the corresponding analyses. For example, some hemodynamic parameters and end points impacting the volume and type of fluid administered were unavailable in this study, which may have influenced the volume of fluids administered. Further large multicenter prospective studies evaluating the effect of fluid balance on clinical outcomes in children with severe sepsis are required to determine whether this information could inform future iterations of sepsis guidelines as to the safe volume for fluid resuscitation.

5. Conclusion

The observed variability in crystalloid practice was multifaceted. High crystalloid administration might be associated with a favorable outcome in infants undergoing major elective abdominal surgery, although the difference did not achieve significance. Further study in the design of clinical trials of new therapies to optimize the treatment of NEC is needed to better elucidate which factors influence clinical outcomes for infants with necrotizing enterocolitis who undergo surgical procedures.

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Author contributions

Xin Xie, Chunbao Guo designed, analyzed, and measured the data. Chun Deng, Siyuan Guo helped design the experiments, performed the statistical analysis, and evaluated the manuscript; Chunbao Guo analyzed and interpreted the data, and wrote the paper.

References

[1] El-Dib M, Narang S, Lee E, et al. Red blood cell transfusion, feeding and necrotizing enterocolitis in preterm infants. J Perinatol 2011;31:183–7.
[2] Stey A, Barnert ES, Tseng CH, et al. Outcomes and costs of surgical treatments of necrotizing enterocolitis. Pediatrics 2015;135:e1190–7.
[3] Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.
[4] Xu H, Dai Q, Xu Y, et al. Time trends and risk factor associated with premature birth and infants deaths due to prematurity in Hubei Province, China from 2001 to 2012. BMC Pregnancy Childbirth 2015;15:329.
[5] Zhao X, Chen Y, Qiu G, et al. Reducing preterm births in China. Lancet 2012;380:1144–5.
[6] Gephart SM, McGrath JM, Effken JA, et al. Necrotizing enterocolitis risk: state of the science. Adv Neonatal Care 2012;12:77–87.
[7] Holte K, Klarskov B, Christensen DS, et al. Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized, double-blind study. Ann Surg 2004;240:892–9.
[8] Prowle JR, Chua HR, Bagshaw SM, et al. Clinical review: volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review. Crit Care 2012;16:230.
[9] Kambhampati G, Ross EA, Alsabbagh MM, et al. Perioperative fluid balance and acute kidney injury. Clin Exp Nephrol 2012;16:730–8.
[10] Dass B, Shimada M, Kambhampati G, et al. Fluid balance as an early indicator of acute kidney injury in CV surgery. Clin Nephrol 2012; 77:438–44.
[11] Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. J Intensive Care 2016;4:27.
[12] Regenbogen SE, Shah NJ, Collins SD, et al. Population-based assessment of intraoperative fluid administration practices across three surgical specialties. Ann Surg 2017;265:930–40.
[13] Lowell JA, Schifferdecker C, Driscoll DF, et al. Postoperative fluid overload: not a benign problem. Crit Care Med 1990;18:728–33.
[14] Bagshaw SM, Brophy PD, Cruz D, et al. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. Crit Care 2008;12:169.
[15] Lilot M, Ehrenfeld JM, Lee C, et al. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Br J Anaesth 2015;114: 767–76.
[16] Hiltebrand LB, Kimberger O, Arnberger M, et al. Crystalloids versus colloids for goal-directed fluid therapy in major surgery. Crit Care 2009;13:R40.
[17] Donati A, Loggi S, Preiser JC, et al. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 2007;132:1817–24.
[18] Upadya A, Tilluckdharry L, Muralidharan V, et al. Fluid balance and weaning outcomes. Intensive Care Med 2005;31:1643–7.
[19] Peake SL, Delaney A, et al. ARISE Investigators, ANZICS Clinical Trials GroupGoal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496–506.
[20] Glatz T, Kulemann B, Marjanovic G, et al. Postoperative fluid overload is a risk factor for adverse surgical outcome in patients undergoing esophagectomy for esophageal cancer: a retrospective study in 335 patients. BMC Surg 2017;17:6.
[21] Simpson RG, Quayle J, Stylianides N, et al. Intravenous fluid and electrolyte administration in elective gastrointestinal surgery: mechanisms of excessive therapy. Ann R Coll Surg Engl 2017;99:497–503.
[22] Sun Y, Chai F, Pan C, et al. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery-a systematic review and meta-analysis of randomized controlled trials. Crit Care 2017;21:141.
[23] Barak M, Rudin M, Vofsi O, et al. Fluid administration during abdominal surgery influences on coagulation in the postoperative period. Curr Surg 2004;61:459–62.
[24] Adamina M, Kehlet H, Tomlinson GA, et al. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery 2011;149:830–40.

[25] Mayer J, Boldt J, Mengistu AM, et al. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. Crit Care 2010;14:R18.

[26] Haanschoten MC, Kreeftenberg HG, Arthur Bouwman R, et al. Use of postoperative peak arterial lactate level to predict outcome after cardiac surgery. J Cardiothorac Vasc Anesth 2017;31:45–53.

[27] Scott HF, Brou L, Deakyne SJ, et al. Association between early lactate levels and 30-day mortality in clinically suspected sepsis in children. JAMA Pediatr 2017;171:249–55.

[28] Nguyen HB, Loomba M, Yang JJ, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflamm (Lond) 2010;7:6.

[29] Su L, Tang B, Liu Y, et al. P(v-a)CO2/C(a-v)O2-directed resuscitation does not improve prognosis compared with SvO2 in severe sepsis and septic shock: a prospective multicenter randomized controlled clinical study. J Crit Care 2018;48:314–20.

[30] de Souza JC, Fraga JC. Is mortality rate influenced by the site of involvement in neonates undergoing laparotomy for necrotizing enterocolitis? J Pediatr Surg 2009;44:1534–9.

[31] Thyoka M, de Coppi P, Eaton S, et al. Advanced necrotizing enterocolitis part 1: mortality. Eur J Pediatr Surg 2012;22: 8–12.