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The Relationship of Perioperative Fluid Administration to Outcomes in Colorectal and Pancreatic Surgery: A Review of the Literature

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Abstract

Optimal perioperative fluid administration in major gastrointestinal surgery remains a challenging clinical problem. Traditional dogma of a liberal approach to fluid administration in order to counteract potential hypovolemia and decreased end-organ perfusion can often result in fluid overload, perhaps negatively impacting perioperative outcomes. This hypothesis has been investigated in several types of gastrointestinal surgery. We discuss the current literature on perioperative fluid administration in colorectal and pancreatic surgery and highlight the controversies that still exist.

Keywords

fluid; colorectal; pancreatic; surgery; outcomes

INTRODUCTION

Defining the role of perioperative fluid administration in association with outcomes in major gastrointestinal abdominal surgery remains a challenge. Beginning in the 1920s, Alfred Blalock pioneered our understanding of the basic mechanisms of hypovolemic shock and demonstrated the therapeutic role of plasma and blood transfusion to counteract volume losses. His contributions were invaluable towards saving many lives of soldiers during World War II [1,2]. This work laid the foundation for routine administration of intraoperative fluids during surgery to avoid perioperative hypovolemia. Decades later, the concept of the “third space” was put forth by Tom Shires in a study in which he attempted to examine the effects of major abdominal surgery on whole body extracellular fluid volumes compared to a control cohort undergoing minor non-abdominal surgery. He found that the patients undergoing major abdominal surgery had significant decreases in their extracellular fluid volumes that he could not account for by blood loss or evaporative losses [3]. As a result, Shires hypothesized that the extracellular fluid loss could be due to internal distribution or third-spacing. Accounting for this loss during surgery was advised to prevent

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untoward effects due to hypovolemia empirically; thus, fluid practices favoring liberal administration gained traction.

Surprisingly, modern anesthetic guidelines for intraoperative fluid (IOF) replacement are not evidenced based, but rather have been empirically determined. These guidelines typically recommend crystalloid maintenance fluid rates that range from 10–15 ml/kg/hr with replacement of blood volume losses with crystalloid at a 3:1 ratio or colloid at a 1:1 ratio [4–6]. As most patients undergoing major abdominal surgery have not had any oral intake after midnight the day of their operation, some studies suggest administering as much as 2 liters of crystalloid preoperatively and/or intraoperatively may aid in compensating for dehydration. These studies also suggest that patients who have undergone bowel preparation may even be further dehydrated [7,8]. This management will often result in fluid overload, which is associated with a number of negative consequences, including but not limited to, pulmonary edema, cardiac dysrhythmias, and increased excretory work of the kidneys, as well as a number gastrointestinal complications, such as impaired gut motility, mucosal edema, and bowel anastomotic dehiscence [9,10]. The idea that restricting post-operative fluid administration could lead to improvements in postoperative morbidity was first tested by Lobo et al. in 2002 in a small study (N = 20) in elective colorectal surgery patients [11]. While this study was small, it had a significant impact, as it laid the foundation for further clinical trials that have investigated the impact of IOF restriction on perioperative outcomes in major abdominal surgery. Several randomized clinical trials have since been reported demonstrating that restrictive IOF administration as compared to liberal administration can result in decreased morbidity and length of stay [12,13].

Yet, there are still others that argue that neither liberal nor restrictive IOF practices are ideal, but rather fluid that is administered based on hemodynamic measurements is preferred [14]. This concept also comes from recently published randomized clinical trials in gastrointestinal surgery that have employed techniques to measure hemodynamics and administer fluid based on “what the patient needs [15–17].”

The Enhanced Recovery After Surgery (ERAS) Society, formed in 2010, is a multidisciplinary society dedicated to the science of perioperative surgical care in an effort to minimize morbidity and improve recovery. ERAS protocols were developed to provide evidence-based management guidelines in patients undergoing major abdominal surgery. These protocols have been examined in surgeries ranging from elective colorectal surgery to aortic aneurysm repair [18]. With respect to colorectal and pancreatic surgery, the ERAS protocols call for a “near zero” fluid balance without specification as to what exactly falls outside of “near zero” range, nor exactly what methods should be used (intraoperative hemodynamic measurement tools) to achieve this. In addition, ERAS protocols in colorectal surgery, for example, include no bowel preparation, no preoperative fasting until 2 hr prior to surgery, and early postoperative feeding. Similar fast-track protocols, including other forms of major surgery (musculoskeletal, urologic, gynecologic), have recommended preoperative carbohydrate administration [19]. The concept of preoperative carbohydrate administration was introduced in an attempt to replicate metabolic responses to eating breakfast, thus ameliorating surgical stress response. Although some studies demonstrated a decrease in length of hospital stay with this practice, a recent meta-analysis has shown no

difference in complication rates and highlights inherent study biases in assessing subjective outcomes [20,21]. Nonetheless, evidence for the overall effectiveness of ERAS protocols is now slowly emerging, with results in colorectal surgery demonstrating an improvement in morbidity [22]. Conversely, ERAS protocols in pancreatic surgery have yet to be reported in randomized trials [23].

It is important to recognize that the recommendations of the “near zero” fluid balance in the ERAS protocol for pancreaticoduodenectomy (PD) are largely based on the literature in colorectal surgery [24]. This begs the question: do studies in colorectal surgery apply to operations such as PD? This is an important question, as the recent literature examining the relationship of IOF on perioperative outcomes in PD are conflicted as to whether fluids have any impact on perioperative outcomes. Given the heterogeneity in study design, type of surgery, and ultimately recommendations, we sought to review the literature of this recent body of research to clarify and summarize the major findings, and highlight the current controversies that exist.

Colorectal Surgery

The role of perioperative fluid management in colorectal surgery has been studied in several randomized trials, shown in Table I, which have been included in subsequent meta-analyses. Lobo et al. randomized 20 patients who underwent elective hemicolectomies and sigmoidectomies into two cohorts of postoperative fluid management: a standard cohort, in which patients received greater than 3 liters of water and 154 mmol of sodium per day; and a restricted cohort, in which patients received less than 2 liters of water and 77 mmol of sodium per day [11]. It is important to note that IOF administration was not regulated in this study. The primary endpoint was gastric emptying time. This study found that patients in the standard cohort had longer gastric emptying times, a greater delay in return of bowel function, and experienced more complications. As a result, the authors concluded that an excess of salt and water might lead to more complications in contrast to fluid restriction [11]. However, MacKay et al. later conducted a larger study (N = 80), in which patients who underwent IOF restriction (crystalloid at 10 ml/kg/hr) were randomized to either a restricted or standard cohort similar to the above study by Lobo et al. The authors found no difference in return of bowel function or length of stay between restricted and standard postoperative fluid regimens [25].

The largest prospective multicenter trial devoted to this issue was published by Brandstrup et al. in 2003 [12]. These authors sought to investigate restricted versus standard perioperative fluid regimens, using complications as the primary outcome and death/adverse events as secondary outcomes [12]. Prior to this study, no trials had yet been performed to assess the combined effects of intraoperative and postoperative fluids on outcomes. In this multicenter trial, 141 patients were randomized into either standard or restricted fluid regimens. In the standard regimen, patients were intraoperatively preloaded with 500 ml of Hydroxyethyl starch 6% in normal saline (HAES 6%) for epidural anesthesia, and third space losses were replaced with normal saline, while neither was done in the restricted regimen. Operative blood loss was replaced more conservatively with HAES 6% in the restricted regimen, while normal saline and HAES 6% were used in the standard regimen.

Postoperatively, restricted regimen patients were given glucose 5% and/or HAES 6%, and given furosemide for weight gain greater than 1 kg. Standard regimen patients were resuscitated with crystalloid. On statistical analysis, fewer patients in the restrictive fluid cohort experienced complications, and fewer complications per patient were found as well [12]. These complications ranged from minor (i.e., superficial wound infection, pulmonary congestion, cystitis) to major (i.e., anastomotic leakage, bleeding, sepsis). Mortality was 4.7% in the standard cohort, while it was zero in the restricted cohort ($P = 0.12$). Although this difference was not statistically significant, it is certainly noteworthy and perhaps may have been significant with a larger sample size.

Nisanevich et al. similarly randomized 152 patients to either a restrictive or liberal arm of fluid administration in their study, which included patients undergoing various types of abdominal surgery. The largest subset of these patients (103, 68%) underwent colorectal procedures, while the other 32% of patient operations included small bowel resections, gastric resections, and pancreatic resections [13]. Patients in the liberal arm received an initial bolus of 10 ml/kg of lactated Ringer's (LR) solution, followed by 12 ml/kg/hr intraoperatively. In contrast, patients in the restrictive arm received 4 ml/kg/hr of LR intraoperatively without an initial bolus. Patients in the restrictive arm were associated with shorter hospital stays, more expeditious return of bowel function, and smaller increases in body weight. No mortalities occurred in either group, but the number of patients who experienced complications was less in the restrictive arm ($P < 0.05$) [13].

In contrast, Kabon et al. randomized 253 patients undergoing open colon resection to an IOF rate of 8 ml/kg/hr versus 16–18 ml/kg/hr to primarily examine wound infection rates. The wound infection rates were 11.3% and 8.5% in the two groups, respectively, which was not statistically significant. Length of stay did not differ between the groups either [26].

Holte et al. compared outcomes in patients undergoing fast-track colon surgery, under ERAS protocols, designed to administer minimal intravenous fluids perioperatively while encouraging more expedited PO intake [27]. In this randomized study, patients receiving 5–7 ml/kg/hr of crystalloid versus 18 ml/kg/hr intraoperatively were found to have improvements in postoperative pulmonary function, as measured by pulse oximetry and pulmonary function tests, but no difference in complications, although the restricted fluid group did show a trend towards less complications ($P = 0.08$) [27]. Abraham-Nordling et al. also evaluated the effect of perioperative fluid administration on outcomes, with their restricted and standard cohorts receiving a median of 3050 and 5775 ml of intravenous fluids, respectively. The authors found that while neither the median hospital stay nor readmission rate were different between groups, the number of patients who experienced complications, both major and minor, was significantly less in the restricted group ($P = 0.027$) [22].

The challenge of interpreting the aforementioned trials is twofold: not only have these studies varied in their approach to aspects of fluid management, that is, perioperative versus only postoperative and/or intraoperative, but also with use of the terms such as "restricted", "standard", and "liberal", in describing their ideas of fluid restriction. Three meta-analyses have been published including these randomized studies in the past 5 years, the first of

which was by Rahbari et al., in an attempt to define these terms [28–30]. Of the three, the Rahbari et al. meta-analysis is the only one to focus on perioperative fluid administration in colorectal surgery, while the others included various studies with significant percentages of patients who had undergone other forms of gastrointestinal surgery as well. Rahbari et al. described standard fluid therapy based on the textbook, *Miller's Anaesthesia,* as the following below:

"Administration of 10 ml per kg bodyweight of any colloidal fluid preparation for preblock hydration where applicable; administration of 5–7 ml of any crystalloid solution for compensatory intravascular volume expansion; administration of 4 ml per kg per hour for the first 10 kg, 2 ml per kg per hour for the second 10 kg, and 1 ml per hour for each additional kilogram bodyweight for deficit and maintenance; administration of 4–6 ml per kg bodyweight per hour for loss to the so-called third space; and administration of either 3 ml of any crystalloid solution or 1 ml of any colloidal solution for every millilitre of blood lost. An additional 10% of the calculated mean is added to the calculated ranges for possible measurement inaccuracies regarding amount of blood lost and fluid administered. Any approach to perioperative fluid therapy resulting in larger amounts of fluid administered, that is larger than the calculated ranges plus 10%, is considered supplemental. Any approach to perioperative fluid therapy resulting in smaller amounts of fluid administered, that is smaller than the calculated ranges minus 10%, is considered restrictive [28]."

Using the above to define restricted, standard, and supplemental, Rahbari et al. concluded that restrictive perioperative fluid regimens, when compared to standard fluid regimens, could reduce postoperative morbidity (nonspecifically) in patients undergoing colorectal surgery [28].

Further, Rahbari et al. incorporated studies [15–17], which analyzed IOF monitoring via Doppler-guided fluid challenges, and found this method of hemodynamic monitoring and physiological "goal-directed" fluid therapies to be associated with decreased morbidity. The randomized controlled trial (N = 57) by Conway et al. examined the effect of transesophageal Doppler-guided IOF administration during elective colorectal resection by administering fluid challenges based on stroke volumes. The authors found no difference in length of stay or duration of time until tolerating an oral diet; however, five patients in the control cohort (vs. zero in the experimental cohort) required critical care postoperatively due to tachyarrythmias or cardiac failure [16]. Wakeling et al. followed with a randomized controlled trial including 128 patients undergoing colorectal resection, using transesophageal Doppler-guided fluid administration based on central venous pressure (CVP) and found not only a decrease in overall morbidity in the experimental group, but decreased length of stay and time until tolerating an oral diet as well [17]. Finally, Noblett et al. conducted a double-blind prospective randomized controlled trial in 108 patients undergoing elective colorectal resection, with patients in the experimental cohort receiving fluids based on transesophageal Doppler monitoring of stroke volumes. Patients in the experimental cohort were found to be associated with a decreased length of stay, earlier tolerating of diet, fewer complications, and a reduced rise in perioperative interleukin 6 [15]. Yet, routine use of transesophageal Doppler remains impractical at many institutions at this time. The use of forms of noninvasive hemodynamic monitoring via arterial catheters and

pulse oximetry in abdominal surgery are being investigated [31,32]. Furthermore, the concept of fluid administration based on hemodynamic monitoring underscores the debates on the accuracy of physiological parameters in predicting fluid responsiveness intraoperatively. For example, volume expansion-induced changes in pulse pressure variation, and not arterial pressure, has been shown to be potentially predictive of changes in cardiac output intraoperatively [33]. In addition, a recent meta-analysis of clinical trials analyzing the relationship of CVP and fluid responsiveness concluded that the current data does not support using CVP to guide fluid therapy [34]. Moreover, studies comparing goal-directed therapies versus restrictive perioperative fluid regimens have not yet been reported.

Pancreatic Surgery

Pancreatic surgery, particularly PD, is another type of gastrointestinal surgery in which it has been hypothesized that perioperative fluid management might impact perioperative morbidity. PD is an operation that is characterized by long duration, extensive dissection, potential for large volume blood loss, and a high complication rate. These characteristics make it an ideal operation to base this hypothesis. Several studies have focused on the issue of fluid management in pancreatic surgery; however, unlike colorectal surgery, this body of literature is lacking comparatively in prospective randomized studies. There is one randomized study underway in PD (NCT01058746) that is yet to be completed. A summary of the existing studies is shown in Table II.

The first prospective randomized study to make conclusions regarding fluid practices in PD and complications was not originally designed to address this question. Jarnagin et al. reported on a randomized trial of acute normovolemic hemodilution (ANH) in PD, which was powered to determine if ANH could decrease the need for allogeneic red blood cell transfusion rates [35]. In this trial, patients in the ANH arm received an average of over 2 liters of fluid intraoperatively more than control arm patients. The investigators observed that in the ANH arm, not only the frequency, but also the severity of complications related to the pancreatic anastomosis were increased [35]. It is important to point out that this trial was not designed specifically to investigate the relationship of IOF administration to perioperative outcomes, and this association was discovered on retrospective analysis of the acquired data. ANH introduces a different physiology in these patients, which quite limits the ability to generalize the results of this study to the overall patient population.

Thus far, four retrospective analyses have since been published examining perioperative fluid administration and perioperative outcomes in PD [36–39]. The first of these studies, by Melis et al., examined 188 patients, who were separated into two groups based on the median amount (mL) of intraoperative crystalloid received only. Patient comorbidities did not differ between groups. The authors found that the amount of intraoperative crystalloid received was not associated with surgical morbidity, mortality, or length of stay [36]. Yet, it is important to note several limitations of this study. Other fluids received, such as colloid, hetastarch, and blood products, were simply compared between groups and not factored into the analysis of postoperative outcomes. As 47.7% and 64.7% of patients in each group respectively received intraoperative blood products, this fluid group was not insignificant. In

addition, comparing groups by fluid volume does not account for other potential confounding variables, such as operative time and patient weight.

Grant et al. similarly examined a cohort of 1,030 patients who had undergone pancreatic resection, but this included all pancreatic resections, as 351 (34%) of these resections were not PDs. However, in contrast to Melis et al., intraoperative volumes including colloid administration were incorporated in statistical analyses. This study also did not find a statistically significant correlation between IOF volume and postoperative complications [37]. But given that more than one-third of the patients in this study had not undergone PD (most of the non-PD operations in this subset were distal pancreatectomies), this variable may have contributed to the lack of statistical significance reported. Among the limitations acknowledged by both studies were that IOF was determined by length of surgery and blood loss, and those variables would have to be controlled for in a randomized study.

We have studied the relationship of IOF administration to perioperative outcomes in 124 patients undergoing PD at Robert Wood Johnson University Hospital [38]. We attempted to minimize the aforementioned limitations of IOF by controlling for patient weight and operative times by calculating fluids as a rate, in ml/kg/hr. We performed regression analyses comparing independent perioperative variables, including IOF rate, to four outcomes variables: length of stay, complications per patient, severity of complications, and 30-day mortality. IOF rate correlated with one or more perioperative outcomes both on univariate and multivariate analysis. The intimate relationship between fluids and blood loss was again illustrated in our results as well, as blood loss significantly correlated with outcomes. In an attempt to separate the effects of blood loss versus IOF on outcomes, we analyzed outcomes in the lower 75^{th} percentile of blood loss, but both variables still correlated significantly with at least one perioperative outcome. Further, we identified that potentially patients with lower preoperative serum albumin (≤3.0 g/dL) levels could be particularly sensitive to fluid overload. We felt that our findings of a significant correlation between IOF administration rate and perioperative outcomes, in light of the negative results in the other studies, could be partially explained by our greater blood loss and operative times, as well as greater heterogeneity in anesthetic management of IOF administration [38].

Wright et al. retrospectively examined the effects of cumulative postoperative fluid balances on perioperative outcomes in 169 patients undergoing PD. This study stratified patients by fluid volume, and groups (further stratified into quartiles) were delineated by overall fluid balances at 0, 24, 48, and 72 hr postoperatively. Fluid volume included both crystalloid and colloid products. Higher quartiles in each time period were associated with greater blood loss, transfusions, morbidity, and longer length of hospital stay. This study did find a significant association between increasing fluid balances at the 48–72 hr intervals on multivariate analysis with increasing morbidity and length of hospital stay. Yet, limitations of this study included its retrospective nature, a lack of daily weights, and a lack of standardized fluid protocols [39].

Most recently, Lavu et al. published a single-center, prospective trial randomizing 264 patients to one of two perioperative fluid regimens. In the standard regimen group, patients were administered 15 ml/kg/hr of lactated ringers intraoperatively followed by 2 ml/kg/hr on

postoperative day zero. In the fluid-restricted group, patients were administered 9 ml/kg/hr of lactated ringers and 1 ml/kg/hr of three percent hypertonic saline intraoperatively, followed by 1 ml/kg/hr of hypertonic saline on postoperative day zero. Hypertonic saline was chosen as a means to maximize intravascular volume and minimize third-spacing. While reoperations, readmissions, length of stay, and mortality did not differ between the groups, total number of complications was decreased by 25% in the fluid-restricted group. Limitations of the study included the fact that it was powered to detect a 33% reduction in complications; but nonetheless, these results can be interpreted as a positive trial. This is the first such randomized controlled trial indicating that restrictive perioperative fluid practices can positively impact perioperative outcomes. To what degree the results of this study depended on the use of hypertonic saline versus simply using a restricted regimen will need to be examined in future clinical trials [40].

CONCLUSION

Perioperative fluid administration in major abdominal surgery is undergoing a critical review by surgical investigators, as standard practices that have been in place for decades are being challenged. The concept that fluid restriction or the avoidance of fluid overload in major abdominal surgery can influence perioperative outcomes, such as morbidity and length of stay, is gaining traction. What is not clear at this time is the optimal fluid administration practice: should it be fluid restriction, per se, versus maintaining a state of zero fluid balance? Is a state of zero fluid balance a realistic clinical goal, or is this merely theoretical? Does this concept apply to all types of major abdominal surgery? The majority of the best studies have been done in colorectal surgery, but these results may not apply to PD, which has very different physiological effects on the body. Moreover, the patient population that undergoes PD is often malnourished, which further complicates fluid management. Intraoperative hemodynamic monitoring using transesophageal Doppler ultrasound has been implemented in randomized trials in colorectal surgery, as the advantage of this allows for fluid management customized to an individual’s physiologic status. Yet, this type of hemodynamic monitoring may be impractical to be routinely initiated at this time. As a result, new methods of noninvasive hemodynamic monitoring via arterial catheters and pulse oximetry are currently being investigated that may allow this type of fluid management to be conducted more practically. All of these current findings and controversies underscore the need for more randomized trials in specific types of gastrointestinal surgery in order for us to better understand the relationship between perioperative fluid administration and optimal perioperative outcomes.

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TABLE I

Comparison of Colorectal Study Characteristics

	Study type	N	Surgery type	Restriction?		ERAS?	Significant difference?		Return of bowel function measured?
				Intraoperative	Postoperative		Morbidity	Length of stay	
Lobo et al. [11]	Randomized trial	20	Elective colectomy	No	Yes	No	Yes	Yes	Yes
MacKay et al. [25]	Randomized trial	80	Elective colorectal surgery	Yes	Yes	No	No	No	No
Brandstrup et al. [12]	Randomized trial	141	Elective colorectal surgery	Yes	Yes	No	Yes	Not reported	Not reported
Nisanevich et al. [13]	Randomized trial	152	Elective abdominal surgery	Yes	No	No	Yes	Yes	Yes
Kabon et al. [26]	Randomized trial	253	Elective colectomy	Yes	No	No	No	No	No
Holte et al. [27]	Randomized trial	32	Elective colectomy	Yes	Yes[a]	Yes	Yes	No	No
Abraham-Nordling et al. [22]	Randomized trial	161	Elective colorectal surgery	Yes	Yes	Yes	Yes	No	No
Conway et al. [16]	Randomized trial	57	Elective abdominal surgery	Doppler	No	No	Yes[b]	No	No
Wakeling et al. [17]	Randomized trial	128	Elective colorectal surgery	Doppler	No	No	Yes	Yes	Yes
Noblett et al. [15]	Randomized trial	108	Elective colorectal surgery	Doppler	No	No	Yes	Yes	Yes

ERAS, Enhanced Recovery After Surgery protocol.

[a] Recovery room only.

[b] Significant difference in critical care admissions ($P = 0.02$).

TABLE II

Comparison of Pancreatic Study Characteristics

	Study type	N	Surgery type	Fluid Management	Fluids analyzed	Units	Morbidity	LOS
Melis et al. [36]	Retrospective	188	PD	Intraoperative	Crystalloid	ml	No	No
Grant et al. [37]	Retrospective	1030	Pancreatectomies	Intraoperative	Crystalloid and colloid	ml	No	No
Eng et al. [38]	Retrospective	124	PD	Intraoperative	Crystalloid, colloid, blood products	ml/kg/hr	Yes	Yes
Wright et al. [39]	Retrospective	169	PD	Postoperative	Crystalloid, colloid, blood products	ml	Yes	Yes
Lavu et al. [40]	Randomized trial	264	PD	Perioperative	Crystalloid and hypertonic saline	ml/kg/hr	Yes	No

LOS, length of stay; PD, pancreaticoduodenectomy.