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Fluid administration and morbidity in transhiatal esophagectomy

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Abstract

Background—Esophagectomy is associated with significant morbidity. Optimizing perioperative fluid administration is one potential strategy to mitigate morbidity. We sought to investigate the relationship of intraoperative fluid (IOF) administration to outcomes in patients undergoing transhiatal esophagectomy with particular attention to malnourished patients, who may be more susceptible to the effects of fluid overload.

Material and methods—Patients who underwent transhiatal esophagectomy from 2000–2013 were identified from a retrospective database. IOF rates (mL/kg/hr) were determined and their relationship to outcomes compared. To examine the impact of malnutrition, we stratified patients based on median preoperative serum albumin and compared outcomes.

Results and discussion—211 patients comprised the cohort. 74% of patients underwent esophagectomy for esophageal adenocarcinoma. Linear regression analyses were performed comparing independent perioperative variables to four outcomes variables: length of stay, complications per patient, major complications, and Clavien-Dindo classification. IOF rate was significantly associated with three of four outcomes on univariate analysis. Significantly more patients with a preoperative albumin level ≥ 3.7 g/dL who received more than the median IOF rate experienced more severe complications.

Conclusions—Increased intraoperative fluid administration is associated with perioperative morbidity in patients undergoing transhiatal esophagectomy. Patients with lower preoperative albumin levels may be particularly sensitive to the effects of volume overload.

Keywords

Fluids; Morbidity; Transhiatal esophagectomy

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Disclosures
None.

1. Introduction

Esophagectomy is a procedure associated with significant morbidity and mortality. Pulmonary complications and anastomotic leak rates are frequently reported, with morbidity and mortality rates approaching 50% and 10% respectively in large patient cohorts [1,2]. Strategies to minimize morbidity have focused on improving patient selection through the development of preoperative scoring systems based on risk factors identified from retrospective analyses of esophagectomies [3,4]. Another approach has been to improve perioperative care. Recently, the implementation of standardized perioperative and multidisciplinary care pathways in esophageal carcinoma patients has been associated with decreased lengths of hospital stay [5]. One aspect of such pathways includes the standardization of perioperative fluid management. Both prospective and retrospective studies in colorectal and pancreatic surgery have demonstrated that fluid restrictive practices (or the avoidance of volume overload) are associated with improved perioperative outcomes [6–12].

Liberal perioperative fluid administration can lead to fluid overload, which has negative consequences on a number of organ systems including cardiopulmonary, gastrointestinal, and renal complications [6,9,13]. Likewise, preoperative factors such as malnutrition, reflected by hypoalbuminemia, are associated with morbidity in major abdominal surgery [14]. Hypoalbuminemia leads to greater intravascular volume loss during periods of fluid administration and can thus exacerbate the negative consequences of volume overload. We demonstrated this in patients undergoing pancreaticoduodenectomy at our institution, in which hypoalbuminemic patients who received a greater intraoperative fluid rate experienced more severe complications [10].

The association between fluid administration and perioperative outcomes in esophagectomy has been limited primarily to transthoracic esophagectomy (TTE). These studies report an association of perioperative fluid administration with a number of complications, particularly respiratory [5,15–17]. Compared to TTE, transhiatal esophagectomy (THE) is associated with shorter operative times and length of stay, but similar blood loss. TTE patients experience more respiratory complications and wound infections, while THE patients experience more anastomotic leaks and strictures [18]. Given the technical differences in these procedures and their differences in complication profiles, we sought to investigate the relationship of intraoperative fluid administration to perioperative outcomes in patients undergoing transhiatal esophagectomy.

2. Methods

A retrospective analysis was performed based on data from an institutional review board-approved, retrospectively acquired database at Robert Wood Johnson University Hospital (New Brunswick, NJ). Patients who underwent transhiatal esophagectomy from 2000–2013 with complete data on intra-operative fluid administration were identified. All patients underwent concurrent placement of a feeding jejunostomy for postoperative enteral nutrition. Each surgery was performed by two attending surgeons: a surgical oncologist and

a thoracic surgeon. Anesthetic approaches to fluid resuscitation and blood loss were not standardized, although typically blood was replaced with crystalloid and colloid at 3:1 and 1:1 ratios respectively.

Collected data included preoperative patient demographics, co-morbidities, intraoperative variables (fluid administration, transfusion of blood products, estimated blood loss, operative time), and postoperative outcomes. Intraoperative fluid (IOF) administration was determined by combining administered crystalloid, colloid, and blood products based on anesthesia records and analyzed as a fluid rate (mL/kg/hr), as we have previously demonstrated [10]. We used intraoperative fluid rates for analyses rather than total fluid volumes because it allowed us to control for differences in patient weight and operative time, which are two variables that can impact total fluid volumes. Postoperative outcomes analyzed included mortality, complications per patient, complication severity (Clavien-Dindo classification), and length of stay [19].

We stratified the entire cohort by median IOF rate and conducted Student's *t*-tests, chi-squared tests, and Wilcoxon-Mann-Whitney rank sum tests for appropriate variables (continuous, ordinal, etc.). This analysis was also performed in subgroups stratified by median preoperative serum albumin level (3.7 g/dL). Univariate and multivariate logistic regression analyses of perioperative variables were conducted on the aforementioned postoperative outcomes. Statistical significance was accepted at a *P*-value 0.05.

3. Results

From February 2000 to November 2013, a total of 211 patients underwent transhiatal esophagectomy, with their demographics shown in Table 1. In the patient cohort, 177 (84%) were male, and the median age was 63 (range 40–82). 125 (59%) patients received neoadjuvant therapy, 111 (89%) of whom underwent chemotherapy and radiation. 153 (73%) patients underwent esophagectomy for esophageal adenocarcinoma. Table 2 shows perioperative outcomes. Median IOF rate was 17.26 mL/kg/hr. Median length of stay was 9 days (range 5–107). Median perioperative Clavien-Dindo classification was 2, with the mean number of complications per patient 1.3. The anastomotic leak rate was 17.5%. 93 (44%) patients experienced major complications (Clavien-Dindo classification 3–5). One patient in the cohort experienced an intraoperative mortality (0.5%). There were no postoperative mortalities at 30 days.

When stratifying patients by the median IOF rate of 17.26 mL/kg/hr, 39/105 (37%) patients in the lower IOF rate cohort experienced major complications, while this proportion was 54/106 (51%) in the higher IOF rate cohort ($P < 0.05$), Table 3 and Figure 1A. Pulmonary morbidity (37 vs. 30%), cardiac arrhythmias (22 vs. 19%), and anastomotic leak rates (22 vs. 15%) were increased in the higher IOF rate cohort, but the increases were not statistically significant. Complications per patient and length of stay were not significantly different between the groups.

To further analyze the relationship of IOF rate with outcomes, univariate and multivariate analyses were performed comparing independent perioperative variables to the following

outcomes variables: length of stay, complications per patient, major complications, and Clavien-Dindo classification. Table 4 shows the univariate analysis, which demonstrates that IOF rate is significantly associated with three of the four outcomes variables (complications per patient, major complications, Clavien-Dindo classification). IOF rate and intraoperative transfusions were associated with three of the four outcomes variables, while age was associated with two. Of note, preoperative serum albumin level was not associated with any of the outcomes variables. On multivariate analysis, IOF rate approached significance with major complications ($P = 0.08$) and complications per patient ($P = 0.07$). Only a history of smoking was significant with complications per patient on multivariate analysis.

We have previously shown in patients undergoing pancreaticoduodenectomy that malnourished patients are a group in that may be particularly sensitive to the harmful effects of volume overload [10]. To investigate the relationship of malnutrition and IOF rate to morbidity in THE patients, we stratified the patients by the median preoperative serum albumin (3.7 g/dL) and compared IOF rates to outcomes. Within each albumin subgroup, patients were stratified based on IOF rate, and outcomes were compared. More patients in the lower albumin subgroup who received a higher IOF rate experienced major complications (26/50, 52% vs. 16/49, 33%) when compared with lower IOF rate patients, Figure 1B. A summary of the complications in both albumin subgroups is shown in Tables 5 and 6. In the higher albumin subgroup, on the contrary, IOF rate was not significantly associated with morbidity in any of the outcomes variables.

4. Discussion

Established practices of liberal perioperative fluid administration are being challenged in a variety of gastrointestinal operations, as prospective randomized trials comparing restrictive versus liberal fluid practices have demonstrated improved perioperative outcomes [6–8,11]. While this evidence has been mounting, there is still controversy as to what type of abdominal operations this may apply to, as well as what types of fluid administrative practices constitute “restrictive”. In fact, randomized trials in abdominal surgery using hemo-dynamic measurements to guide fluid administration (so-called “goal-directed therapy”) have demonstrated improved outcomes without administering significantly less fluid [20–22]. One recent study prospectively investigated the effects of goal-directed IOF management based on stroke volume variation in thoracic surgery requiring single-lung ventilation in 27 patients, 16 of whom underwent esophagectomy. Patients in this study did not experience pulmonary fluid overload based on perioperative extravascular lung water index [23]. Thus, these studies have allowed some speculation that perhaps the clinically relevant aspect of this is the avoidance of fluid overload, rather than restricting fluid per se. This idea is reflected in current Enhanced Recovery After Surgery (ERAS) protocols of certain types of gastrointestinal surgery [24].

While the ideal method of fluid administration is investigated, it remains unclear as to whether variations in fluid practices affect all types of major abdominal and thoracic surgery or perhaps only certain operations. The majority of prospective randomized trials investigating this have been in the setting of elective colorectal surgery, although recently studies in pancreatic surgery are gaining [6–8,11]. There have been none in esophagectomy.

Esophagectomy remains a challenging operation with significant perioperative morbidity and mortality. Large cohort studies have reported 30-day mortality rates to be 10% and morbidity approaching 50% for both transhiatal and transthoracic approaches [25]. Pulmonary complications after transthoracic esophagectomy remain a significant source of overall morbidity. The development of pulmonary complications appears to be multifactorial, ranging from the pain associated with a thoracotomy incision to the potential adverse effects of single-lung ventilation (ex. barotrauma and the requirement of higher FiO₂ potentially causing alveolar damage). Consequently, interventions such as thoracic epidural anesthesia and the use of lower tidal volumes have been associated with some improvement in outcomes [26–28].

Several studies have retrospectively investigated the relationship of perioperative fluid administration and outcomes in transthoracic esophagectomy. Kita *et al.* reported on a total of 112 patients at a single institution who underwent transthoracic esophagectomy for esophageal carcinoma, both before and after implementation of an intraoperative fluid restrictive regimen. The authors found that increased intra-operative fluid balance was associated with an increased need for tracheostomy and bronchoscopy postoperatively [15]. Wei *et al.* later analyzed 99 patients and found increased cumulative fluid balance from postoperative day zero to two to be associated with complications, particularly cardiopulmonary [16]. Casado *et al.* found both intraoperative and postoperative fluid balance to be associated with pulmonary complications in their cohort of 45 patients as well [17]. Markar *et al.* reported on a 20-year, single institution experience on 595 patients who underwent esophagectomy via various approaches (the vast majority thoracoabdominal) and the effects of gradual implementation of a multidisciplinary perioperative care pathway over time. This pathway included a target of 1.5 to 2 L of intraoperative crystalloid administration. Results showed decreases in blood loss, intensive care unit stay, and hospital stay, but with unchanged morbidity and mortality rates [5].

Our study demonstrates an association between intra-operative fluid administration and outcomes in a large cohort of patients undergoing transhiatal esophagectomy. In contrast to the existing studies on transthoracic esophagectomy, IOF administration was not significantly associated with pulmonary complications in particular. This is most likely due to the absence of a thoracic incision and single-lung ventilation in THE. Our mortality rate was low, with one event in the cohort of 211, which makes it difficult to assess an association between increased fluid rates and mortality. However, our major complication rate was high (44%), and this allowed us to better appreciate the relationship of patients who received high IOF rates with significantly greater rates of major complications. Our finding that pulmonary complications, arrhythmias, and anastomotic leaks were not significantly increased in the higher IOF rate cohort suggests that if indeed there is an effect of volume overload on complications, that it is distributed rather evenly among these categories. Nonetheless, the association of increased IOF with overall morbidity in patients undergoing THE is consistent with the growing literature on the effects of various fluid administration practices in other types of major gastrointestinal surgery.

Moreover, in our previous analysis of IOF administration in patients undergoing pancreaticoduodenectomy, we identified that relatively hypoalbuminemic patients may be

particularly sensitive to the effects of fluid overload. Although the median IOF rate in this subset of patients was greater than the median IOF rate of the total cohort, this difference was not statistically significant. These patients experienced more severe postoperative complications by 90 days [10]. As in pancreatic cancer, esophageal carcinoma is a disease in which patients often present malnourished. In this current study, our analysis yielded similar results, as hypoalbuminemic esophagectomy patients also appeared to be more sensitive to fluid overload. This association is further supported by our findings that hypoalbuminemia itself was not independently associated with outcomes. This suggests that particular attention should be given to prudent fluid administration regimens in malnourished patients both in our current clinical practice as well as future prospective studies, as these patients may be the most susceptible to the effects of fluid overload.

We acknowledge several limitations with this study. Due to its retrospective nature, we cannot make any conclusions regarding a causal relationship between fluid administration and perioperative outcomes in THE patients. Certain variables like blood loss (and subsequently transfusions) can greatly affect the amount of intraoperative fluid a patient receives, and it is very difficult to separate the effects of fluids from blood loss in these retrospective studies. While we did not find that IOF rate was a significant independent predictor of perioperative outcomes, we did find a number of correlations that were significant. Together with the literature on the association of fluids in patients undergoing TTE, we argue this constitutes sufficient evidence to justify further investigation in prospective randomized trials in esophagectomy. In addition, we were unable to collect reliable data for postoperative fluids and thus were unable to assess total perioperative fluid administration, which may have weakened the association between increased fluids and worse perioperative outcomes.

In conclusion, our findings demonstrate that increased intraoperative fluid administration is associated with perioperative morbidity in patients undergoing transhiatal esophagectomy for esophageal carcinoma. Relatively hypoalbuminemic patients, in particular, may be sensitive to the effects of fluid overload. Prospective randomized trials are needed to determine if there is a causal relationship between perioperative fluids and outcomes in esophagectomy.

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Fig. 1.
MAJOR COMPLICATIONS IN RELATION TO INTRAOPERATIVE FLUID RATE.
 Percentage of patients experiencing major complications in relation to intraoperative fluid (IOF) rates below and above the median IOF rate. (A) Overall patient cohort, $n = 105$ and 106 in the Low and High groups respectively, $P < 0.05$. (B) (Note: for this analysis, total $n = 194$, as 17 patients did not have a documented preoperative serum albumin level.) IOF rate subgroups stratified by median preoperative serum albumin level, with $n = 49$ and 50 in the Low and High subgroups in the ≤ 3.7 g/dL cohort, $P = 0.05$; $n = 48$ and 47 in the Low and High subgroups in the > 3.7 g/dL cohort, $P = 0.68$.

Table 1

Patient demographics. DM (diabetes mellitus), HTN (hypertension), CAD (coronary artery disease, COPD (chronic obstructive pulmonary disease).

N	211
Median age, y (range)	63 (40–82)
Male, n (%)	177 (83.9)
Past medical history, n (%)	
DM	32 (15.2)
HTN	98 (46.5)
CAD	43 (20.4)
COPD	14 (6.6)
History of smoking	156 (73.9)
Diagnosis	3 (0–3)
Adenocarcinoma	153 (72.5)
Squamous cell carcinoma	27 (12.8)
Other	31 (14.7)
Median co-morbidity index, ASA score (range)	3 (1–4)
Mean preoperative weight, kg (SD)	83.5 (22.2)
Median preoperative serum albumin, g/dL (SD)	3.7 (0.45)
Neoadjuvant therapy, n (%)	125 (59.2)

Table 2

Perioperative outcomes.

N	211
Median intraoperative fluid rate, ml/kg/hr (range)	17.26 (5.12–51.94)
Mean operative time, min (SD)	273 (61)
Mean estimated blood loss, ml (SD)	597 (734)
Intraoperative transfusion, n (%)	43 (20.4)
Median length of stay, days (range)	9 (5–107)
Clavien-Dindo classification, n (%)	
0	77 (36.5)
1 to 2	41 (19.4)
3 to 5	93 (44.1)
Mean complications per patient, n (SD)	1.3 (1.4)
Anastomotic leak rate, n (%)	37 (17.5)
Postoperative cardiac arrhythmias, n (%)	41 (19.4)
Pulmonary complications, n (%)	68 (32.2)
Intraoperative mortality, n (%)	1 (0.5)
30-day postoperative mortality, n (%)	0 (0)

Table 3

Morbidity comparison between intraoperative fluid rate groups.

N	105	106
Intraoperative fluid rate, ml/kg/hr	<17.26	>17.26
Clavien-Dindo classification, n (%)		
0	43 (41.0)	34 (32.1)
1 to 2	23 (21.9)	18 (17.0)
3 to 5 *	39 (37.1)	54 (50.9)

* $P < 0.05$.

Table 4

Univariate analysis of perioperative variables (first column) to outcomes variables.

	Length of stay	Clavien-Dindo	Major complications	Complications per Patient
Age	-	0.049	-	0.046
Albumin	-	-	-	-
ASA score	<0.01	-	-	-
Coronary artery disease	-	-	-	-
Diabetes mellitus	-	-	-	-
Estimated blood loss	-	-	-	0.03
Gender	-	-	-	-
Intraoperative fluid rate	-	0.03	0.02	<0.01
Neoadjuvant therapy	-	-	-	-
Operative time	0.04	-	-	-
Smoking	-	-	-	<0.01 *
Transfusion	<0.01	0.047	-	<0.01
Weight	-	-	0.04	-

* statistically significant on multivariate analysis.

Table 5

Summary of complications in the 3.7 g/dL albumin cohort divided into subgroups based on the median IOF rate of the cohort (18.06 mL/kg/hr).

Median IOF rate of the cohort	<18.06	18.06
Number of patients	49	50
Patients with major complications ($P=0.05$)	16	26
Cardiovascular		
Arrhythmia	10	12
Aortic injury intraoperatively	–	1
Cardiac arrest	1	–
Deep venous thrombosis	1	2
Hemiazygous vein injury intraoperatively	–	1
Thrombophlebitis	1	–
Heparin-induced thrombocytopenia	1	–
Myocardial infarction	2	1
Symptomatic anemia	–	1
Uncontrolled hypertension	1	–
Pulmonary		
Acute respiratory distress syndrome	–	2
Hypoxia or respiratory failure	7	10
Pneumonia	3	6
Pleural effusion or pneumothorax	8	12
Vocal cord edema	–	1
Gastrointestinal		
Anastomotic leak	10	11
Chyle leak	2	5
Clostridium difficile colitis	1	–
Delayed Gastric emptying	–	2
Jejunostomy tube clogged	1	–
Splenic injury intraoperatively	–	1
Tracheoesophageal fistula	–	1
Neurologic		
Altered mental status	2	–
Cerebrovascular accident	1	–
Delirium Tremens	–	1
Recurrent laryngeal nerve injury	3	2
Endocrine		
Uncontrolled hyperglycemia	1	–
Renal		
Acute kidney injury	1	–
Other infections		
Urinary tract infection	–	3

Wound infection/dehiscence of abdominal wound	2	–
30-day Mortality	1	–
Total number of complications	60	75

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Table 6

Summary of complications in the >3.7 g/dL albumin cohort divided into subgroups based on the median IOF rate of the cohort (16.32 mL/kg/hr).

Median IOF rate of the cohort	16.32	>16.32
Number of patients	48	47
Patients with major complications ($P=0.68$)	20	22
Cardiovascular		
Arrhythmia	7	8
Deep venous thrombosis/pulmonary embolism	–	3
Myocardial infarction	–	1
Pulmonary		
Hypoxia or respiratory failure	8	1
Mucous plug	–	1
Pneumonia	4	3
Pleural effusion or pneumothorax	14	12
Gastrointestinal		
Anastomotic leak	8	8
Chyle leak	1	1
Cystic duct injury intraoperatively	1	–
Clostridium difficile colitis	1	–
Delayed Gastric emptying	–	2
Diaphragmatic hernia	–	1
Dysphagia	1	–
Nasogastric tube dislodgement	–	2
Volvulus, small bowel	–	1
Neurologic		
Altered mental status	–	1
Recurrent laryngeal nerve injury	3	2
Other infections		
Mediastinitis	1	–
Urinary tract infection	–	1
Wound infection/dehiscence of abdominal wound	1	1
30-day Mortality	–	–
Total number of complications	50	49