

Effect of intraoperative fluid administration on perioperative outcomes in patients undergoing McKeown esophagogastrectomy

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Abstract

Objective: Fluid therapy is one of the key components of perioperative management. However, evidence of intraoperative fluid (IOF) administration affecting clinical outcomes following McKeown esophagogastrectomy remains limited. This study investigated the impact of IOF on clinical outcomes after McKeown esophagogastrectomy.

Methods: Patients who underwent McKeown esophagogastrectomy between July 2013 and July 2016 were identified. Preoperative, intraoperative and postoperative variables for each eligible patient were retrospectively collected from our electronic medical records and anesthetic records. IOF rates were determined and their relationships to postoperative clinical outcomes were compared.

Results: A total of 546 patients were enrolled in the analysis. The median IOF rate was 8.87 mL/kg/h. We divided the patients into two groups: a low fluid volume group (LFVG <8.87 mL/kg/h, n=273) and a high fluid volume group (HFVG ≥8.87 mL/kg/h, n=273). No statistically significant differences in postoperative clinical outcomes were found between LFVG and HFVG either before or after propensity score matching.

Conclusions: No effect of IOF administration on clinical outcomes in patients undergoing McKeown esophagogastrectomy was identified. Further high-quality studies examining the influence of IOF administration on clinical outcomes following McKeown esophagogastrectomy are still needed.

Keywords: Intraoperative fluid administration; McKeown esophagogastrectomy; clinical outcomes

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Introduction

Esophageal cancer is a highly lethal disease that harms thousands of people's health in China (1,2). McKeown esophagogastrectomy is a common surgical approach for the treatment of esophageal cancer (3). Although improvements have been made in surgical techniques and

perioperative care in recent decades, McKeown esophagogastrectomy is still associated with high morbidity and mortality.

In recent years, enhanced recovery pathways encompassing a large number of perioperative elements have been widely used in elective surgical procedures. Perioperative fluid management is one of the key

components of such pathways. Currently, perioperative fluid therapy has received increasing attention because it is considered to affect perioperative outcomes (4,5). However, there are relatively few data regarding clinical experience of intraoperative fluid (IOF) administration during McKeown esophagogastrectomy.

Therefore, we conducted this retrospective study to investigate the effect of IOF on postoperative clinical outcomes in patients undergoing McKeown esophagogastrectomy.

Materials and methods

Study population

Our retrospective study was approved by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences (No. 16-144/1223), and the requirement for informed consent was waived for the design of our study. A total of 546 patients who underwent McKeown esophagogastrectomy between July 2013 and July 2016 with complete study data were identified.

Data collection

The following data for each eligible patient were retrospectively collected from our electronic medical records and anesthetic records: age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative chemoradiotherapy, smoking history, alcohol history, history of hypertension, diabetes mellitus or coronary artery disease, preoperative blood glucose (GLU), serum creatinine (Cr), albumin (ALB), hematocrit (Hct), tumor histology, anesthetic method (general alone or combined epidural anesthesia), operation time, episodes of intraoperative hypotension and intraoperative hypoxemia, IOF administration volumes (crystalloid, colloid, and blood products), and operation type (open or minimally invasive approach). Postoperative clinical outcomes included total length of hospital stay, postoperative length of stay, postoperative intensive care unit (ICU) admission, tracheal reintubation, reoperation, in-hospital mortality, and postoperative complications, including the occurrence of anastomotic leakage, arrhythmia (atrial fibrillation and ventricular arrhythmia) and postoperative pneumonia.

Fluid administration

The specific approach to fluid resuscitation and blood loss

for each patient in Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College were not standardized and varied with the preference and experience of each anesthesiologist. Typically, blood was replaced with crystalloid at a ratio of 3:1 and colloid at 1:1. IOF was defined by adding volumes of crystalloid, colloid, and blood products (red blood cells and fresh frozen plasma) together based on anesthesia records. To avoid potential confounding variables, we used the IOF rate for analyses, which was calculated by the amount of fluid administered per kg of individual patient's weight per hour of operation time (mL/kg/h). The entire cohort was divided into two groups by median IOF rate.

Definitions

Intraoperative hypotension was determined by the lowest systolic blood pressure <80 mmHg or use of any vasopressor during operation. Intraoperative hypoxemia was defined as arterial oxygen saturation by pulse oximetry <90%. The total length of hospital stay was calculated according to the admission and discharge day. The postoperative length of stay was the period between the day of surgery and the day of discharge or in-hospital death. In-hospital mortality was defined as death occurring during the hospital stay. Postoperative anastomotic leakage was assessed and diagnosed by clinical (clinical signs of cervical incision), endoscopic (an upper endoscopy), radiological [computed tomography, (CT)], or operative findings. Postoperative pneumonia was defined according to the signs and symptoms and confirmed by blood tests and X-ray or CT scans. All included postoperative complications were indicated explicitly in our electronic medical records.

Statistical analysis

Continuous data were expressed as the $\bar{x} \pm s$, and categorical variables were reported as frequency and percentage (n, %). To allow an unbiased comparison, a propensity score matching (PSM) analysis was conducted to minimize intergroup differences in the above uneven baseline characteristics. A logistic regression model with all variables shown in *Table 1* was used to derive the propensity score. The t test, Mann-Whitney U test, Chi-square test, or Fisher's exact test was used for intergroup comparisons when appropriate. A P-value <0.05 (two-tailed) was considered to be significant. All statistical analyses were conducted using SPSS software (Version 22.0; IBM Corp., New York, USA).

Results

Patient and perioperative characteristics

Patient characteristics, preoperative and intraoperative clinical variables of the entire cohort are summarized in Table 1. A total of 546 patients [mean age: 59.9 years old; 458 (83.9%) males and 88 (16.1%) females] were enrolled in the analysis. The median IOF rate was 8.87 mL/kg/h. The patient cohort was divided into two groups by median IOF rate: low fluid volume group (LFVG <8.87 mL/kg/h, n=273) and high fluid volume group (HFVG ≥8.87 mL/kg/h, n=273). The cut-off value of the IOF rate that we used for dividing groups was referred to in the study by Eng *et al.* (6). Some characteristics were not equally distributed between the two groups. A greater proportion

of patients in LFVG were males ($P<0.001$), had higher BMI ($P<0.001$) and higher levels of preoperative GLU ($P=0.002$), Cr ($P<0.001$) and Hct ($P=0.032$). More patients in LFVG had a history of diabetes mellitus ($P=0.002$) compared with patients in HFVG. In addition, the mean operation time in LFVG was longer than that in HFVG ($P<0.001$). There were also significant differences in ASA classification between the two groups ($P=0.016$).

To allow an unbiased comparison, a PSM analysis was conducted to minimize intergroup differences in the above uneven baseline characteristics. We conducted the PSM analysis by Propensity Score Matching for SPSS, Version 3.0.2. This SPSS Dialog was programmed by Felix Thoemmes, Cornell University/University of Tubingen, and Wang Liao, Cornell University. In this Propensity

Table 1 Comparison of preoperative and intraoperative variables between low and high fluid volume groups before PSM

Variables	n (%)			P
	Total (N=546)	LFVG (n=273)	HFVG (n=273)	
Age (year) ($\bar{x}\pm s$)	59.9±7.7	59.7±7.4	60.1±8.0	0.547
Gender (Male)	458 (83.9)	244 (89.4)	214 (78.4)	<0.001
BMI (kg/m ²) ($\bar{x}\pm s$)	23.4±3.1	24.9±2.8	21.9±2.7	<0.001
ASA ≥III	31 (5.7)	9 (3.3)	22 (8.1)	0.016
Hypertension	113 (20.7)	65 (23.8)	48 (17.6)	0.073
Diabetes mellitus	31 (5.7)	24 (8.8)	7 (2.6)	0.002
Coronary artery disease	15 (2.7)	10 (3.7)	5 (1.8)	0.190
Alcohol use	343 (62.8)	177 (64.8)	166 (60.8)	0.330
Smoking history	368 (67.4)	189 (69.2)	179 (65.6)	0.361
Preoperative chemoradiotherapy	79 (14.5)	45 (16.5)	34 (12.5)	0.181
Preoperative laboratory ($\bar{x}\pm s$)				
GLU (mmol/L)	5.4±0.9	5.5±1.0	5.2±0.8	0.002
Cr (μmol/L)	75.3±13.2	78.1±12.6	72.5±13.2	<0.001
ALB (g/L)	44.3±3.2	44.6±3.2	44.1±3.2	0.106
Hct (%)	42.7±4.1	43.0±4.0	42.3±4.2	0.032
Operation time (h) ($\bar{x}\pm s$)	5.9±1.6	6.7±1.6	5.2±1.3	<0.001
Combined epidural	120 (22.0)	63 (23.1)	57 (20.9)	0.535
Intraoperative hypotension	166 (30.4)	80 (29.3)	86 (31.5)	0.577
Intraoperative hypoxemia	96 (17.6)	53 (19.4)	43 (15.8)	0.261
Tumor histology				0.952
Adenocarcinoma	6 (1.1)	3 (1.1)	3 (1.1)	
Squamous	496 (90.8)	249 (91.2)	247 (90.5)	
Other	44 (8.1)	21 (7.7)	23 (8.4)	
Minimally invasive approach	439 (80.4)	217 (79.5)	222 (81.3)	0.590

PSM, propensity score matching; BMI, body mass index; ASA, American Society of Anesthesiologist; GLU, glucose; Cr, serum creatinine; ALB, albumin; Hct, hematocrit; LFVG, low fluid volume group; HFVG, high fluid volume group.

Score Matching for SPSS, Version 3.0.2, a logistic regression model with all variables shown in *Table 1* was used to derive the propensity score. We matched patients in LFVG with the patients in HFVG at a ratio of 1:1 using the nearest neighbor matching with a caliper of 0.2. After propensity matching, 121 patients in LFVG were matched successfully with 121 patients in HFVG. The unmatched patients were removed from the analysis. Finally, baseline covariates between the two matched groups were well balanced with all P values >0.05 (*Table 2*).

Postoperative clinical outcomes

Several complications occurred during the postoperative period (*Table 3*). Overall, two patients died during the hospital stay. The overall in-hospital mortality rate was

0.4%. The mean total hospital stay and mean postoperative hospital stay were 24 and 18 d, respectively. A total of 12 (2.2%) patients had to undergo reoperation because of surgical complications. Sixteen (2.9%) patients required reintubation after surgery. Twelve (2.2%) patients suffered from postoperative arrhythmia, and 71 (13.0%) developed pneumonia in the postoperative phase. The most common complication was anastomotic leakage with an incidence of 17.2% (94 patients).

Influence of IOF on clinical outcomes

To examine whether IOF influences postoperative clinical outcomes after McKeown esophagogastrectomy, we investigated the postoperative clinical outcomes of this cohort classified by median IOF rate (8.87 mL/kg/h). In

Table 2 Comparison of preoperative and intraoperative variables between low and high fluid volume groups after PSM

Variables	n (%)		P
	LFVG (N=121)	HFVG (N=121)	
Age (year) ($\bar{x}\pm s$)	59.4±7.9	59.7±7.9	0.763
Gender (Male)	104 (86.0)	98 (81.0)	0.299
BMI (kg/m ²) ($\bar{x}\pm s$)	23.2±2.0	23.2±2.7	0.777
ASA ≥III	5 (4.1)	7 (5.8)	0.554
Hypertension	27 (22.3)	29 (24.0)	0.760
Diabetes mellitus	4 (3.3)	3 (2.5)	0.701
Coronary artery disease	3 (2.5)	3 (2.5)	1.000
Alcohol use	75 (62.0)	77 (63.6)	0.790
Smoking history	87 (71.9)	78 (64.5)	0.214
Preoperative chemoradiotherapy	18 (14.9)	17 (14.0)	0.855
Preoperative laboratory ($\bar{x}\pm s$)			
GLU (mmol/L)	5.3±1.0	5.3±0.9	0.705
Cr (μmol/L)	75.4±11.9	74.0±14.5	0.424
ALB (g/L)	44.3±3.1	44.3±3.1	0.983
Hct (%)	43.0±4.0	42.7±4.4	0.672
Operation time (h) ($\bar{x}\pm s$)	5.8±1.3	5.7±1.5	0.417
Combined epidural	26 (21.5)	26 (21.5)	1.000
Intraoperative hypotension	41 (33.9)	33 (27.3)	0.264
Intraoperative hypoxemia	19 (15.7)	19 (15.7)	1.000
Tumor histology			
Adenocarcinoma	1 (0.8)	1 (0.8)	
Squamous	109 (90.1)	110 (90.9)	
Other	11 (9.1)	10 (8.3)	
Minimally invasive approach	99 (81.8)	102 (84.3)	0.607

PSM, propensity score matching; BMI, body mass index; ASA, American Society of Anesthesiologist; GLU, glucose; Cr, serum creatinine; ALB, albumin; Hct, hematocrit; LFVG, low fluid volume group; HFVG, high fluid volume group.

Table 3 Comparison of postoperative clinical outcomes before and after PSM between low and high fluid volume groups

Postoperative outcomes	Total (N=546) [n (%)]	Before matching			After matching		
		LFVG (N=273) [n (%)]	HFVG (N=273) [n (%)]	P	LFVG (N=121) [n (%)]	HFVG (N=121) [n (%)]	P
Postoperative pneumonia	71 (13.0)	34 (12.5)	37 (13.6)	0.703	15 (12.4)	18 (14.9)	0.574
ICU admission	36 (6.6)	19 (7.0)	17 (6.2)	0.730	10 (8.3)	9 (7.4)	0.811
Reintubation	16 (2.9)	7 (2.6)	9 (3.3)	0.612	4 (3.3)	6 (5.0)	0.518
Reoperation	12 (2.2)	4 (1.5)	8 (2.9)	0.243	1 (0.8)	3 (2.5)	0.313
Arrhythmia	12 (2.2)	6 (2.2)	6 (2.2)	1.000	3 (2.5)	2 (1.7)	0.651
Anastomotic leak	94 (17.2)	51 (18.7)	43 (15.8)	0.364	23 (19.0)	20 (16.5)	0.614
Total hospital stay (d) ($\bar{x}\pm s$)	24±17	25±19	22±15	0.106	24±23	23±13	0.592
Postoperative hospital stay (d) ($\bar{x}\pm s$)	18±17	19±19	17±15	0.282	19±23	18±13	0.592
In-hospital mortality	2 (0.4)	1 (0.4)	1 (0.4)	1.000	1 (0.8)	0 (0)	0.316

PSM, propensity score matching; ICU, intensive care unit; LFVG, low fluid volume group; HFVG, high fluid volume group.

Table 3, we present the results of comparisons of postoperative clinical outcomes between LFVG and HFVG before and after PSM. Before PSM, the IOF administration had no influence on the length of hospitalization and in-hospital mortality. In addition, the incidence of all specific complications (postoperative pneumonia, arrhythmia, anastomotic leak) was not changed significantly by the IOF administration. Additionally, there was no significant difference in the rates of ICU admission, reintubation and reoperation between LFVG and HFVG. With all baseline covariates being well-balanced between the two groups after PSM, no statistically significant differences in postoperative clinical outcomes were found between LFVG and HFVG. Thus, there was no difference in postoperative clinical outcomes between LFVG and HFVG either before or after PSM.

Discussion

The aim of this retrospective study was to investigate the importance of IOF when performing McKeown esophagogastratomy. In our study of 546 patients, the median IOF rate during surgery was 8.87 mL/kg/h. Overall, no statistically significant differences in postoperative clinical outcomes were found between LFVG and HFVG either before or after PSM.

Fluid therapy is an important part of the management of perioperative patients for maintaining organ perfusion (7). At present, there are three types of fluid therapy strategies: liberal fluid therapy, restrictive fluid therapy and goal-directed fluid therapy (GDFT) (7). However, there is still

controversy regarding the optimum fluid therapy strategy, although fluid therapy strategy during the perioperative period has been extensively studied. Schol *et al.*'s study determined restrictive fluid therapy to be the preferred fluid management policy during elective surgery because it reduced the complication rate compared with liberal fluid management policy (8). Shin *et al.*'s study indicated that IOF dosing at liberal and restrictive margins is related to poor postoperative outcomes (9). The recent work by Hendrix *et al.* showed that restrictive IOF therapy is associated with decreased morbidity and length of stay following hyperthermic intraperitoneal chemoperfusion (10). Recently, the view of "liberal vs. restrictive fluid strategy" has been questioned, and an increasing number of studies support the application of GDFT (11,12). A study on the effects of liberal, restrictive and goal-directed fluid therapies on perioperative outcomes was performed by Corcoran *et al.* in 2012 (13). It was shown that GDFT was superior to liberal fluid therapy regarding the improvement of perioperative outcomes, while it remains uncertain whether GDFT is better than restrictive fluid strategy. Furthermore, many studies have demonstrated that intraoperative GDFT may not improve clinical outcomes following some elective major surgeries (14-16).

Esophagectomy continues to be a challenging procedure for both surgeons and anesthesiologists. There is increasing evidence that enhanced recovery pathways improve postoperative outcomes after many types of major surgeries, including esophagectomy (17). Perioperative fluid management is one of the key components of such pathways. Both insufficient and excessive fluid

administration can lead to poor clinical outcomes, such as pulmonary complications and anastomotic leakage (18,19). It has been reported that anastomotic leakage and pulmonary complications account for up to 80% of all morbid complications following esophagectomy (20). Although many studies have recommended GDFT, little research has been performed to investigate the influence of GDFT on clinical outcomes after esophagectomy. A recent study by Veelo *et al.* indicated that the implementation of GDFT during esophagectomy did not reduce overall morbidity, mortality or hospital length of stay (21). However, a recent study showed that the combination of GDFT with an enhanced recovery after surgery (ERAS) program could enhance postoperative gastrointestinal recovery but did not affect the incidence of complications (22). Thus, how to “maintain the balance” is still a question.

At present, there are relatively few findings regarding the impact of IOF on postoperative outcomes of patients undergoing esophagectomy. The study by Casado *et al.* reported that fluid administration was a risk factor for respiratory complications after esophageal surgery (18). Eng *et al.* found that increased IOF administration (>17.26 mL/kg/h) was associated with perioperative morbidity in patients undergoing transhiatal esophagectomy (6). However, our study demonstrates that there is no difference in postoperative clinical outcomes between LFVG and HFVG. This result may be partly attributed to the difference of IOF administration. The median IOF rate in our study (8.87 mL/kg/h) is considerably less than that in Eng *et al.*'s study (17.26 mL/kg/h). Another possible explanation may be the difference in tumor histology. The most common tumor histology in our study was squamous (90.8%), while 72.5% was adenocarcinoma in Eng *et al.*'s work. In addition, different fluid regimens, surgical approaches and end points used in existing studies may contribute to the difference in conclusions. To date, no practice consensus exists regarding perioperative fluid management, which makes it challenging to draw a conclusion.

Some limitations still exist in our study. First, this study is an observational one, and we could not remove all confounding factors, although PSM analysis was applied. Second, we only included postoperative complications, which were indicated explicitly in our electronic medical records. As our study was retrospective in nature, it is impossible for all complications to have been accurately recorded. Third, the matching rate in PSM analysis was

relatively low, as only 44.3% (121/273) of patients in LFVG were successfully matched with patients in HFVG. The sample size after matching may be insufficient to detect a true influence of IOF administration on clinical outcomes after McKeown esophagectomy.

Conclusions

The median IOF rate of McKeown esophagectomy in our study was 8.87 mL/kg/h. No effect of IOF administration on clinical outcomes in patients undergoing McKeown esophagectomy was identified. Further high-quality studies examining the influence of IOF administration on clinical outcomes following McKeown esophagectomy are still needed.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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