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Cardiovascular

Impact of intraoperative goal-directed fluid therapy on major morbidity and mortality after transthoracic oesophagectomy: a multicentre, randomised controlled trial

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Abstract

Background: Transthoracic oesophagectomy is associated with major morbidity and mortality, which may be reduced by goal-directed therapy (GDT). The aim of this multicentre, RCT was to evaluate the impact of intraoperative GDT on major morbidity and mortality in patients undergoing transthoracic oesophagectomy.
Methods: Adult patients undergoing transthoracic oesophagectomy were randomised to receive either minimally invasive intraoperative GDT (stroke volume variation <8%, plus systolic BP maintained >90 mm Hg by pressors as necessary) or haemodynamic management left to the discretion of attending senior anaesthetists (control group; systolic BP >90 mm Hg alone). The primary outcome was the incidence of death or major complications (reoperation for bleeding, anastomotic leakage, pneumonia, reintubation, >48 h ventilation). A Cox proportional hazard model was used to examine whether the effects of GDT on morbidity and mortality were independent of other potential confounders.
Results: A total of 232 patients (80.6% male; age range: 36–83 yr) were randomised to either GDT (n=115) or to the control group (n=117). After surgery, major morbidity and mortality were less frequent in 22/115 (19.1%) subjects randomised to GDT, compared with 41/117 (35.0%) subjects assigned to the control group {absolute risk reduction: 15.9% (95% confidence interval [CI]: 4.7–27.2%); P=0.006}. GDT was also associated with fewer episodes of atrial fibrillation (odds ratio [OR]: 0.18 [95% CI: 0.05–0.65]), respiratory failure (OR: 0.27 [95% CI: 0.09–0.83]), use of mini-tracheotomy (OR: 0.29 [95% CI: 0.10–0.81]), and readmission to ICU (OR: 0.09 [95% CI: 0.01–0.67]). GDT was independently associated with morbidity and mortality (hazard ratio: 0.51 [95% CI: 0.30–0.87]; P=0.013).
Conclusions: Intraoperative GDT may reduce major morbidity and mortality, and shorten hospital stay, after transthoracic oesophagectomy.
Clinical trial registration: UMIN000018705

Keywords: goal-directed therapy; haemodynamic monitoring; morbidity; mortality; multicentre randomised controlled trial; postoperative; transthoracic oesophagectomy; stroke volume; stroke volume variation

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Editor's key points

- Morbidity and mortality occur frequently after transthoracic oesophagectomy.
- The authors examined whether intraoperative goal-directed therapy reduced morbidity and mortality in Japanese patients undergoing transthoracic oesophagectomy.
- Minimally invasive intraoperative goal-directed therapy (stroke volume variation <8% plus systolic BP maintained >90 mm Hg with pressors as necessary) was compared with haemodynamic management aimed at ensuring systolic BP>90 mm Hg alone.
- Postoperative morbidity and mortality was less frequent in 22/115 (19.1%) patients randomised to GDT (absolute risk reduction: 15.9% [95% confidence interval: 4.7–27.2%]).
- Intraoperative GDT may reduce major morbidity and mortality, and shorten hospital stay after transthoracic oesophagectomy.

Transthoracic oesophagectomy is a challenging procedure with a high incidence of postoperative major morbidity and mortality. Despite advances in surgical techniques and preoperative chemoradiotherapy, major morbidity still occurs in approximately 30% patients, with an in-hospital mortality rate of approximately 3%.[1,2] Intraoperative excessive fluid loading may contribute to respiratory failure, bowel dysfunction, and anastomotic leakage as a result of intestinal oedema. Hypovolaemia increases the rate of perioperative complications such as cardiac ischaemia and renal failure and may compromise newly constructed anastomoses.[3,4] Appropriate perioperative fluid management has been reported to reduce postoperative complications in patients who undergo oesophagectomy.[5]

Static indices fail to predict fluid responsiveness in the perioperative period.[6,7] Dynamic indices, including the stroke volume (SV) and SV variation (SVV), have been increasingly used for perioperative volume assessment.[8,9] With recent advances in the technology of haemodynamic monitors, dynamic indices can be monitored through minimally invasive haemodynamic monitoring.[10] Goal-directed therapy (GDT), which monitors dynamic indices to facilitate increased oxygen delivery and prevent tissue hypoperfusion, has been reported to improve the outcome after cardiac and noncardiac surgeries.[11–13]

Feldheiser and colleagues[14] presented a consensus statement regarding perioperative management for gastrointestinal surgery and recommended the use of GDT for high-risk patients.[4] However, the use of intraoperative GDT for patients undergoing oesophagectomy has been underexplored. Therefore, we designed a prospective, multicentre, RCT to assess the impact of intraoperative GDT based on minimally invasive haemodynamic monitoring on outcomes of transthoracic oesophagectomy.

Methods

Study design

The protocol of the current study was approved by the institutional review board of Osaka City University Hospital (May 28, 2015) and each of the participating hospitals. Written informed consent was obtained from all enrolled patients. The trial was registered prospectively with the Japanese National Institute of Public Health trial registration repository (UMIN000018705). Patients were screened for eligibility from August 2015 to October 2017.

Inclusion criteria

Adult patients >20 yr old undergoing elective open transthoracic oesophagectomy or thoraco-laparoscopic oesophagectomy were eligible.

Exclusion criteria

Patients requiring extended surgical procedures, such as free jejunum reconstruction with vascular anastomosis, were excluded, in addition to atrial fibrillation, cardiac failure (New York Heart Association [NYHA] Class IV), dyspnoea (Hugh-Jones classification III–IV), coagulation disorders, established hepatorenal dysfunction, or all.

Perioperative management

No premedication was administered, and solid food and clear fluid intake were allowed until 12 and 3 h before surgery, respectively, for all patients except those with oesophageal obstruction. All subjects received general anaesthesia with or without epidural anaesthesia. A thoracic epidural catheter was inserted at the level between T6 and T10, and a test dose comprising lidocaine 1%, 1.5 ml, with epinephrine (10 μg ml^{-1}) was administered for confirmation of accurate placement. Subsequently, general anaesthesia was induced with propofol, remifentanil, and rocuronium and maintained with sevoflurane, desflurane, or propofol. The depth of general anaesthesia was controlled to maintain a bispectral index (BIS monitor v4.0; Medtronic Inc., Minneapolis, MN, USA) of 45–60. Intraoperative analgesia was achieved with fentanyl, remifentanil, and epidural anaesthesia. The trachea was intubated and subjects were ventilated with a tidal volume (V_T) of 7–8 ml kg^{-1} (ideal body weight) throughout the procedure. The frequency of ventilation was controlled such that the end-tidal carbon dioxide was 4.7–5.3 kPa. During the transthoracic procedure, one-lung ventilation was used for all patients. An arterial line was inserted after the airway was secured, and the Vigileo-FloTrac system (Edwards Lifesciences, Irvine, CA, USA) was connected for haemodynamic monitoring in the GDT group.

Postoperative pain control was achieved with continuous epidural administration of levobupivacaine 0.25% at a rate of 2–5 ml h^{-1} or i.v. administration of fentanyl. Postoperative care and management decision was performed by surgeons who were blinded to the group allocation. After surgery, all subjects were admitted to the ICU at least until the first postoperative day. Postoperative haemodynamic management was similar in both groups, with use of the Vigileo-FloTrac system at the discretion of the surgeons. Subjects were discharged from the ICU once their condition was stable and the following criteria were fulfilled: (a) respiratory stability, defined as oxygen saturation>94% with an oxygen mask (≤5 L min^{-1}); (b) haemodynamic stability, defined as systolic BP>100 mm Hg and urine output>1 ml kg^{-1} h^{-1} with less than two

inotropic drugs; and (c) absence of unstable arrhythmias requiring drug treatment.

Randomisation

After written informed consent had been obtained, eligible patients were randomised to undergo surgery with intraoperative GDT (GDT group) or conventional haemodynamic management (control group). Randomisation was performed by a research assistant in our university using Research Randomizer (http://www.randomizer.org/). Subjects were blinded to their allocated group.

Intraoperative haemodynamic protocol

Haemodynamic parameters, including the arterial BP, SV, SVV, SV index, systemic vascular resistance, systemic vascular resistance index, cardiac output, and cardiac index, were measured using the Vigileo-FloTrac system. In the control group, the goal of intraoperative haemodynamic management was to maintain a systolic BP>90 mm Hg. The anaesthesia care providers were blinded to the measurements obtained by the Vigileo-FloTrac system for the entire duration of surgery. Fluid and vasoactive drugs were administered when deemed necessary by the attending anaesthesiologists. In the GDT group, haemodynamic control was achieved using the Vigileo-FloTrac system according to a predetermined protocol (Fig. 1) based on a previous study that showed the beneficial effects of GDT during high-risk abdominal surgery.[15] Baseline bicarbonate Ringer's solution (Bicanate®, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan; Na^+: 130 mEq L^{-1}, K^+: 4 mEq L^{-1}, Mg^{2+}: 2 mEq L^{-1}, Ca^{2+}: 3 mEq L^{-1}, Cl^-: 109 mEq L^{-1}, HCO_3^-: 28 mEq L^{-1}, citrate^{3-}: 4 mEq L^{-1}) was administered at a rate of 3 ml kg^{-1} h^{-1} in both groups. After the induction of anaesthesia, the measured SV was set as the baseline volume for patients with an SVV≤12%. If the SVV>12%, fluid with 250 ml of hydroxyethyl starch 6% (Voluven®, Otsuka Pharmaceutical Co. Ltd.) was administered over 20 min. This fluid challenge was repeated up to two times until the SVV≤12%; the SV measured at that time was then set as the baseline volume. During surgery, if the SVV exceeded 12%, or if it remained 8–12% and the percentage decrease in SV was >10% for at least 2 min, 250 ml of colloid (hydroxyethyl starch 6% or albumin 5%) was administered over 20 min; this was repeated until a stable haemodynamic condition (SVV<13% and SV decrease <10%) was obtained. The maximum amount of 6% hydroxyethyl starch that could be administered was 50 ml kg^{-1}. In addition, when the SVV remained <8%, vasoactive drugs (phenylephrine or ephedrine, dopamine, or both) were administered for maintenance of the systolic BP at >90 mm Hg.

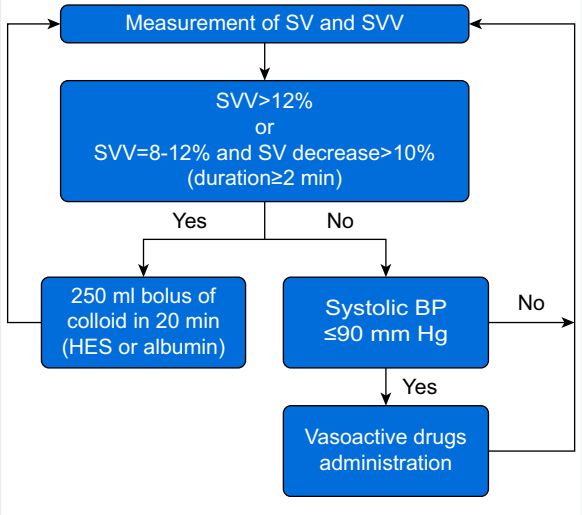

Fig 1. Algorithm for intraoperative goal-directed therapy in subjects undergoing transthoracic oesophagectomy. HES, hydroxyethyl starch; SV, stroke volume; SVV, stroke volume variation.

Primary outcome

The primary outcome was the incidence of major complications (including mortality),[1] including reoperation for bleeding, anastomotic leakage, pneumonia, reintubation, and prolonged ventilation (>48 h).

Secondary outcomes

We assessed the following secondary outcomes: duration of ventilation after surgery, ICU and hospital length of stay, time to oral intake, and the incidence of clinically detected complications (including sepsis, wound infection, renal failure, pulmonary embolism, DVT, intestinal obstruction, arrhythmias, acute myocardial infarction, pleural effusion requiring drainage, atelectasis, pneumothorax, delirium, new-onset stroke, respiratory failure, and readmission to the ICU). Intraoperative and postoperative data were collected by researchers who were blinded to the study-group assignments.

Statistical analysis

All results are expressed as mean (standard deviation) or median (inter-quartile range) values unless otherwise indicated. The Student *t*-test and the Mann–Whitney *U*-test were used to compare perioperative continuous variables between the GDT and control groups. Categorical variables were compared using the χ^2 test or Fisher's exact test. Survival of subjects with postoperative morbidity and mortality within 30 days after surgery was analysed using the Kaplan-Meier method followed by the log-rank test.

Cox proportional hazard model

A Cox proportional hazard model was used to examine the independent effects of perioperative factors, including GDT, on the risk of postoperative morbidity and mortality. The results are expressed as hazard ratios with 95% confidence intervals (CIs). The model included perioperative prognostic factors that were found to be important in the previous study.[1] Preoperative chemo-radiotherapy was also included in this model. Secondary outcomes were compared using multivariate logistic regression analyses adjusting for age and preoperative chemo-radiotherapy. For all analyses, a *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using StatFlex version 6.0 (Artech Co., Ltd, Osaka, Japan).

Table 1 Subject characteristics. Data are expressed as mean (standard deviation) or median [inter-quartile range]. ASA, American Society of Anesthesiologists; %VC, percent vital capacity; FEV1.0, forced expiratory volume in 1 s; GDT, goal-directed therapy; NYHA, New York Heart Association; TNM, Tumour Node Metastasis; UICC, Union for International Cancer Control.

Variables	GDT group (n=115)	Control group (n=117)
Sex, male (%)	91 (79.1)	96 (82.1)
Age (yr)	42–83	36–82
Height (cm)	164 (7.91)	164 (7.12)
Weight (kg)	57.0 [48.9–63.9]	56.7 [49.5–64.7]
ASA physical status		
1/2	10/101	5/99
3/4	4/0	13/0
NYHA classification		
I/II	109/6	108/6
III	0/0	3/0
Smoker, n (%)	93 (80.9)	93 (79.5)
Brinkman index	600 [250–900]	660 [318–1000]
Chronic alcohol consumption, n (%)	103 (89.6)	96 (82.1)
Preoperative complication		
Hypertension, n (%)	43 (37.4)	56 (47.9)
Diabetes mellitus, n (%)	15 (13.0)	20 (17.1)
Asthma, n (%)	3 (2.6)	3 (2.6)
Ischaemic heart disease, n (%)	8 (7.0)	11 (9.4)
Cerebral vascular disease, n (%)	11 (9.6)	9 (7.7)
Chronic obstructive pulmonary disease, n (%)	2 (1.7)	5 (4.3)
Hypothyroidism, n (%)	3 (2.6)	1 (0.9)
Respiratory function		
%VC (%)	104 (15.5)	103 (16.5)
$FEV_{1.0}$ (L)	2.72 [2.23–2.98]	2.59 [2.15–3.05]
$FEV_{1.0}$% (%)	74.2 [69.4–80.1]	74.7 [69.8–80.2]
UICC-TNM stage		
I/II/III/IV	29/35/47/4	23/36/46/12
Number of patients receiving chemotherapy, n (%)	74 (64.3)	88 (75.2)
Number of patients receiving radiation therapy, n (%)	9 (7.3)	24 (19.1)
Systolic BP (mm Hg)		
≤89/110–130/131–170/≥171	1/47/58/9	4/50/48/15
HR (beats min^{-1})		
50–80/81–100 or 40–49/≥101 or ≤39	67/43/5	61/44/12

Table 2 Intraoperative data. Data are expressed as median [inter-quartile range].

Variables	GDT group (n=115)	Control group (n=117)	P-value
Number of subjects receiving epidural anaesthesia, n (%)	88 (76.5)	79 (67.5)	0.127
Thoracoscopy/artificial pneumothorax			
+/+, +/−, −/−	90/6/19	87/1/29	0.058
Laparoscopy			
+/−	78/37	88/29	0.212
Operation time (min)	524 [456–612]	525 [456–607]	0.773
Anaesthesia time (min)	582 [515–678]	591 [514–670]	0.675
One-lung ventilation time (min)	257 [206–310]	244 [199–293]	0.114
Crystalloid infusion (ml)	2600 [2150–3300]	3000 [2450–3575]	0.001*
Colloid infusion (ml)	1250 [1000–1750]	1500 [1000–2000]	0.191
Total number of bolus colloid administrations	5 [4–6]		
Total infusion (ml)	4000 [3350–4800]	4550 [3850–5175]	<0.001*
Total phenylephrine administration (μg)	350 [100–750]	550 [150–1500]	0.004*
Total ephedrine administration (mg)	10.0 [5.0–20.0]	15.0 [5.0–20.0]	0.286
Number of patients administered dopamine, n (%)	39 (33.9)	42 (35.9)	0.751
Transfusion, n (%)	12 (10.4)	21 (17.9)	0.101
Transfusion amount (ml)	560 [350–770]	560 [560–1040]	
Urine output (ml)	730 [420–1190]	710 [400–1155]	0.918
Blood loss (ml)	295 [180–430]	300 [178–510]	0.319
Occurrence of atrial fibrillation during surgery, n (%)	3 (2.6)	0 (0)	0.079

*P<0.05 statistically significant. GDT, goal-directed therapy.

Table 3 Postoperative outcomes. Data are expressed as median [inter-quartile range].

Variables	GDT group (*n*=115)	Control group (*n*=117)	*P*-value
Ventilation time (h)	15.0 [13.0–16.0]	15.0 [14.0–17.0]	0.080
ICU duration (days)	2.0 [2.0–2.0]	2.0 [2.0–3.0]	0.521
Length of hospital stay (days)	24.0 [18.5–37.0]	29.0 [21.0–45.5]	0.010*
Start day for oral ingestion (days)	8.0 [7.0–10.5]	8.0 [7.0–21.0]	0.051
Postoperative morbidity at POD7			
Respiratory failure, *n* (%)	26 (22.6)	44 (37.6)	0.013*
Infection, *n* (%)	42 (36.5)	46 (39.3)	0.661
Renal failure, *n* (%)	1 (0.9)	6 (5.1)	0.058
Gastrointestinal disturbance, *n* (%)	10 (8.7)	11 (9.4)	0.851
Cardiac disease, *n* (%)	11 (9.6)	16 (13.7)	0.329
Neurological disorder, *n* (%)	1 (0.9)	7 (6.0)	0.033*
Wound infection, *n* (%)	2 (1.7)	4 (3.4)	0.420
Transfusion, *n* (%)	0 (0)	3 (2.6)	0.084
Requirement of pain management, *n* (%)	20 (17.4)	17 (14.5)	0.552
Postoperative major morbidity and mortality	22 (19.1)	41 (35.0)	0.006*
Re-operation, *n* (%)	1 (0.9)	9 (7.7)	0.011*
Anastomotic leakage, *n* (%)	7 (6.1)	8 (6.8)	0.816
Re-intubation, *n* (%)	4 (3.5)	19 (16.2)	0.001*
Ventilation time≥48 h, *n* (%)	5 (4.3)	15 (12.8)	0.022*
Pneumonia, *n* (%)	14 (12.2)	26 (22.2)	0.043*
6-Month mortality, *n* (%)	0 (0)	4 (3.4)	0.046*
Postoperative complications			
Sepsis, *n* (%)	0 (0)	3 (2.6)	0.084
Wound infection, *n* (%)	11 (9.6)	6 (5.1)	0.195
Renal failure, *n* (%)	3 (2.6)	8 (6.8)	0.130
Renal failure requiring dialysis, *n* (%)	0 (0)	2 (1.7)	0.159
Pulmonary embolism, *n* (%)	2 (1.7)	0 (0)	0.152
DVT, *n* (%)	0 (0)	0 (0)	1.000
Intestinal obstruction, *n* (%)	1 (0.9)	4 (3.4)	0.181
Atrial fibrillation, *n* (%)	3 (2.6)	15 (12.8)	0.004*
Arrhythmias except for atrial fibrillation, *n* (%)	3 (2.6)	3 (2.6)	0.983
Acute myocardial infarction, *n* (%)	0 (0)	0 (0)	1.000
Pleural effusion requiring drainage, *n* (%)	17 (14.8)	28 (23.9)	0.078
Atelectasis, *n* (%)	9 (7.8)	18 (15.4)	0.073
Pneumothorax, *n* (%)	1 (0.9)	8 (6.8)	0.019*
Delirium, *n* (%)	7 (6.1)	8 (6.8)	0.816
New-onset stroke, *n* (%)	0 (0)	1 (0.9)	0.342
Respiratory failure requiring tracheotomy, *n* (%)	4 (3.5)	14 (12.0)	0.016*
Use of mini-tracheotomy, *n* (%)	5 (4.3)	16 (13.7)	0.013*
Re-admission to ICU, *n* (%)	1 (0.9)	11 (9.4)	0.003*

*$P<0.05$ statistically significant. Respiratory failure: receiving O2 administration or artificial respiration including NPPV; infection: administered antibiotics or body temperature ≥38.0°C; renal failure: urine output ≤500 ml day−1 or ≥30% increase of serum creatinine compared with preoperative value; gastrointestinal disturbance: food intake disorder including tube feeding; cardiac disease: acute coronary syndrome, atrial fibrillation, ventricular arrhythmia, and hypotension requiring fluid therapy (fluid bolus >200 ml) or inotropic therapy; neurological disorder: disorder of consciousness, delirium, or cerebral ischaemia; wound infection: requiring surgical treatment, drainage or antibiotics administration; requirement of pain management: administering opioids or local anaesthetics. DVT, deep venous thrombosis; GDT, goal-directed therapy; NPPV, noninvasive positive pressure ventilation; POD, postoperative day.

Sample size estimation

In a study based on the Society of Thoracic Surgeons General Thoracic Database, the incidence of postoperative morbidity and mortality was 24%.[1] Previous studies have reported that perioperative GDT reduced the incidence of postoperative complications by 15.0–17.4% after major abdominal surgery.[16,15] Therefore, we hypothesised that intraoperative GDT would reduce the incidence of postoperative morbidity and mortality by 16%. A power analysis based on the hypothesis indicated that a sample size of 102 would be adequate to detect a difference of 16% between the GDT and control groups, with a power of 0.80 and an alpha of 0.05. Considering a dropout rate of 10%, we enrolled 120 patients in each group.

Results

Subject characteristics

A total of 240 subjects were randomised after recruitment from four hospitals (Osaka City University Hospital: 207 subjects; Osaka City General Hospital: 28 subjects; Sumitomo Hospital, Osaka: four subjects; and Osaka Rosai Hospital: one subject). Five subjects in the GDT group and three in the control group were excluded because their surgery was cancelled after the randomisation procedure (Supplementary Fig. S1), resulting in 115 in the GDT group and 117 in the control group in the final analysis (Table 1; Supplementary Table S1). Thoracoscopic and laparoscopic surgery was performed in similar proportions between the two groups (Table 2). The crystalloid

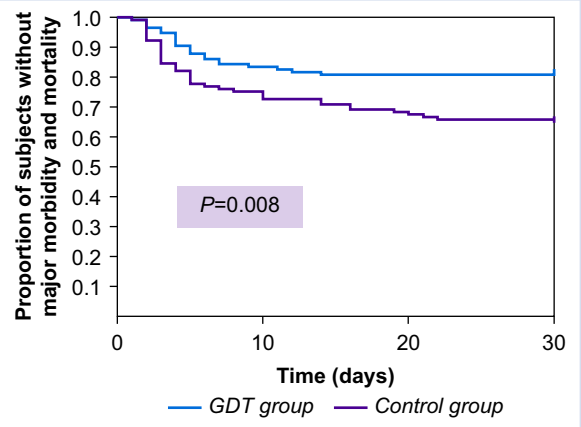

Fig 2. Survival curves according to the occurrence of postoperative major morbidity and mortality in subjects with (GDT group) or without (control group) goal-directed therapy during transthoracic oesophagectomy in the full analysis set. GDT, goal-directed therapy.

and total infused volumes, and the amount of phenylephrine administered during surgery were lower in the GDT group. The median for the total number of bolus colloid administrations during surgery was five (inter-quartile range: 4–6).

Primary outcome

Postoperative morbidity and mortality was less frequent in 22/115 (19.1%) patients randomised to GDT, compared with 41/117 (35.0%) subjects assigned to the control group (absolute risk reduction: 15.9% [95% CI: 4.7–27.2%]; P=0.006; Table 3; Supplementary Table S2). No GDT subject died within 6 months of surgery, compared with 4/117 (3.4%) subjects assigned to the control group (P=0.046) who died as a result of respiratory failure, pneumonia, cardiac arrest, anastomotic leakage, or all (Supplementary Table S3).

Table 4 Cox proportional hazard model for major morbidity and mortality: n=232. A total of 63 (27.2%) subjects sustained major morbidity and mortality after surgery.

Factor	Full analysis set		
	Hazard ratio	95% CI	P-value
Intraoperative GDT	0.51	0.30–0.87	0.013*
Age	1.04	1.01–1.07	0.012*
ASA physical status	0.96	0.46–1.98	0.903
Smoker	1.50	0.76–2.98	0.246
Ischaemic heart disease (preoperative complication)	1.01	0.41–2.47	0.990
Preoperative chemo-radiotherapy	0.85	0.49–1.46	0.554

*P<0.05 statistically significant.
CI, confidence interval; GDT, goal-directed therapy.

Secondary outcomes

Morbidity

Postoperative morbidity that was not deemed as major in the primary outcome definition is further detailed in Table 3. GDT was associated with less morbidity (Fig. 2), including atrial fibrillation (odds ratio [OR]: 0.18 [95% CI: 0.05–0.65]), respiratory failure (OR: 0.27 [95% CI: 0.09–0.83]), use of mini-tracheotomy (OR: 0.29 [95% CI: 0.10–0.81]), and readmission to ICU (OR: 0.09 [95% CI: 0.01–0.67]). Timepoints at which complications occurred after surgery are detailed in Supplementary Table S2. The hospital stay was shorter for patients assigned to GDT compared with the control group (P=0.010).

Predictors of postoperative morbidity/mortality

Cox proportional hazard regression analysis (Table 4) found that intraoperative GDT was independently associated with less frequent postoperative morbidity and mortality (hazard ratio: 0.51 [95% CI, 0.30–0.87]; P=0.013).

Post hoc analysis

Adjusting for age and preoperative chemo-radiotherapy, the incidence of atrial fibrillation, respiratory failure requiring tracheotomy, use of mini-tracheotomy, and re-admission to ICU remained lower in patients assigned to the intraoperative GDT group (Supplementary Table S4).

Discussion

In this multicentre, RCT, we found that intraoperative GDT reduced morbidity and mortality and shortened the hospital stay after transthoracic oesophagectomy. Multivariate analysis revealed that intraoperative GDT was an independent prognostic factor for postoperative morbidity and mortality.

Perioperative GDT appears to be beneficial for patients undergoing higher risk surgeries[17,18]; our data suggest that GDT should also be considered for use in oesophagectomy. Previous non-randomised studies have reported mixed results on the impact of intraoperative GDT on patients undergoing oesophagectomy.[3,4,19] Taniguchi and colleagues[4] assessed the impact of perioperative GDT combined with an enhanced recovery after surgery program on the postoperative outcomes of oesophagectomy, and found that postoperative recovery was faster in patients who received GDT than in those who received conventional haemodynamic management. However, there were no differences in the incidence of postoperative complications within 30 days and the length of hospitalisation. Veelo and colleagues[19] compared the postoperative outcomes of oesophagectomy before and after the implementation of GDT. Although there was no difference in the overall morbidity and mortality rates, length of hospitalisation was lower in patients who received GDT. A small, insufficiently powered, randomised trial conducted by

Bahlmann and colleagues[3] reported that GDT did not reduce early or late postoperative complications after transthoracic oesophagectomy.

There are several reasons for the beneficial effects of intraoperative GDT seen in the present study. First, the volume of fluid was lower in the GDT group than in the control group. This indicates that intraoperative GDT enables anaesthesiologists to avoid unnecessary fluid administration during surgery. This fluid restriction can reduce the incidence of postoperative complications. Second, GDT can facilitate appropriate fluid loading during surgery. Volume expansion in response to the occurrence of absolute hypovolaemia appears to be more reasonable because the volume effect of fluid loading is reportedly 'context-sensitive'.[20] Simultaneous fluid loading during absolute hypovolaemia as a result of acute bleeding and dehydration can be more effective because >90% of the infused volume remains within the vascular lumen.[21] After volume expansion in normovolaemic conditions, approximately two-thirds of the infused volume rapidly shifts toward the interstitial space.[22] Intraoperative GDT, which is based on dynamic indices, allows fluid loading at an appropriate timing, thus reducing the incidence of postoperative complications.

The predictability of SVV during one-lung ventilation remains debatable, particularly in open-chest conditions. A previous study[23] showed that the SVV shows good predictability even in patients with one-lung ventilation (sensitivity: 82%, specificity: 92%). Another study[24] also indicated that this parameter was a good predictor of fluid responsiveness in patients with one-lung ventilation, with an area under the receiver operating characteristic curve (AUC) of 0.767. Conversely, Jeong and colleagues[25] reported that the SVV was a poor predictor of fluid responsiveness during one-lung ventilation, with an AUC of 0.53. These inconsistent results could be attributed to the special conditions in which thoracic surgery is performed. During one-lung ventilation, some blood flow (shunt) remains in the non-dependent lung despite hypoxic pulmonary vasoconstriction, which has no effect on the generation of SVV. Moreover, thoracic surgery is commonly performed in open-chest conditions, wherein the pressure generated from the dependent lung is transmitted to the atmosphere to some extent. Also, the lung and heart are occasionally compressed during the surgical procedure; this can affect SVV values. Accordingly, the use of this parameter for GDT during thoracic surgery should be limited. However, in a previous study by Xu and colleagues,[26] goal-directed fluid restriction using the SVV and cardiac index improved intraoperative oxygenation, reduced postoperative complications, and shortened the hospital stay, even in patients with one-lung ventilation. Our protocol was in accordance with that used in a previous study, where intraoperative GDT could reduce the incidence of morbidity and mortality after abdominal surgery.[15] Furthermore, it was found that GDT based on a combination of dynamic indices of fluid responsiveness and other optimisation parameters, such as SV and cardiac output, was more effective than that based on dynamic indices of fluid responsiveness alone.[27] Accordingly, we used both SV and the SVV to achieve appropriate fluid loading. As shown in the recent meta-analysis,[17] there are a variety of protocols used for GDT in surgical settings, and trials with adequate powers are necessary. Our study followed a randomised controlled design and had an adequate power; therefore, the level of evidence is higher than that in previous studies.[3,4,19]

Our study also has several methodological limitations. First, GDT was performed only during the intraoperative period. Use of GDT throughout the perioperative period may be more effective in improving the patients' outcomes. Second, V_T was set at 7–8 ml kg^{-1} throughout the procedure. Lung-protective ventilation with a lower V_T and appropriate PEEP is becoming a standard of care in the perioperative period. However, as shown in a previous study,[28] the predictability of the SVV is lower at a lower (6 ml kg^{-1}) V_T than at a higher (8 ml kg^{-1}) V_T. Therefore, we set V_T to a minimum of 7 ml kg^{-1} in the current study. Third, the length of hospital stay after surgery varies among different countries.[3,4,19,29] This may be because of the insurance system. However, considering the lower incidence of postoperative complications in the GDT group, the favourable effect of GDT on the length of hospital stay may be applicable to patients in other countries. Fourth, in the control group, intraoperative haemodynamic management was guided solely by maintaining systolic BP>90 mm Hg. Attending anaesthesiologists managed fluid and vasoactive drug administration by considering haemodynamic parameters such as HR and urine output. Although these decisions were made by experienced anaesthesiologists (board certified with the Japanese Society of Anesthesiologists), there may be variability in the haemodynamic management of the control group. Fifth, although the groups appear not to be closely matched in some respects, our retrospectively conducted sub-group analyses suggested similar results to the main study.

In conclusion, the findings of this prospective, multicentre, RCT suggest that intraoperative GDT based on SV and the SVV can reduce the incidence of morbidity and mortality and shorten the hospital stay after transthoracic oesophagectomy.

Authors' contributions

Study design: AM, KS, YO, KN
Patient recruitment: AM, KS, RW, TJ, YH, KT, TF, NO, YO, RO
Data collection: AM, RW, TJ, YH, TF, NO, RO
Data analysis: AM, KS, KT, YO, KN
Writing up of the first draft of the paper: AM
Revising the paper: KS, RW, TJ, YH, KT, TF, NO, YO, RO
Drafting the final manuscript: KN
Final manuscript was approved: all authors

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Declarations of interest

KS received speaker fees from Edwards Lifesciences. The remaining authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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References

1. Wright CD, Kucharczuk JC, O'Brien SM, et al. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *J Thorac Cardiovasc Surg* 2009; **137**: 587–96
2. Raymond DP, Seder CW, Wright CD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. *Ann Thorac Surg* 2016; **102**: 207–14
3. Bahlmann H, Halldestam I, Nilsson L. Goal-directed therapy during transthoracic oesophageal resection does not improve outcome: randomised controlled trial. *Eur J Anaesthesiol* 2019; **36**: 153–61
4. Taniguchi H, Sasaki T, Fujita H, et al. Effects of goal-directed fluid therapy on enhanced postoperative recovery: an interventional comparative observational study with a historical control group on oesophagectomy combined with ERAS program. *Clin Nutr ESPEN* 2018; **23**: 184–93
5. Casado D, Lopez F, Marti R. Perioperative fluid management and major respiratory complications in patients undergoing esophagectomy. *Dis Esophagus* 2010; **23**: 523–8
6. Suehiro K, Rinka H, Ishikawa J, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing airway pressure release ventilation. *Anaesth Intensive Care* 2012; **40**: 767–72
7. Cannesson M, Musard H, Desebbe O, et al. The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. *Anesth Analg* 2009; **108**: 513–7
8. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002; **121**: 2000–8
9. Preisman S, Kogan S, Berkenstadt H, et al. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. *Br J Anaesth* 2005; **95**: 746–55
10. Suehiro K, Tanaka K, Mukai A, et al. Hemodynamic monitoring and management in high-risk surgery: a survey among Japanese anesthesiologists. *J Anesth* 2016; **30**: 526–9
11. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–9
12. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002; **97**: 820–6
13. Giglio MT, Marucci M, Testini M, et al. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **103**: 637–46
14. Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand* 2016; **60**: 289–334
15. Cannesson M, Ramsingh D, Rinehart J, et al. Perioperative goal-directed therapy and postoperative outcomes in patients undergoing high-risk abdominal surgery: a historical-prospective, comparative effectiveness study. *Crit Care* 2015; **19**: 261
16. Salzwedel C, Puig J, Carstens A, et al. Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. *Crit Care* 2013; **17**: R191
17. Chong MA, Wang Y, Berbenetz NM, et al. Does goal-directed haemodynamic and fluid therapy improve perioperative outcomes? A systematic review and meta-analysis. *Eur J Anaesthesiol* 2018; **35**: 469–83
18. Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy – what is the evidence in surgical patients? The effect on different risk groups. *Crit Care* 2013; **17**: 209
19. Veelo DP, van Berge Henegouwen MI, Ouwehand KS, et al. Effect of goal-directed therapy on outcome after esophageal surgery: a quality improvement study. *PLoS One* 2017; **12**, e0172806
20. Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40
21. Rehm M, Orth V, Kreimeier U, et al. Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. *Anesthesiology* 2000; **92**: 657–64
22. Rehm M, Haller M, Orth V, et al. Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. *Anesthesiology* 2001; **95**: 849–56
23. Suehiro K, Okutani R. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing one-lung ventilation. *J Cardiothorac Vasc Anesth* 2010; **24**: 772–5
24. Fu Q, Duan M, Zhao F, Mi W. Evaluation of stroke volume variation and pulse pressure variation as predictors of fluid responsiveness in patients undergoing protective one-lung ventilation. *Drug Discov Ther* 2015; **9**: 296–302
25. Jeong DM, Ahn HJ, Park HW, et al. Stroke volume variation and pulse pressure variation are not useful for predicting fluid responsiveness in thoracic surgery. *Anesth Analg* 2017; **125**: 1158–65
26. Xu H, Shu SH, Wang D, et al. Goal-directed fluid restriction using stroke volume variation and cardiac index during one-lung ventilation: a randomized controlled trial. *J Thorac Dis* 2017; **9**: 2992–3004

27. Deng QW, Tan WC, Zhao BC, et al. Is goal-directed fluid therapy based on dynamic variables alone sufficient to improve clinical outcomes among patients undergoing surgery? A meta-analysis. *Crit Care* 2018; **22**: 298
28. Suehiro K, Okutani R. Influence of tidal volume for stroke volume variation to predict fluid responsiveness in patients undergoing one-lung ventilation. *J Anesth* 2011; **25**: 777–80
29. Giwa F, Salami A, Abioye AI. Hospital esophagectomy volume and postoperative length of stay: a systematic review and meta-analysis. *Am J Surg* 2018; **215**: 155–62

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