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ORIGINAL ARTICLE

Goal-directed therapy with bolus albumin 5% is not superior to bolus ringer acetate in maintaining systemic and mesenteric oxygen delivery in major upper abdominal surgery

A randomised controlled trial

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BACKGROUND Goal-directed therapy (GDT) is increasingly used in abdominal surgery. Whether crystalloids can exert the same effect as colloid, and how this may affect perfusion, is still unclear. The effect of GDT on the systemic oxygen delivery index (sDO_2I) and the mesenteric oxygen delivery index (mDO_2I) can be quantified by measuring cardiac index and flow in the superior mesenteric artery, respectively.

OBJECTIVE The aim of this study was to test the hypothesis that intra-operative GDT with bolus human albumin 5% is superior to GDT with bolus ringer acetate in maintaining sDO_2I and mDO_2I in elective major upper gastrointestinal cancer surgery.

DESIGN Randomised controlled double blinded trial.

SETTING Odense University Hospital, Denmark, from May 2014 to June 2015.

PATIENTS A total of 89 adults scheduled for elective major upper gastrointestinal cancer surgery were randomised and data from 60 were analysed. *Exclusion criteria:* contraindications for using the LiDCOplus system, known allergy to albumin, pre-operative renal failure, pancreatic cancer and pre-operative down staging using chemotherapy and/or radiation therapy, pregnancy.

INTERVENTIONS Patients were randomised to intra-operative GDT with either bolus human albumin or ringer acetate 250 ml, guided by pulse pressure variation and stroke volume.

MAIN OUTCOME MEASURES Changes in sDO_2I and mDO_2I. Secondary outcomes were changes in other haemodynamic variables, fluid balance, blood transfusions, fluid-related complications and length of stay (LOS) in ICU and hospital.

RESULTS Median [IQR] sDO_2I was 522 [420 to 665] ml min^{-1} m^{-2} in the ringer acetate group and 490 [363 to 676] ml min^{-1} m^{-2} in the human albumin group, $P = 0.36$. Median [IQR] mDO_2I was 12.1 [5.8 to 28.7] ml min^{-1} m^{-2} in the ringer acetate group and 17.0 [7.6 to 27.5] ml min^{-1} m^{-2} in the human albumin group, $P = 0.17$. Other haemodynamic comparisons did not differ significantly. More trial fluid was administered in the ringer acetate group. We found no significant difference in transfusions, complications or LOS.

CONCLUSION Bolus human albumin 5% was not superior to bolus ringer acetate in maintaining systemic or mesenteric oxygen delivery in elective major upper gastrointestinal cancer surgery, despite the administration of larger volumes of trial fluid in the ringer acetate group. No significant difference was seen in fluid-related complications or LOS.

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Introduction

The topics of peri-operative fluid therapy and goal-directed therapy (GDT) have received much attention in recent years. With GDT, haemodynamic variables are manipulated to individualised or predefined targets by administration of intravenous fluids and vasopressors or inotropic agents with the aim of improving tissue perfusion, oxygen delivery and ultimately tissue recovery. This approach can potentially reduce morbidity and mortality, reduce length of hospital stay and therefore lower healthcare costs. Systematic reviews suggest that GDT improves outcome when used during the peri-operative period in major surgery, and most profoundly in high-risk patients.[1–3] Even so, a number of recently performed randomised clinical trials have failed to confirm this benefit.[4–6]

The choice of fluid type has also been debated. The current evidence with peri-operative GDT is predominantly based on studies evaluating bolus administration of colloids in the form of hydroxyethyl starch (HES) solutions. Studies of fluid resuscitation in patients with critical illness have demonstrated increased morbidity and mortality with the use of HES compared with crystalloids,[7,8] and albumin may be a safer choice than HES in these patients.[9] In cardiopulmonary bypass surgery, systematic reviews suggest that albumin is associated with lower peri-operative blood loss when compared with HES.[10] Studies, comparing colloids with crystalloids in the peri-operative setting have yet to demonstrate a convincing and guideline changing effect.

The current study was designed to compare the effect of human albumin 5% with balanced crystalloid Ringer's acetate on intra-operative global and mesenteric oxygen delivery, and haemodynamic stability within a GDT protocol, hypothesising that human albumin is superior to balanced crystalloid.

Methods

This single centre, double blind, randomised controlled trial was approved by The Regional Committees on Health Research Ethics for Southern Denmark (Ref: S-20130021) on 3 March 2014, and was registered at https://eudract.ema.europa.eu/, Identifier: 2013-002217-36. It was conducted at Odense University Hospital, Denmark. The study started 1 May 2014. The trial was conducted in accordance with the Helsinki declaration and guideline for good clinical practice, and monitored by an external agency.

Patients

Adults aged 18 years or older undergoing elective upper gastrointestinal cancer surgery (oesophagectomy, total gastrectomy, pancreaticoduodenectomy and total pancreatectomy) were enrolled. Exclusion criteria were as follows: unsuitable for the use of the LiDCOplus system (lithium treatment, body weight <40 kg, significant cardiac arrhythmias, aortic valve regurgitation), contraindications for albumin (known allergic reactions to albumin), pre-operative renal failure estimated glomerular filtration rate (eGFR) (eGFR $< 30\,ml\,min^{-1}\,1.73\,m^{-2}$ or renal replacement therapy), pancreatic cancer and pre-operative down staging using chemotherapy and/or radiation therapy, pregnancy. Patients were not recruited when members of the investigating team were unavailable. Patients were a priori excluded from analysis if there was unresectable disease, the LiDCO cardiac output (CO) monitor could not be calibrated or the relevant ultrasound measurements were not obtainable.

Randomisation

Patients were screened for eligibility at the pre-operative anaesthetic consultation and were included on the day of surgery after informed consent. Randomisation was then performed using opaque envelopes containing project-ID and study group allocation from a computer-generated random sequence and stratified by surgical procedure (abdominal or thoraco-abdominal) to treatment with either colloid or crystalloid. Patients and the attending anaesthesiologist performing the intra-operative GDT protocol were blinded to group allocation. Due to logistic reasons, the nurse administering the trial fluid could not be blinded. Surgical staff, as well as staff involved in postoperative care and discharge planning, were also blinded to group allocation.

Anaesthesia and intra-operative monitoring

A standard fasting regime was followed. Standard monitoring included pulse oximetry, three lead electrocardiography, invasive arterial and central blood pressure measurement, and spirometry with inspiratory and expiratory oxygen, carbon dioxide and volatile agent analysis. In addition, bispectral index score (BIS, monitoring of anaesthesia depth, BISx Power Link, Philips Medical Systems, Eindhoven, The Netherlands) and central temperature were continuously monitored.

General anaesthesia was induced with fentanyl (1 to $3\,\mu g\,kg^{-1}$) and propofol (1 to $3\,mg\,kg^{-1}$), and neuromuscular blockade with cisatracurium ($0.15\,mg\,kg^{-1}$). Anaesthesia was maintained with sevoflurane in oxygen enriched air. A thoracic epidural catheter (level Th 6 to 7) was inserted and an infusion of epidural bupivacaine ($5\,mg\,ml^{-1}$) 3 to $6\,ml\,h^{-1}$ was continued during surgery.

Mechanical ventilation was performed with tidal volumes (V_t) 6 to $8\,ml\,kg^{-1}$ ideal body weight and positive end-expiratory pressure (PEEP) PEEP 5 to 8 mmHg. In thoraco-abdominal oesophageal surgery, the abdominal dissection was performed first, then, following a change to propofol-remifentanil anaesthesia, a double lumen endotracheal tube was inserted. The patient was positioned in the left lateral decubitus jack-knife position and one-lung ventilation of the left lung was established.

All patients were extubated and transferred for postoperative care and observation in an ICU for at least 24 h following the start of surgery until the next morning. The decision to discharge from hospital was at the discretion of the surgeon in charge of the patient.

Systemic and mesenteric flow monitoring

The LiDCOplus (LiDCO Ltd, Cambridge, UK) monitor was attached and calibrated after induction of anaesthesia. This device uses a transpulmonary lithium indicator dilution technique. Patient-specific calibration from three independently measured COs was obtained. Establishment and calibration of the LiDCOplus monitor was carried out by a member of the research team. Stroke volume index (SVI), cardiac index (*CI*), systemic oxygen delivery index (sDO_2I), systemic vascular resistance index (SVRI) and pulse pressure variation (PPV) were continuously monitored in all patients in the intra-operative period, whereafter the LiDCOplus system was disconnected.

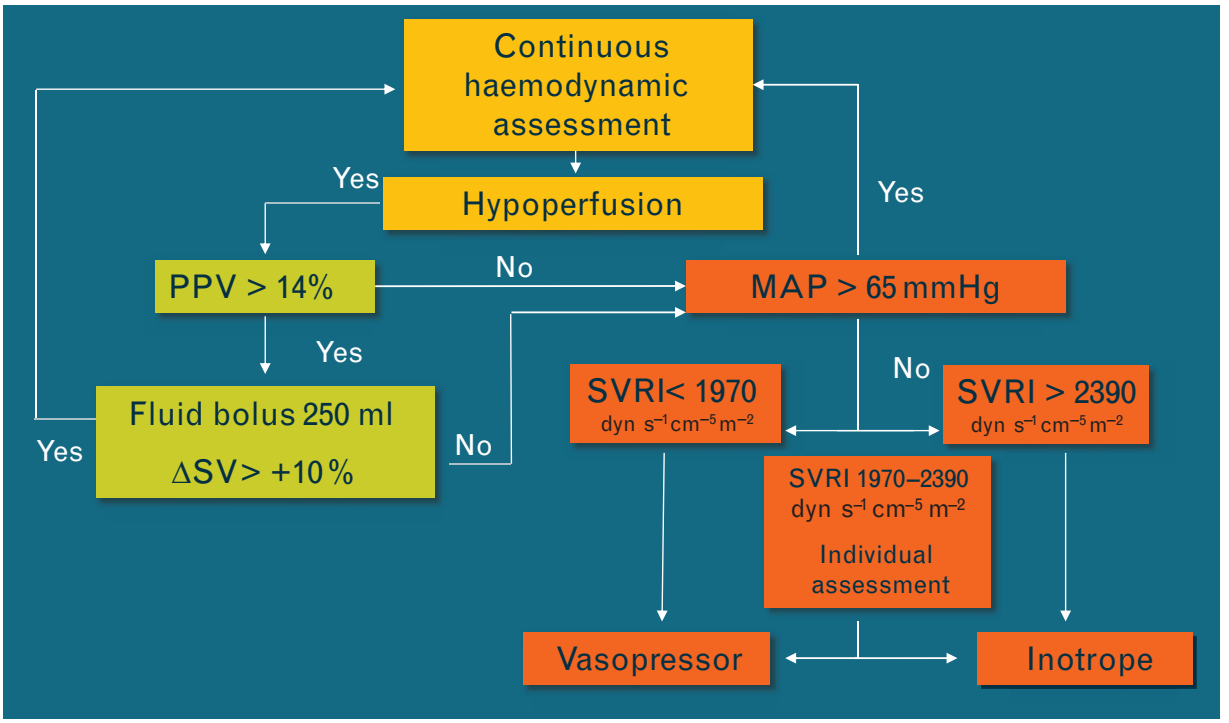
Blood flow in the superior mesenteric artery (SMA) was measured with dedicated intra-operative ultrasound transducers (B-K Medical, Herlev, Denmark) working at 5 MHz and at a maximum insonation angle of 60°. Using identical scanner unit settings, standard examination procedure and under the assumption that the SMA cross section area is circular, sequential and repeated measurements of the SMA area on frozen images were used to calculate blood flow [volumetric blood flow: $\pi \times \text{radius}^2 \times$ time average mean blood flow velocity (TAMV) $\times 60$].

Fluid administration and goal-directed therapy algorithm

Ringer-acetat (Fresenius Kabi AP, Uppsala, Sverige) was administered in all patients with a baseline infusion rate of 3 ml kg^{-1} h^{-1} (5 ml kg^{-1} h^{-1} during open abdominal surgery) to cover insensible loss during surgery. Transfusion with blood products was administered according to national guidelines in addition to the GDT algorithm. In patients with type 1 diabetes, 10% glucose solution 120 ml h^{-1} was infused, and rapidly acting insulin administered to maintain a normal level of blood glucose.

The treatment algorithm (Fig. 1) was followed during abdominal surgery. In open thoracic surgery, the intervention period ended at the opening of thorax, where PPV is no longer valid. Baseline infusion of ringer-acetat 3 ml kg^{-1} was continued and further haemodynamic interventions were at the discretion of the anaesthesiologist. In all other patients, the intervention continued according to protocol until the surgical procedure was complete.

Fig. 1



Treatment algorithm. Fluid bolus albumin 5% or ringer acetate, according to study group allocation. Vasopressor: infusion noradrenaline; inotrope: bolus ephedrine up to 100 mg, hereafter infusion dopamine. MAP, mean arterial pressure; PPV, pulse pressure variation; SV, stroke volume; SVR, systemic vascular resistance.

Fluid boluses of 250 ml were infused over 5 to 10 min, according to protocol, when PPV was more than 14%. If PPV was 14% or lower and the patient was hypotensive [mean arterial pressure (MAP) < 65 mmHg], vasopressor or inopressor was administered. When SVRI was less than 1970 dyn s^{-1} cm^{-5} m^{-2}, infusion of noradrenaline was initiated. If SVRI was more than 2390 dyn s^{-1} cm^{-5} m^{-2}, $^{-2}$, the choice was bolus ephedrine up to a cumulative total of 100 mg, followed by an infusion of dopamine, if needed.

Treatment goals

(1) Peripheral oxygen saturation (SpO_2) more than 94%.
(2) MAP more than 65 mmHg.
(3) Heart rate (HR) 60 to 100 bpm.
(4) PPV less than 14%.
(5) Urine output more than 0.5 ml kg^{-1} h^{-1}.
(6) SVRI 1970 to 2390 dyn s^{-1} cm^{-5} m^{-2}.
(7) Haemoglobin (Hb) more than 5.0 mmol l^{-1} (8.06 g dl^{-1}).
(8) Central venous pressure (CVP) 8 to 12 mmHg (standard PEEP 5 to 8 mmHg).
(9) BIS 40 to 60.

Intervention

Bolus fluids were administered according to the GDT algorithm (Fig. 1) in both groups. The human albumin group received boluses of human albumin 5% (CSL Behring GmbH, Marburg, Germany), and the ringer-acetat group received boluses of a balanced salt solution containing acetate (Ringerfundin; B. Braun, Melsungen, Germany).

Assessments

General data and pre-operative biochemistry data were collected from the chart and the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity[11] was calculated in all patients.

Haemodynamic data were registered at T0 (after calibration, immediately after induction of anaesthesia), T1 (start of laparoscopy), T2 (start of laparotomy), T60 (60 min after T2), T120 (120 min after T2), T240 (240 min after T2) continuing every hour until the end of surgery.

At every time point, the following Were recorded:

(1) *CI* (l min^{-1} m^{-2}), SVI (ml m^{-2}), SVRI (dyn s^{-1} cm^{-5} m^{-2}), PPV (%), DO_2I (ml min^{-1} m^{-2}).
(2) MAP (mmHg), HR (bpm), CVP (mmHg).
(3) Vasopressor (μg kg^{-1} min^{-1}).
(4) Arterial blood gas analysis.

SMA flow was measured by the surgeon immediately after establishment of pneumoperitoneum (T1) and thereafter at every time point from T2 forward until the abdomen was closed. Three independent measurements were performed at each time point and the median value was noted. The following measures were recorded:

(1) Arterial cross sectional area.
(2) Mean flow velocity (cm s^{-1}).
(3) Maximum flow velocity (cm s^{-1}).

SMA volumetric blood flow: $\pi \times$ radius $2 \times$ TAMV $\times$ 60.

Regional oxygen delivery in SMA (mDO_2) was calculated by multiplying mean flow velocity and arterial oxygen content (ml O_2 per ml blood):

(1) $mDO_2 = \text{flow} \times CaO_2$
(2) $CaO_2 = [(PO_2 \times 0.0031) + (Hb \times SaO_2 \times 1.34)]$ - $1.34)] \times 100^{-1}$.[12]

Postoperative assessments included fluid balance (after 24 h), body weight (the first 3 postoperative days), time to first flatus and passing stool.

Data were collected by the investigator or delegated members of the study group.

Complications

Diagnosis and management of complications were undertaken by non research staff. Complications and length of stay (LOS) were recorded by a study group member, blinded to study group allocation. Verification of complications was based on a retrospective review of charts, and radiological and laboratory investigations. End-point fluid-related complications were predefined and included pneumonia, wound infection, acute myocardial infarction, acute renal failure, arrhythmia, pulmonary oedema, intra-abdominal hypertension, surgical anastomotic leak, mechanical ventilation and the use of vasopressor/inotropes. The defining criteria for complications are provided in Suppl. File 1, http://links.lww.com/EJA/A264.

Endpoints

The primary endpoints were changes in sDO_2I and mDO_2I.

The secondary endpoints were intra-operative changes in other haemodynamic variables (SVI, *CI*, SVRI MAP, HR), fluid balance, number of transfusions, incidence of fluid-related postoperative complications, time to bowel function, and ICU and hospital LOS.

Statistical analysis

Power analysis indicated that a sample size of 22 patients per group would be required to detect a 20% increase in DO_2I (from 400 ml kg^{-1} min^{-1} m^{-2}, SD 100) and a 25% increase in mDO_2I (from 20 ml kg^{-1} min^{-1} m^{-2}, SD 5), giving an alpha error of 0.05 (two sided) and a power of 0.9. The inclusion period in this feasibility study was 1 year. It was planned to include a minimum of 30 patients per group.

Continuous, normally distributed data were compared using paired Student's *t* test. Continuous, nonnormally

distributed data were compared using the two sample Wilcoxon rank sum test. Binominal data were compared using χ^2 analysis and Fisher's exact test for small samples. Significance level was set at P less than 0.05. Multiple regression analyses (linear, logistic and duration models) were used to adjust for non matched pre-operative and intra-operative data. Power analyses (level 0.05) were performed using two-sample proportion power tests and R-square-based power calculations for multiple regression analysis; a power of 0.80 was considered acceptable.[13]

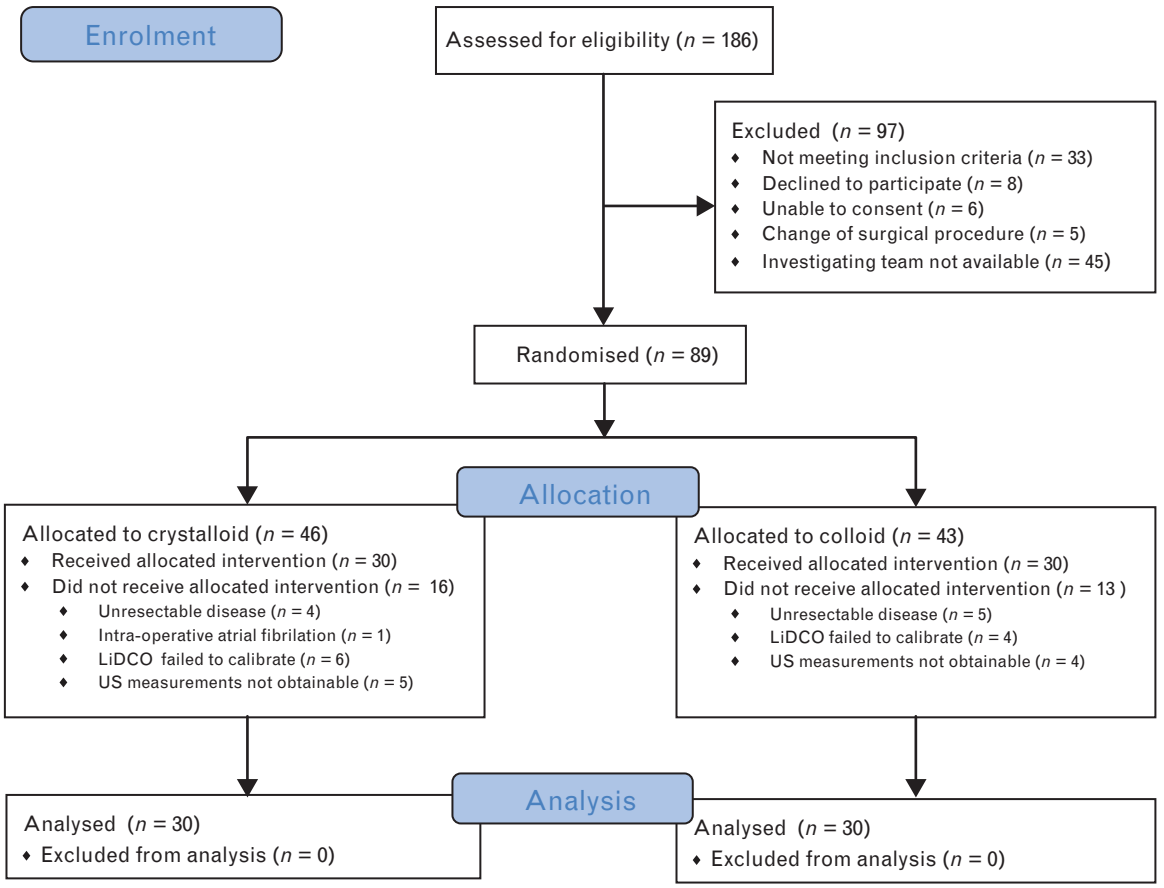
As we consider the surgical approach (thoraco-abdominal or abdominal) to be an important potentially confounding control variable, we included it to control for level differences. To account for the potentially different effect of the intervention in thoraco-abdominal and abdominal surgical approach, we included an interaction between these variables.

Different regression models were used. For continuous outcome variables (fluid administration and balances), linear regression analysis is used. However, for outcome variables measuring a time-to-event spell (LOS, bowel function), a duration model is used. For outcomes observed repeatedly (haemodynamic data), we took advantage of the repeated measures for each patient and used a random effect panel model with a random variance term for patients. Finally, for presence of complications or not, we used a binary logit regression. While odds ratios are reported for the logit models and elasticities (% effects) for the duration models, we reported estimated coefficients for the linear models. For postoperative complications, the one-sided powers for comparison of proportions are reported. STATA 15.0/IC statistical software (STATA Corp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC) version 9.4 were used for statistical analyses. Data analysis was performed before unblinding the trial.

Results

The first patient was enrolled on 6 May 2014 and thereafter patients were recruited consecutively until June 2015. A total of 186 patients were screened for eligibility. Patient flow is presented in Fig. 2. Ultimately, 60 patients were included in the analysis.

Fig. 2



Patient enrolment flow chart. The flow of patients through this trial investigating the effect of colloid versus crystalloid based goal-directed fluid therapy in major upper abdominal cancer surgery. US, ultrasound.

Table 1 Baseline characteristics

	HA, $n = 30$	RA, $n = 30$
Age (years)	68 [62 to 71]	65 [59 to 72]
Male	23 (70)	19 (63)
Body weight (kg)	75 [69 to 87]	76 [68 to 87]
Body height (cm)	172 [166 to 180]	175 [170 to 180]
ASA score		
2	22 (73)	25 (83)
3	8 (27)	5 (17)
POSSUM physiology score	15 [14 to 20]	15 [13 to 19]
POSSUM predicted mortality	3.75 [0.4 to 9.4]	2.35 [0.4 to 6.1]
Duration of surgery (min)	297 [267 to 348]	328 [295 to 348]
Pre-operative chemotherapy	17 (57)	13 (43)

Baseline data are presented as median [IQR] or absolute number (%). ASA, American Association of Anesthesiologists; HA, human albumin allocation group; POSSUM, Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; RA, ringer acetate allocation group.

Table 2 Distribution of surgical procedures

Procedure	HA, $n = 30$	RA, $n = 30$	*P*
Gastrectomy, *n*	7 (23)	1 (3)	0.05
Oesophageal resection, *n*	14 (47)	12 (40)	0.80
Pancreatectomy, *n*	1 (3)	2 (7)	1.00
Pancreaticoduodenectomy, *n*	8 (27)	15 (50)	0.11

Distribution of surgical procedures. Data are presented as absolute number (%). HA, human albumin allocation group; RA, ringer acetate allocation group.

Baseline characteristics were comparable in the two groups (Table 1). More patients in the human albumin group underwent gastrectomy, while in the ringer-acetat group the trend was more in favour of pancreaticoduodenectomy. The ratio for oesophageal surgery with thoraco-abdominal approach was equal in the groups (Table 2).

Table 3 presents peri-operative fluid administration and balance.

Intra-operatively, significantly more trial fluid was administered in the ringer-acetat group. No significant difference was seen in overall intra-operative fluid balance, or after 24 h. Weight gain on the third postoperative day, however, tended to be more pronounced in the crystalloid group. Intra-operative bleeding was comparable between groups. Wound drain production after 24 h tended to be higher in the human albumin group.

Adjustment for procedure (thoracic or abdominal approach) demonstrated an even larger difference in administration of trial fluid in the subgroup who underwent an abdominal approach (677 ml compared with 124 ml in the thoraco-abdominal subgroup) in multivariate regression analysis including all previously mentioned covariates.

We found no difference in administration of blood products or in peri-operative blood loss. Median Hb levels were significantly lower in the human albumin group after 60, 120 and 240 min (Fig. 3).

Primary endpoints

Oxygen delivery did not differ significantly between the groups, neither systemic nor regional (Fig. 4a and b). Median [IQR] sDO_2I was 522 [420 to 665] ml min^{-1} m^{-2} in the ringer-acetat group and 490 [363 to 676] ml min^{-1} m^{-2} in the human albumin group, $P = 0.36$. Median mDO_2I was 12.1 [5.8 to 28.7] ml min^{-1} m^{-2} in the ringer-acetat group and 17.0 [7.6 to 27.5] ml min^{-1} m^{-2} in the human albumin group, $P = 0.17$. Baseline values were comparable.

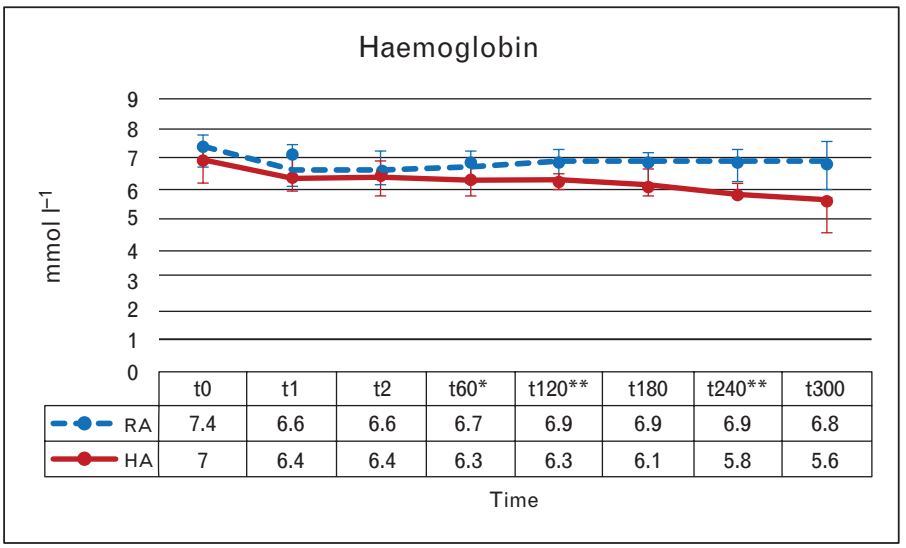
Adjusting for the effect of repeated measurements or the effect of time did not alter the results. This was supported

Table 3 Peri-operative fluid administration and balance

	HA, $n = 30$	RA, $n = 30$	*P*
Intra-operative input			
Blinded trial fluid (ml)	1000 [500 to 1250]	1375 [750 to 1750]	<0.01
Crystalloid, open label (ml)	2632 [2200 to 3200]	2662 [2300 to 3200]	0.74
Albumin, open label	0 [0 to 0]	0 [0 to 0]	
Blood products	0 [0 to 0]	0 [0 to 0]	
Intra-operative output			
Perspiration (ml)	1846 [1392 to 2442]	1899 [1755 to 2468]	0.42
Blood loss (ml)	615 [440 to 1100]	785 [540 to 1000]	0.28
Urine output (ml)	505 [280 to 695]	425 [305 to 770]	0.71
Intra-operative fluid balance (ml)	698 [−3 to 990]	720 [360 to 1341]	0.30
Input first 24 h			
Crystalloid, open label (ml)	5107 [4582 to 6455]	5187 [4330 to 6043]	0.93
Albumin, open label (ml)	0 [0 to 0]	0 [0 to 0]	
Blood products (ml)	0 [0 to 0]	0 [0 to 0]	
Oral intake (ml)	228 [140 to 293]	178 [133 to 222]	0.28
Output first 24 h			
Wound drain (ml)	300 [160 to 520]	190 [100 to 273]	0.08
Gastric drain (ml)	50 [0 to 200]	85 [0 to 400]	0.36
Blood loss (ml)	690 [470 to 1130]	810 [570 to 1030]	0.44
Urine output (ml)	2020 [1255 to 2350]	1428 [1170 to 2043]	0.19
Fluid balance first 24 h (ml)	1494 [611 to 2727]	2192 [1087 to 2717]	0.30
Weight gain (kg) at 72 h (postoperative day 3)	1.7 [1 to 4]	5.25 [1.9 to 6.1]	0.07

Intra-operative fluid administration and balance. Data are presented as median [IQR]. Perspiration was calculated using 3 ml kg^{-1} h^{-1} during surgery with closed abdomen and 5 ml kg^{-1} h^{-1} during surgery with open abdomen. HA, human albumin allocation group; RA, ringer acetate allocation group.

Fig. 3



	t0	t1	t2	t60*	t120**	t180	t240**	t300
RA	7.4	6.6	6.6	6.7	6.9	6.9	6.9	6.8
HA	7	6.4	6.4	6.3	6.3	6.1	5.8	5.6

Changes in haemoglobin levels presented as median [IQR]. *$P < 0.05$, **$P < 0.001$. HA, human albumin group; RA, ringer acetate group. Time: t0, baseline; t1, start of laparoscopy; t2, start of laparotomy; t60, 60 min after t2; t120, 120 min after t2; t240, 240 min after t2; t300, 300 min after t2.

by regression analyses, which did not indicate effects with P values below 0.10.

Secondary endpoints

Secondary haemodynamic endpoints are presented in Fig. 5a–g. In general, no significant differences were seen, except a lower heart rate in the human albumin group. PPV and SVR were normal or low in all patients.

Only four patients required norepinephrine during surgery, all allocated to the ringer-acetat group. No patients required inotropes. In the first postoperative hours in the ICU, six patients in the human albumin group versus ten patients in the ringer-acetat group required norepinephrine ($P = 0.24$).

Median time to first flatus was 88 [71 to 111] h in the ringer-acetat group and 78.5 [62 to 106] h in the human albumin group. The difference was NS for a simple comparison ($P = 0.89$), but statistically significant when including control variables ($P = 0.03$). Median time to passing stools was 135.5 [100 to 162] h in the ringer-acetat group versus 121 [99 to 148] h in the human albumin group ($P = 0.45$). Again, this difference was nonsignificant for a simple comparison ($P = 0.45$) but indicated a shorter time to first flatus in the human albumin group when including control variables ($P = 0.006$).

Complications are presented in Table 4. The total number of complications was 28 in the ringer-acetat group and 22 in the human albumin group and varied from zero to 10 per patient. The number of patients with one or more complications was similar in the two groups. Adjusting for covariates did not improve the level of significance. Grading complications according to Clavien-Dindo[14] added no significant difference between the groups.

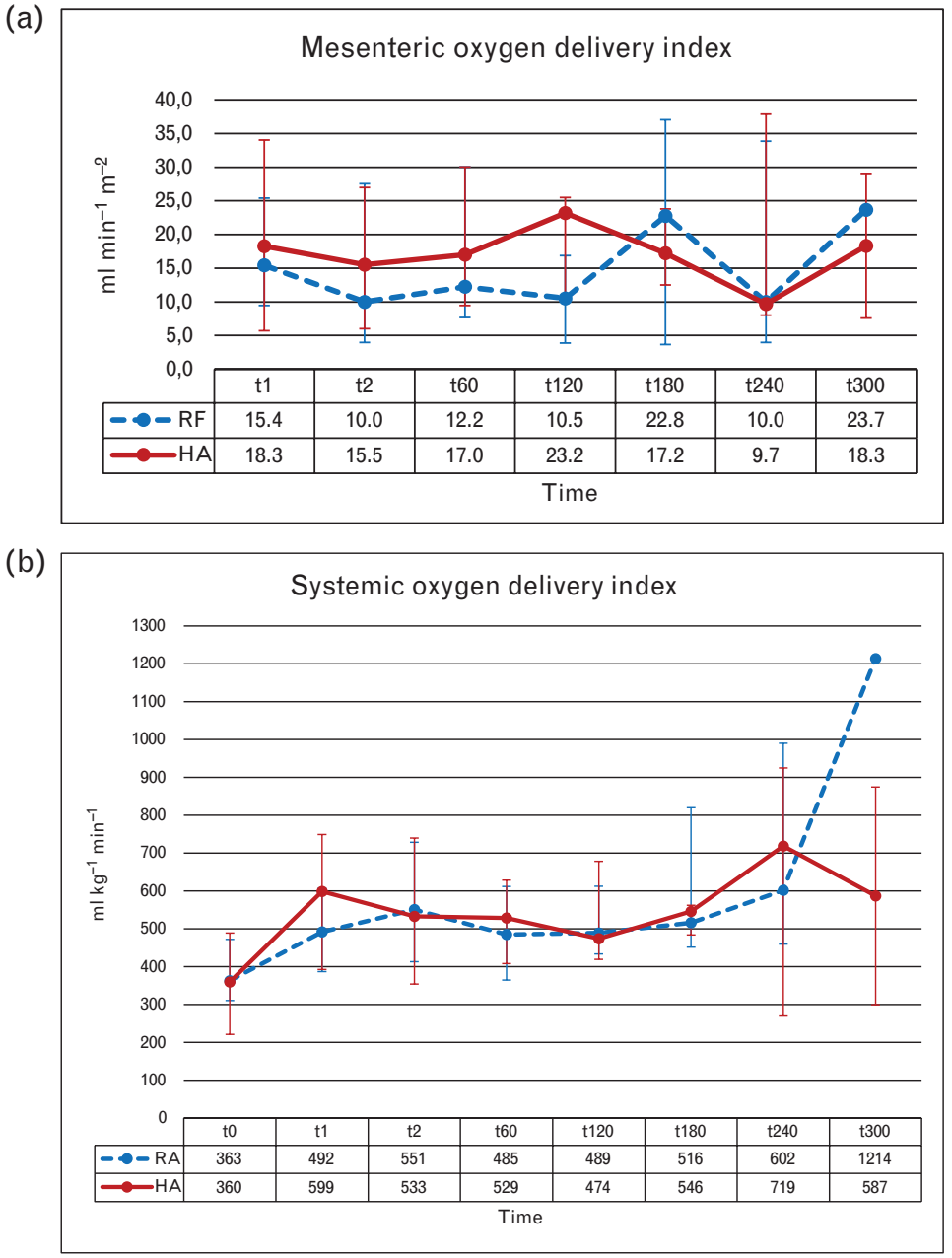
Median LOS in ICU was 21.5 [20.5 to 34.0] h in the ringer-acetat group and 21.0 [20.0 to 24.0] h in the human albumin group ($P = 0.58$). Eleven patients in the human albumin group required more than 48 h of ICU therapy, compared with six in the ringer-acetat group, $P = 0.25$. Median LOS in hospital was 10 [8 to 15] days in the ringer-acetat group and 10 [9 to 13] days in the human albumin group ($P = 0.77$). Adjusting for procedure type (thoracotomy) revealed a 1.1% longer ICU LOS in the human albumin group after abdominal approach versus 0.5% longer ICU LOS in the human albumin group after thoraco-abdominal approach ($P = 0.05$). Similarly, in multivariate analysis, hospital LOS was 5.5% longer in the human albumin group ($P < 0.02$) after adjusting for procedure type.

Discussion

The current randomised, double blinded, clinical study adds to current knowledge that crystalloid and albumin bolus infusions in a PPV-based or SV-based GDT algorithm affect systemic and regional oxygen delivery equally in the intra-operative phase of elective major upper gastrointestinal cancer surgery.

Microcirculatory flow and perfusion are the ideal endpoints in GDT studies, but unfortunately not easily measured. This study is unique in attempting to describe the effect of the fluid strategy on regional oxygen delivery. We chose to measure SMA flow and calculate mDO_2I, since it is both easily accessible and highly

Fig. 4



(a and b) Median mesenteric and systemic oxygen delivery presented with IQR. No statistically significant difference was seen at any time. HA, human albumin group; RA, ringer acetate group. Time: t0, baseline; t1, start of laparoscopy; t2, start of laparotomy; t60, 60 min after t2; t120, 120 min after t2; t240, 240 min after t2; t300, 300 min after t2.

relevant in major upper gastrointestinal cancer surgery. We believe that decreased SMA flow velocity is associated with increased risk of anastomotic leakage in abdominal surgery. The ultrasound method, used in this study, seem feasible, but requires training and maintenance of skills. Hiltebrand *et al.*[15] used ultrasound duplex SMA flow in an animal model and demonstrated a clear association between changes in microcirculatory blood flow in the jejunum mucosa, measured by laser Doppler flowmetry, and intramural intestinal tissue oxygen tension and metabolic markers in the small intestine. Sources of error and factors limiting accuracy in SMA duplex ultrasound measuring are discussed in detail elsewhere.[16]

Systemic oxygen delivery was measured using the LiDCOplus system and pulse power analysis. This method is described elsewhere.[17] Hb and SaO_2 values were updated

Fig. 5

(a–g) Changes in other haemodynamic parameters presented as median [IQR]. $*P < 0.05$. HA, human albumin group; RA, ringer acetate group; SMA, superior mesenteric artery. Time: t0, baseline; t1, start of laparoscopy; t2, start of laparotomy; t60, 60 min after t2; t120, 120 min after t2; t240, 240 min after t2; t300, 300 min after t2.

Table 4 Postoperative complications

	HA, $n = 30$	RA, $n = 30$	*P*	OR (95% CI)	Power
Cardiac arrhythmias, *n*	4 (13)	5 (17)	1.00	0.77 (0.19 to 3.20)	0.06
Anastomotic leakage, *n*	4 (13)	2 (7)	0.67	2.15 (0.36 to 12.8)	0.10
Pulmonary oedema, *n*	1 (3)	3 (10)	0.61	0.31 (0.03 to 3.17)	0.16
Mechanical ventilation, *n*	4 (13)	5 (17)	1.00	0.77 (0.19 to 3.20)	0.06
Inotrope and/or vasopressor, *n*	6 (20)	10 (33)	0.38	0.30 (0.15 to 1.62)	0.26
Pneumonia, *n*	0 (0)	2 (7)	0.49	n/a	0.22
Wound infection, *n*	1 (3)	1 (3)	1.00	n/a	n/a
Acute coronary syndrome, *n*	1 (3)	0 (0)	1.00	n/a	0.06
Acute kidney injury, *n*	1 (3)	0 (0)	1.00	n/a	0.06
≥1 Complications, *n*	7 (23)	8 (27)	1.00	0.84 (0.26 to 2.70)	0.06
Clavien–Dindo grade ≥3B, *n*	7 (23)	11 (37)	0.40	0.53 (0.17 to 1.62)	0.28

Postoperative complications. Data are presented as absolute numbers (%). *P* was calculated using Fisher's exact test for small numbers. CI, confidence interval; Clavien–Dindo grade at least 3B, complications requiring intervention under general anaesthesia; HA, human albumin allocation group; n/a, not available; OR, odds ratio for developing the mentioned complication in the HA group; RA, ringer acetate allocation group.

in the system at every measuring point. Theoretically, acute iatrogenic haemodilution will decrease oxygen delivery in nonresponders by lowering the haematocrit without increasing flow.[18,19] Red blood cell mass and the oxygen carrying capacity, however, is the same. We aimed at avoiding significant iatrogenic haemodilution by using a combined PPV and SV-based algorithm to assess volume responsiveness and by only administering 250-ml fluid challenges. We did, however, see a decrease in Hb levels, especially in the human albumin group, despite comparable blood loss in the groups. This corresponds well with previous studies, demonstrating a higher degree of haemodilution with the use of colloids, compared with crystalloids and may be due to the fact, that albumin remains in the bloodstream longer than crystalloids.[20,21]

GDT in open thoracic surgery is controversial. In general, the recommendation is to keep a restrictive fluid strategy due to the risk of postoperative lung injury, possibly correlated to fluid overload.[22] In adjusted analyses we found a significantly longer LOS in human albumin patients after thoracotomy despite a less positive fluid balance in the human albumin group. Patients for open thoracic surgery were placed in a lateral decubitus jackknife position, which, in itself, causes significant haemodynamic changes. We chose to reduce baseline infusion of crystalloids and suspend the GDT algorithm during thoracotomy, due to the poorly validated correlation between PPV and volume responsiveness in one lung ventilation and open thorax.

The choice of fluid type for GDT has been a hot topic for decades.[23–25] In 2013, the European Medicines Agency decided to blacklist HES in sepsis, burn injuries and critically ill patients. This decision was based on results from large RCTs demonstrating increased morbidity and mortality in critically ill patients. These studies, however, did not use a GDT algorithm. Accordingly, the reported amount of HES given significantly exceeded that expected during surgery. Furthermore, the comparison of the critically ill and patients for scheduled surgery should be questioned.

Studies that investigate peri-operative GDT with synthetic colloids are numerous but often small. Most have evaluated protocols suggesting fluid bolus with synthetic colloids.[26–30] A convincing proof that colloids are superior to crystalloids is still pending. Theoretically, colloids are more effective in expanding intravascular volume and therefore induce a more sustained effect on haemodynamic endpoints.[31] Three randomised clinical trials compared HES solutions to crystalloid in an intra-operative GDT protocol with the conclusion that lower volumes of fluid were needed to reach haemodynamic endpoints with colloids, but without any effect on mortality. Joosten *et al.*[32] used a closed loop GDT system and demonstrated a lower intra-operative fluid balance and fewer postoperative complications in the colloid group. Marjanovic *et al.*[33] proposed a benefit of colloids on intestinal anastomotic healing when compared with crystalloid infusions in an animal model. Ghodraty *et al.*[34] demonstrated improved intestinal motility after abdominal surgery when patients received peri-operative colloids instead of crystalloids.

We chose to avoid synthetic colloids. The safety of albumin was questioned in a Cochrane analysis[35] but not found to increase mortality compared with crystalloids in the SAFE study (Saline versus Albumin Fluid Evaluation) in critically ill patients a few years later.[36] Human albumin 5% exerts the same volume expanding effect and oncotic pressure as HES with an osmolality of 300 $mOsm\,l^{-1}$. In addition, albumin seems to interact with the endothelial glycocalyx and may protect against fluid extravasation.[31] Albumin however, is a transfusion product and thus associated with the risk of infections and immunologic reactions. Furthermore, albumin is expensive and may not be accessible in all countries. In Denmark, albumin can be used at the physician's discretion.

The current study is limited by several factors. First, this was a small single-centre study, powered to investigate the differences in sDO_2I and mDO_2I. Accordingly, the power of the study turned out to be low for secondary outcomes, including LOS in hospital (power = 0.33 and

0.52, respectively) and complication rates (power = 0.06 to 0.28). Thus, these results must be interpreted with caution. Future studies, investigating postoperative morbidity, should include a larger number of patients. Second, we had some technical difficulties with the LiDCOplus system, as well as with the duplex flow measuring, resulting in missing data. Duplex flow measures demonstrated great variability, and SMA flow may depend on operator and patient factors. The latter includes functional status of the bowel, medication, central haemodynamic status, physical status, vessel atherosclerosis and others. Thereby the quality of our primary endpoint analyses may be compromised. Third, the LiDCOplus system was not calibrated until after the induction of anaesthesia. Baseline values may be affected by the cardiovascular effect of anaesthesia and airway handling. Fourth, the amount of open label crystalloids used was quite high in both groups and we can speculate that this would have diluted the GDT effect. Fifth, we included patients for both abdominal and thoracoabdominal procedures. Stratifying results for the type of surgery (pancreatic/gastric surgery versus oesophageal resections) pointed towards a negative effect of albumin in the last-mentioned subgroup in terms of LOS in ICU and hospital. This may partially be explained by the combined abdominal/thoracic surgical approach. Finally, it must be taken into account that the intervention period ended at skin closure. The fluid regimen in the ICU was not GDT based and a possible intra-operative effect may be masked by postoperative hypovolaemia or hypervolaemia.

In conclusion, GDT with bolus human albumin 5% was not superior to GDT with bolus ringer-acetat in terms of changes in systemic and mesenteric oxygen delivery, despite the administration of larger volumes of trial fluid in the ringer-acetat group. No difference was seen in fluid-related complications or LOS in hospital or ICU. These results suggest that GDT with bolus crystalloids is comparable with GDT with bolus colloids in maintaining haemodynamic stability as well as systemic and regional perfusion in major upper gastrointestinal cancer surgery. Larger studies are needed to evaluate the effect on morbidity and mortality.

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