BJA

British Journal of Anaesthesia, 127 (4): 521–531 (2021)

doi: 10.1016/j.bja.2021.06.031
Advance Access Publication Date: 11 August 2021
Cardiovascular

Goal-directed fluid therapy in emergency abdominal surgery: a randomised multicentre trial

Anne A. Aaen[1,*], Anders W. Voldby[2], Nicolas Storm[3], Jeppe Kildsig[3], Egon G. Hansen[4], Erik Zimmermann-Nielsen[5], Kenneth M. Jensen[6], Pernille Tibæk[7], Anette Mortensen[8], Ann M. Møller[4] and Birgitte Brandstrup[2]

[1]Department of Anaesthesia, Holbæk Hospital, Part of Copenhagen University Hospitals, Holbaek, Denmark, [2]Department of Surgery, Holbæk Hospital, Part of Copenhagen University Hospitals, Holbaek, Denmark, [3]Department of Surgery, Herlev University Hospital, Herlev, Denmark, [4]Department of Anaesthesia, Herlev University Hospital, Herlev, Denmark, [5]Department of Surgery, Odense University Hospital, Odense, Denmark, [6]Department of Anaesthesia, Odense University Hospital, Odense, Denmark, [7]Department of Surgery, Slagelse Hospital, Part of Copenhagen University Hospitals, Slagelse, Zealand, Denmark and [8]Department of Anaesthesia, Slagelse Hospital, Part of Copenhagen University Hospitals, Slagelse, Zealand, Denmark

*Corresponding author. E-mails: aaaa@regionsjaelland.dk, anneaaa@hotmail.dk

Abstract

Background: More than 50% of patients have a major complication after emergency gastrointestinal surgery. Intravenous (i.v.) fluid therapy is a life-saving part of treatment, but evidence to guide what i.v. fluid strategy results in the best outcome is lacking. We hypothesised that goal-directed fluid therapy during surgery (GDT group) reduces the risk of major complications or death in patients undergoing major emergency gastrointestinal surgery compared with standard i.v. fluid therapy (STD group).

Methods: In a randomised, assessor-blinded, two-arm, multicentre trial, we included 312 adult patients with gastrointestinal obstruction or perforation. Patients in the GDT group received i.v. fluid to near-maximal stroke volume. Patients in the STD group received i.v. fluid following best clinical practice. Postoperative target was 0–2 L fluid balance. The primary outcome was a composite of major complications or death within 90 days. Secondary outcomes were time in intensive care, time on ventilator, time in dialysis, hospital stay, and minor complications.

Results: In a modified intention-to-treat analysis, we found no difference in the primary outcome between groups: 45 (30%) (GDT group) *vs* 39 (25%) (STD group) (odds ratio=1.24; 95% confidence interval, 0.75–2.05; P=0.40). Hospital stay was longer in the GDT group: median (inter-quartile range), 7 (4–12) *vs* 6 days (4–8.5) (P=0.04); no other differences were found.

Conclusion: Compared with pressure-guided i.v. fluid therapy (STD group), flow-guided fluid therapy to near-maximal stroke volume (GDT group) did not improve the outcome after surgery for bowel obstruction or gastrointestinal perforation but may have prolonged hospital stay.

Clinical trial registration: EudraCT number 2015-000563-14; the Danish Scientific Ethics Committee and the Danish Data Protection Agency (REG-18-2015).

Keywords: complications; emergency gastrointestinal surgery; goal-directed fluid therapy; intraoperative; randomised controlled trial

Received: 21 January 2021; **Accepted:** 23 June 2021

Editor's key points

- Intravenous fluids are used to restore and replace fluid loss during major surgery.
- A flow-directed strategy aiming to optimise stroke volume may improve individual titration of i.v. fluid administration.
- This trial did not observe any benefits of goal-directed fluid optimisation in patients undergoing emergency laparotomy.

In Denmark approximately 4500 patients (78 per 100 000 individuals) undergo emergency gastrointestinal (GI) surgery each year.[1] The risk of postoperative complications or death after emergency GI surgeries is high, with major complications up to 50%[2] and overall 30-day mortality about 14%.[3–6] Patients with intestinal perforation or bowel obstruction often suffer from hypovolaemia combined with dehydration and sepsis. Thus, intravenous (i.v.) fluid therapy is an inherent and life-saving part of the treatment. The surgery is performed within a few hours from arrival to the hospital, which leaves limited time for optimisation of the circulation. Although several treatment improvements have been introduced in the past decade, we lack clinical randomised trials providing high-quality evidence for guiding fluid therapy in emergency surgery.[7,8]

Studies of elective surgical patients and experimental studies have shown that a too restrictive fluid strategy and a too liberal fluid strategy is harmful: a too restrictive fluid administration may cause diminished blood flow and poor wound healing. Untreated shock compromises perfusion of vital organs, circulatory collapse, and death. When i.v. fluid administration is too liberal, it increases the risk of cardiopulmonary complications, pulmonary oedema, cardiac arrhythmias, and respiratory distress.[9] In addition, fluid excess might lead to intestinal oedema with poor collagen proliferation, poor wound healing, and a risk of anastomotic leakage.[10–13] Based on these findings, the Society for Enhanced Recovery After Surgery (ERAS) recommends a positive perioperative fluid balance of no more than 2.5 L.[14] The traditional pressure-guided fluid therapy (arterial blood pressure, central venous pressure, or both) has the ability to detect hypovolaemia but not to determine circulatory filling, that is when the fluid infusions should be stopped. Flow-guided fluid therapy, however, has the potential to detect hypovolaemia and determine when additional fluid no longer increases the stroke volume (SV) and thus, at which point fluid administration should be ceased: vasopressors should be added if the blood pressure remains low.

The objective of this trial was to test the hypothesis that SV-guided i.v. fluid administration aimed at both treating hypovolaemia and avoiding fluid overload could reduce a composite of postoperative complications and death, compared with a standard fluid protocol, in patients undergoing emergency surgery for bowel obstruction or GI perforation.

Methods

Ethics and registration

The Danish Scientific Ethics Committee and the Danish Data Protection Agency (REG-18-2015) approved the protocol. The study was classified as a drug trial by the Danish Medicines Agency and registered in EudraCT (2015-000563-14). The reporting of the trial adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[15]

Study population

We included adult (≥18 yr) patients in need of emergency surgery for obstructive bowel disease or GI perforation, verified by a CT scan. The presence of an anaesthesiologist trained in the protocol was mandatory for inclusion. We excluded moribund patients (ASA score of 5), patients with terminal cancer needing palliative surgery, patients who had undergone surgery within the past 30 days including iatrogenic perforation, patients receiving regular renal replacement therapy, patients unable to give informed consent, and pregnant women.

Patients were screened for inclusion at five hospitals located in three regions of Denmark: Herlev Hospital, Holbaek Hospital, Odense Hospital, Slagelse Hospital, and Svendborg Hospital.

The local investigator thoroughly informed eligible patients before surgery both orally and in writing about the study. The patients signed a consent form to participate in the study. The ethics committee accepted deviation from the usual time for consideration (24 h) and accepted same-day consent. In addition, we asked the patients if they wanted to know the result of the study.

Randomisation

The patients were randomly allocated on a one-to-one basis to either a flow-guided fluid therapy group (GDT group) or a pressure-guided fluid therapy group (STD group). The patients were randomised using the online computer system 'OPEN-randomize'. 'OPEN-randomize' also generated the randomisation sequence and, to ensure equal distribution between the groups, stratified the randomisation for each participating hospital and for the diagnosis of either GI obstruction or perforation.

Intervention

The trial protocol has previously been published.[16] In the GDT group the SV-guided fluid therapy commenced at the induction of anaesthesia and continued until the end of surgery (Fig. 1). SV was monitored with an EV1000® platform (Edwards Lifesciences Corporation, Irvine, CA, USA) through an arterial line connected to a FloTrac sensor®. Human albumin 5% was infused in boluses of 3 ml kg^{-1} until the increase in SV was less than 10%. Thereafter, the flowchart shown in Fig. 1 was followed. Changes in SV caused by external factors such as pneumoperitoneum, changes in body position, alternation in ventilator settings, or the administration of vasopressor or inotropic drugs did not initiate fluid administration but were noted in the data file. Maintenance fluid of 2 ml kg^{-1} h^{-1} including all i.v. medications (antibiotics, anaesthetics, etc.) replaced perspiration and urinary output. In cases of hypotension despite optimised SV, vasopressors were given to maintain MAP above 65 mm Hg.

In the STD group, i.v. fluid was given to ensure MAP >65 mm Hg and diuresis >0.5 ml kg^{-1} h^{-1}. In cases of hypotension despite relevant fluid administration, vasopressors

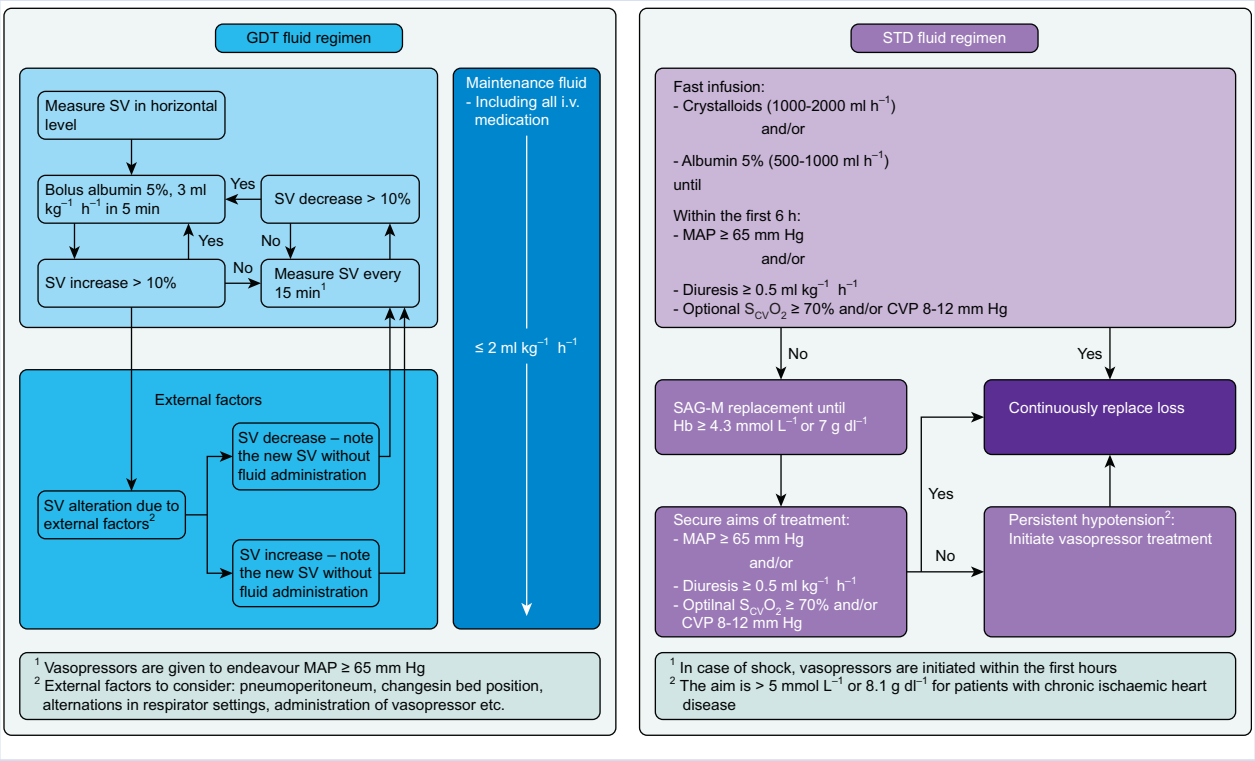

Fig 1. Intraoperative fluid treatment in the randomisation groups. CVP, central venous pressure; GDT, goal-directed fluid therapy; Hb, haemoglobin; SAG-M, packed red blood cells; STD, standard i.v. fluid therapy; SV, stroke volume.

were given to maintain MAP >65 mm Hg. This algorithm was used in the peptic ulcer perforation (PULP) study.[1]

In both groups, blood loss was estimated from the content of the suction canisters and the weight difference of the dressings. In case of large blood losses, extra fluid or blood products were given at the discretion of the anaesthesiologist to a target Hb ≥4.3 mmol L^{-1} or 7 g dl^{-1} (5.0 mmol L^{-1} or 8.1 g dl^{-1} in patients with chronic ischaemic heart disease).

Postoperative treatment

In both GDT and STD groups, a postoperative 0–2 L balance was targeted. In the GDT group a fluid balance above 2 L or a body weight increase of more than 2 kg was treated with furosemide. The administration of furosemide was not protocolised in the STD group.

To avoid a risk of renal failure, we targeted a diuresis at >0.5 ml kg^{-1} h^{-1} postoperatively.

In case of pathological fluid losses on the surgical ward (drains, aspiration, high-output stoma, etc.), the patients were given i.v. fluid resembling the volume and electrolyte composition of the fluid lost. The patients in both groups were weighed daily, and fluid loss and administration were registered until the patients were able to eat and drink sufficiently, were discharged, or to the seventh postoperative day. All patients were allowed to drink freely as soon as possible after surgery. If a patient required a reoperation, the allocated treatment was discontinued, and the patient was treated in accordance with the standard of care.

Additional treatments

The anaesthetic method and drugs used followed standard guidelines in both groups.[16] An arterial catheter was placed to continuously monitor blood pressure and to provide arterial blood for analysis during the surgical procedure.

Patients undergoing laparoscopic surgery did not receive routine epidural analgesia, but if surgery was converted from laparoscopic to open, an epidural catheter was offered postoperatively. Patients undergoing a laparotomy received preoperative or postoperative epidural analgesia. Postoperative oral or i.v. analgesia and anti-emetics were offered in both groups according to national guidelines.

All patients (except those who went directly to the ICU) went to the PACU and stayed there for 2–24 h before transfer to the wards.

All patients received thrombosis prophylaxis (low molecular weight heparin, compression stockings, or both) both intraoperatively and postoperatively, and antibiotics were given according to guidelines and at the surgeon's discretion.

Outcome measures

Definitions for the outcome measures originate from previous trials by Brandstrup and colleagues.[13,17]

The primary outcome was a composite of major complications and death within 90 days postoperatively including: unplanned reoperations, life-threatening bleeding complications, life-threatening thromboembolic events, need for

mechanical ventilation (including noninvasive ventilation), cardiac arrest (survived) including ventricular arrhythmia, and renal failure requiring dialysis.

Secondary outcome measures were minor complications defined in the protocol article[16] as a complication with a need for medical or surgical treatment (see Supplementary Table S1), time in intensive care, time with mechanical respiratory support, time in dialysis, and length of hospital stay (LoS).

All unblinded outcomes were registered in a systematic prospective manner.

Preoperative, intraoperative, and postoperative data were collected in case report forms by the local investigator, who registered all complications until 30 days postoperatively. In addition, major complications and death were registered 90 days postoperatively. After discharge, the local investigator reviewed the medical file and contacted the patients by phone if the patient was alive.

In addition to the outcome measures, we planned two subgroup analyses to explore the following hypotheses:

In patients undergoing emergency surgery for either GI obstruction or perforation

1. Hypovolaemia and fluid overload might compromise cardiac and pulmonary function, resulting in the following postoperative complications: arrhythmia, myocardial infarction, pneumonia, pulmonary congestion, pleural exudation, pulmonary oedema, acute respiratory distress syndrome, and thromboembolic events.
2. Hypovolaemia and fluid overload might cause complications related to tissue healing and infection: superficial or deep wound infection, superficial or deep wound dehiscence, anastomotic leakage, and separation of the stoma from the skin.

Implementation

The units of Good Clinical Practice assessed the study. Patient enrolment was performed by a local investigator who was either a surgeon or an anaesthesiologist trained in the process. Adherence to the protocol was secured in the operation room and in the recovery room by an anaesthesiologist trained in the protocol. On the ward, a local investigator (surgeon) trained in the protocol supervised the i.v. fluid administration and registered the complications. All investigators were regularly educated in the monitoring and treatment of the patients in accordance with the protocol.

Acute anaphylactic reactions, P−Na >155 mmol L^{-1}, central pontine myelinolysis, or seizures were reported to the Danish Medicines Agency.

Blinding

It was not possible to blind the fluid therapy given to the groups. The assessment of the primary outcome was blinded as follows: the patient records were blinded for identity, randomisation, and all information on the provided fluid therapy, fluid balance, and body weight measurements. Blinded assessors reviewed the medical records and registered the postoperative complications. No assessor reviewed files from their own centre. Cases of disagreement with the un-blinded data were settled by another blinded reviewer.

Sample size

National clinical databases showed a mortality risk of 18.2% after surgery for a perforated ulcer, and of 15.7% after emergency colonic surgery.[16] The risk for a major complication in this population of bowel obstruction and bowel perforation was unknown. We estimated that at least 25% of the patients would suffer either a major complication or die. Based on these numbers, we calculated that 149 patients were needed in each group, to detect a reduction in the composite primary outcome from 25% to 12.5% with 80% power at a significance level of 5%. Because the variance is unlikely to follow a normal distribution, we increased the number to 155 patients in each group, or 310 patients. We performed no interim analysis.

Statistics

The protocol dictated a plan for the analysis: the primary outcome was analysed first, followed by the secondary outcome, and then the other parameters.

All data were tested for normality and normal variances and parametric or non-parametric tests were used as appropriate. Fisher's exact test was used to analyse binomial data. Student *t*-test or Mann−Whitney *U*-test was used to analyse continuous data as appropriate. We calculated odds ratio (OR) when relevant. Kaplan−Meier statistics supplemented the mortality and LoS analyses. All tests were two-tailed, and a value of $P \leq 0.05$ accepted as significant. We used the RStudio[18] (2019-07-05) for the analysis. No data were missing for the primary or secondary outcomes. Multiple imputation was not used.

Results

A total of 312 patients were included in the trial between August 2015 and August 2018: 154 patients in the GDT group and 158 in the STD group (Fig. 2). Follow-up was conducted between November 2015 and November 2018. Five patients did not have surgery and three patients withdrew their consent after randomisation but before surgery, leaving 304 patients for analysis in a modified intention-to-treat analysis: 151 patients in the GDT group and 153 patients in the STD group.

During the trial three patients withdrew their consent postoperatively but permitted the use of their data until the end of follow-up. A protocol violation was found in four patients included in the analysis: two did not receive the intervention as planned, and two patients were included despite having undergone surgery within 30 days.

Patients

Baseline characteristics of the patients were similar between the groups (Table 1). The overall median age was 70 yr (interquartile range [IQR], 59−79). A few more patients were female (55%), and the median ASA score was 2. The overall mean sepsis score was 0.8. The majority (66%) had surgery for small bowel obstruction.

Fluid therapy

On the 'day of surgery', the fluid administration was significantly less in the GDT group than in the STD group, median (IQR): 3130 ml (2350−4770 ml) *vs* 3984 ml (2668−5659 ml) ($P=0.0014$). This is explained by the lower volume given

intraoperatively to the GDT group, median (IQR): 1471 ml (1107–2112 ml) *vs* 1952 ml (1478–2782 ml) ($P<0.001$). In the GDT group, a greater part of the fluid was human albumin, median (IQR): 500 ml (300–890 ml) *vs* 0 ml (0–500 ml) ($P<0.001$; Table 2). We observed no differences in the postoperative fluid volume given in the recovery room, the ICU, or on the wards (Table 2). The number of hypotensive episodes (MAP <50 mm Hg) and the dose of vasopressor substances given were similar between the groups. Pre- and intraoperative blood pressures and heart rates are shown in Supplementary Fig. S1.

Primary outcome

The number of patients fulfilling the primary outcome at 90 days postoperatively (blinded assessment) was 45 in the GDT group and 39 in the STD group (OR=1.24; 95% CI, 0.75–2.05; $P=0.40$) (Table 3).

The overall mortality at 90 days was 44 (14%), without difference between the GDT group (24 [16%]) and the STD group (20 [13%]) (OR=1.26; 95% CI, 0.66–2.39; $P=0.50$). The survival curves (Fig. 3) show no significant difference in the estimated probability of survival between the randomisation groups or between the randomisation groups divided into bowel obstruction or GI perforation. The patients with perforation had a greater risk of death compared with patients with bowel obstruction, independent of the randomisation.

Secondary outcomes

LoS (from the end of surgery to discharge) was significantly lower in the STD group, median (IQR): 7 days (4–12) *vs* 6 days (4–8.5) ($P=0.04$; Table 3). No difference between the groups was found for days on mechanical ventilation, days in intensive care, or days in renal replacement therapy.

Adverse events

One patient in the GDT group had P–Na >155 mmol L^{-1} postoperatively.

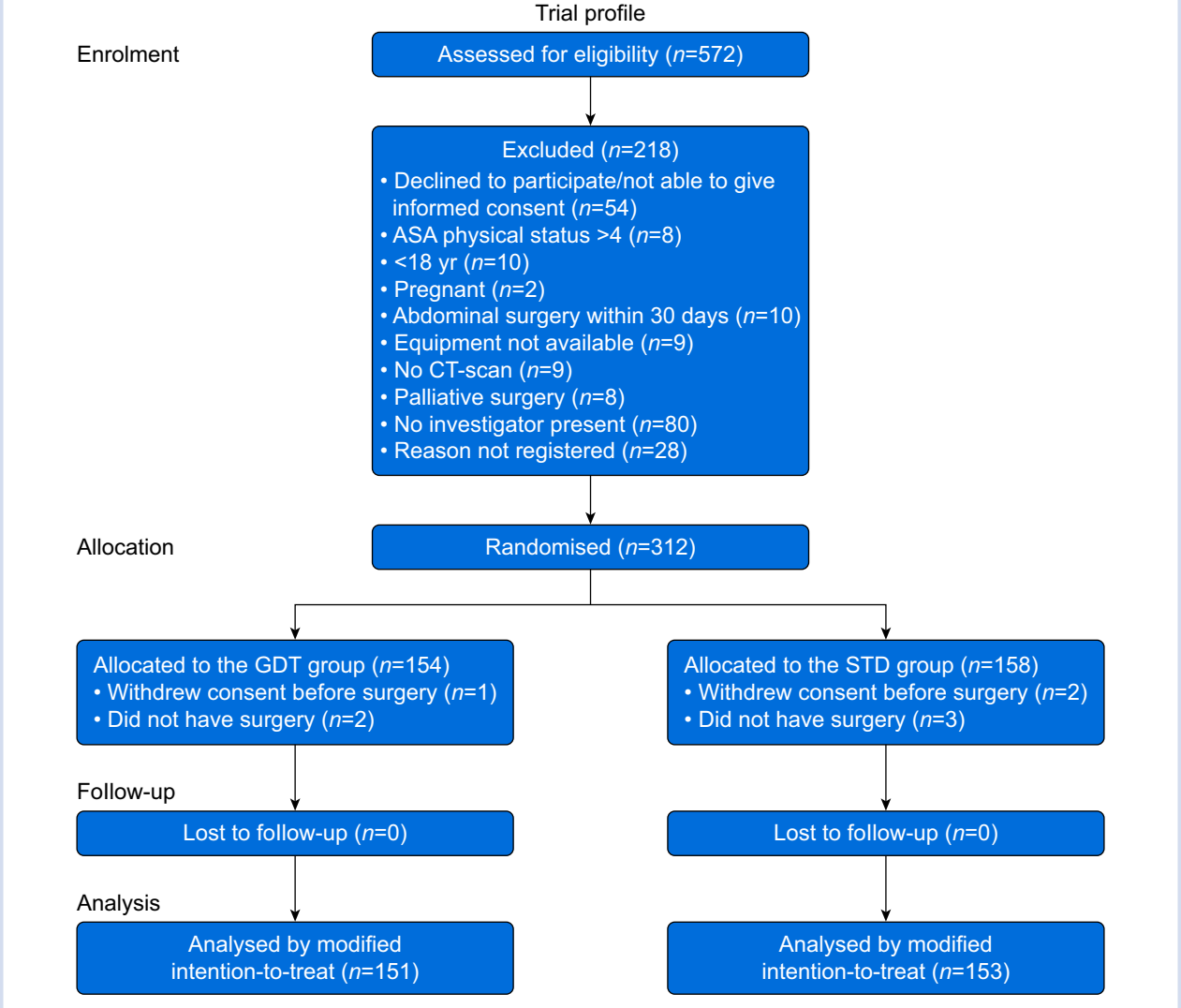

Fig 2. Trial profile. GDT, goal-directed fluid therapy.

Table 1 Demographic and baseline data.

	GDT group (n=151)	STD group (n=153)
Age, median yr (IQR)	70 (59–79)	70 (59–78)
Sex, female/male, no. (%)	81 (54)/70 (46)	87 (57)/66 (43)
BMI, median (IQR)	24 (22–28)	24 (22–27)
ASA physical status, no. (%)		
1	13 (9)	26 (17)
2	71 (47)	74 (48)
3	58 (38)	47 (31)
4	9 (6)	6 (4)
Sepsis score, no. (%):		
0	77 (51)	96 (63)
1	35 (23)	11 (7)
2	29 (19)	38 (25)
3	8 (5)	5 (3)
4	2 (1)	3 (2)
Preoperative active infection*	14 (9)	11 (7)
APACHE II score,† median (IQR)	15 (13–18)	15 (12–17)
Missing data, no. (%)	2 (1)	3 (2)
Patients with comorbidities, no. (%)‡		
Chronic obstructive pulmonary disease/asthma	30 (20)	24 (16)
Ischaemic heart disease	16 (11)	14 (9)
Hypertension	72 (48)	45 (29)
Diabetes mellitus	21 (14)	10 (7)
Cancer, no. (%)		
Active cancer	12 (8)	9 (6)
Disseminated cancer	12 (8)	8 (5)
Previous cancer	18 (12)	22 (14)
Only one comorbidity, no. (%)	42 (28)	52 (34)
Two comorbidities, no. (%)	44 (29)	31 (20)
Three or more comorbidities, no. (%)	52 (34)	40 (26)
Limitations of treatment,¶ no. (%)	5 (3)	7 (5)
Pathology		
Perforation, no. (%)	35 (23)	38 (25)
Stomach ulcer	6 (4)	8 (5)
Duodenal ulcer	5 (3)	8 (5)
Small bowel	5 (3)	4 (3)
Colon rupture (tumour related)	9 (6)	5 (3)
Colonic diverticulum	10 (7)	13 (9)
Obstruction, no. (%)	116 (77)	115 (75)
Small bowel	101 (67)	101 (66)
Volvulus of the caecum	3 (2)	2 (1)
Other colon	12 (8)	12 (8)
Preoperative blood samples, median (IQR)		
C-reactive protein, mg L^{-1}	20 (3–88)	20 (3–104)
Sodium, mmol L^{-1}	139 (134–141)	138 (135–140)
Creatinine, μmol L^{-1}	77 (63–101)	77 (66–97)

IQR, inter-quartile range; GDT, goal-directed fluid therapy during surgery; STD, standard i.v. fluid therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II.

* Patients treated for any type of infection (other than the diagnosis leading to surgery).

† Acute Physiology Age Chronic Health Evaluation, if possible measured preoperatively otherwise immediately postoperatively.

‡ One patient may have more than one comorbidity.

¶ Patients with a limited treatment order before surgery, including no resuscitation in case of cardiac arrest.

Discussion

This study is the first randomised trial to investigate the effects of intraoperative SV-guided fluid optimisation followed by zero-balance fluid therapy in patients undergoing emergency surgery for bowel obstruction or GI perforation. We found no benefit of the GDT-guided regimen on major complications and death after 90 days of follow-up.

The results of previous trials investigating fluid therapy given to optimise SV lack uniformity, and in trials of elective noncardiac surgery the benefit of postoperative complications is unconvincing.[19–21] In 2014, two trials of high-risk patients undergoing planned GI surgery, PeriOperative goal-directed thErapy in Major Abdominal Surgery (POEMAS),[22] and Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome (OPTIMISE),[23] found no positive effect of perioperative cardiac output-guided (flow-guided) fluid therapy on either postoperative complications or on LoS, compared with standard (pressure-guided) fluid treatment. Our finding is in contrast to other previous studies of patients undergoing elective major GI surgery, where perioperative

Table 2 Intraoperative data.

	GDT group (*n*=151)	STD group (*n*=153)	*P* value
Intraoperative i.v. fluid, ml, median (IQR)	1471 (1107–2112)	1952 (1478–2782)	<0.001
Albumin	500 (300–890)	0 (0–500)	<0.001
Ringer acetate	350 (50–700)	1000 (500–1500)	
Normal saline (NaCl 0.9%)	0 (0–150)	0 (0–1000)	
Medicine	300 (130–480)	400 (170–520)	
Blood transfusion (*n*=16)	573 (263–600)	300 (259–450)	0.099
Blood loss (*n*=119), ml, median (IQR)	150 (50–450)	180 (50–388)	
Diuresis, ml, median (IQR)	130 (50–300)	200 (78–330)	
Vasopressor substances, dose in mg, median (IQR)			
Metaoxedrine (*n*=185)	0.7 (0.4–1.3)	0.8 (0.4–1.2)	
Ephedrine (*n*=180)	20 (10–30)	20 (10–40)	
Norepinephrine (*n*=60)	0.27 (0.12–2.07)	0.34 (0.14–1.02)	
Dopamine (*n*=2)	0.60	0.10	
Atropine (*n*=1)/epinephrine (*n*=1)	0/0	1/1.15	
Patients with hypotensive episodes,* no. (%)	26 (17)	19 (12)	
Patients included between 07.00 AM and 19.00 PM	101	97	
Patients included between 19.00 PM and 07.00 AM	51	55	
Operation time, h, median (IQR)	2.5 (1.70–3.43)	2.5 (1.85–3.15)	
Type of operation, no. (%)			
Open surgery	110 (73)	96 (63)	
Laparoscopic surgery	30 (20)	36 (24)	
Laparoscopic converted to open surgery	11 (7)	21 (14)	
Surgical procedure, no. (%)			
Suture of the stomach (gastrorrhaphia)	4 (3)	8 (5)	
Suture of the duodenum (duodenorrhaphia)	6 (4)	8 (5)	
Small bowel resection	24 (16)	26 (17)	
Total colectomy	0	1 (1)	
Left-sided colonic resection (including Hartmann's)	13 (9)	10 (7)	
Right-sided colonic resection	15 (10)	9 (6)	
Formation of a stoma without resection	6 (4)	7 (5)	
Lysis of adhesions	59 (39)	58 (37)	
Laparoscopy with drainage	9 (6)	5 (3)	
Enterotomy with removal of foreign body	2 (1)	5 (3)	
Hernia repair/other procedures	5 (3)/8 (5)	4 (3)/12 (8)	
Formation of an anastomosis, no. (%)	39 (26)	39 (26)	
Formation of a stoma, no. (%)	30 (20)	19 (12)	
Postoperative fluid given (oral and i.v.), ml, median (IQR)			
Postoperative, rest of the 'day-of-surgery'	1638 (900–2785)	1800 (978–3531)	0.35
Total on the 'day-of-surgery'†	3130 (2350–4770)	3984 (2668–5659)	0.0014
1–7 days surgical ward (median, per day)	2038 (1463–2713)	2099 (1240–2506)	0.71
1–7 days intensive care (median, per day)	3446 (2547–3880)	3558 (2640–4766)	0.44
Days with i.v. fluids, surgical ward	4 (2–7)	4 (2–6)	
Patients receiving furosemide once or more 1–7 days, no. (%)	45 (30)	39 (25)	

IQR, inter-quartile range; GDT, goal-directed fluid therapy during surgery; STD, standard i.v. fluid therapy.
* MAP below 50 mm Hg.
† Intraoperative fluid and fluid given the rest of the day of surgery.

GDT has reduced the risk of postoperative complications and shortened LoS.[24,25] In agreement with this, three published cohort studies with historic control groups of patients undergoing emergency GI surgery, have shown a better outcome in the group that included GDT-guided fluid therapy. However, the GDT-guided fluid therapy in these studies was part of a care bundle and was not investigated independently.[25–27] Nevertheless, these results have led to the general recommendation of using GDT-guided fluid therapy in emergency abdominal surgery.

We found that patients in the STD group spent fewer days in hospital. This is somewhat in contrast to earlier reported trials that included patients undergoing planned surgery. In these early trials, LoS was either without difference between the groups compared or was lower in the GDT groups.[24,28,29] The majority of the trials, however, was not blinded, and it is possible that our result and the results of other groups could be biased or a random finding. More patients in the GDT group had a stoma performed, confounding towards a longer LoS.

Most of our patients were ASA 2 and had short duration surgeries. The low ASA physical status scores most probably reflect that Danish citizens have free-of-charge and readily available (short distance) access to medical care. Therefore, co-existing medical conditions are usually well treated (ASA 2). Moreover, the time in surgery does not reflect the severity of disease or a classification as 'moderate surgery'. On the contrary, in a patient with severe sepsis the surgeon can shorten the duration of the procedure, by choosing not to fashion the stoma, to leave the intestines closed with a stapler, or/and to leave the abdomen open (covered with a vacuum dressing), and plan for a second procedure a day or two later. Therefore, only unplanned reoperations were registered as a complication in our trial.

Table 3 Patient outcome.

Gastrointestinal perforation, no. (%)	Clinical unblinded results				Assessor-blinded results			
	GDT group (*n*=151)	STD group (*n*=153)	*P* value	OR (CI 95%)	GDT group (*n*=151)	STD group (*n*=153)	*P* value	OR (95% CI)
Primary composite outcome								
90 days, no. (%)*	44 (29)	39 (25)	0.48	1.20 (0.73–1.99)	45 (30)	39 (25)	0.40	1.24 (0.75–2.05)
Unplanned reoperations†	30 (20)	21 (14)			33 (22)	21 (14)		
Life-threatening bleeding†	2 (1)	5 (3)			3 (2)	4 (3)		
Life-threatening thromboembolic events†	5 (3)	2 (1)			2 (1)	1 (1)		
Cardiac arrest (survived)†	2 (1)	2 (1)			2 (1)	2 (1)		
Need for mechanical ventilation†	7 (5)	9 (6)			5 (3)	5 (3)		
Need for dialysis†	4 (3)	3 (2)			4 (3)	3 (2)		
Death†	24 (16)	20 (13)			24 (16)	20 (13)		
Secondary outcomes								
Death 30 days, no. (%)	18 (12)	16 (11)			18 (12)	16 (11)		
Minor complications								
30 days, no. (%)‡	56 (37)	63 (41)	0.47	0.84 (0.53–1.34)	62 (41)	66 (43)	0.71	0.92 (0.58–1.45)
Cardiopulmonary complications								
90 days, no. (%)	39 (26)	39 (25)	0.95	1.02 (0.61–1.70)	32 (21)	34 (22)	0.83	0.94 (0.55–1.62)
Tissue healing complications								
90 days, no. (%)	32 (21)	26 (17)	0.35	1.31 (0.74–2.33)	34 (23)	25 (16)	0.17	3.49 (0.84–2.64)
Time in hospital, days, median (IQR)	7 (5–13)	6 (4–9)	0.04	–	–	–	–	–
Patients in intensive care								
No. (%)	10 (7)	17 (11)	0.18	0.57 (0.25–1.28)	–	–	–	–
Time in intensive care, days, median (IQR)	3.5 (3–15)	3 (1–8)	0.32	–	–	–	–	–
Patients on mechanical ventilator	4 (3)	6 (4)	0.54	0.67 (0.18–2.41)				
No. (%)					–	–	–	–
Time on mechanical ventilation, days, median (IQR)	10.5 (3–10)	11 (1–14)	0.66	–	–	–	–	–
Patients on dialysis, no. (%)	0	2	–	–	–	–	–	–
Time in dialysis, days, mean	0	7	–	–	–	–	–	–
Bowel obstruction, no. (%)	116 (77)	115 (75)			116 (77)	115 (75)		
Patients with a major complication at 90 days, no. (%)	39 (34)	32 (28)	0.34	1.31 (0.75–2.30)	40 (34)	32 (28)	0.28	1.37 (0.78–2.39)
Mortality at 90 days, no. (%)	15 (13)	11 (10)	0.42	1.40 (0.62–3.20)	15 (13)	11 (10)	0.42	1.40 (0.62–3.20)
Gastrointestinal perforation, no. (%)	35 (23)	38 (25)			35 (23)	38 (25)		
Patients with a major complication at 90 days, no. (%)	15 (43)	15 (39)	0.76	1.15 (0.45–2.92)	15 (43)	15 (39)	0.76	1.15 (0.45–2.92)
Mortality at 90 days, no. (%)	9 (26)	9 (21)	0.84	1.12 (0.38–3.24)	9 (26)	9 (21)	0.84	1.12 (0.38–3.24)

GDT, goal-directed fluid therapy during surgery; STD, standard i.v. fluid therapy; CI, confidence interval; OR, odds ratio; IQR, inter-quartile range.
* Number of patients fulfilling the primary outcome.
† One patient might have more than one complication.
‡ Number of patients with one or more minor complications.

In our study, 21% of the patients had laparoscopic surgery. According to Pucher and colleagues,[30] the national rates of laparoscopy in the UK was 14% in 2018, with possible increasing numbers per year. As seen from our trial, the proportion of emergency laparoscopic surgeries (2015–8) is larger and resembles Danish national rates. In the international literature colloids are typically used for the GDT optimisation.[31] However, at the time we authored the protocol, hydroxy ethyl starch was under suspicion for causing renal insufficiency and possibly increasing the odds of death. Therefore,

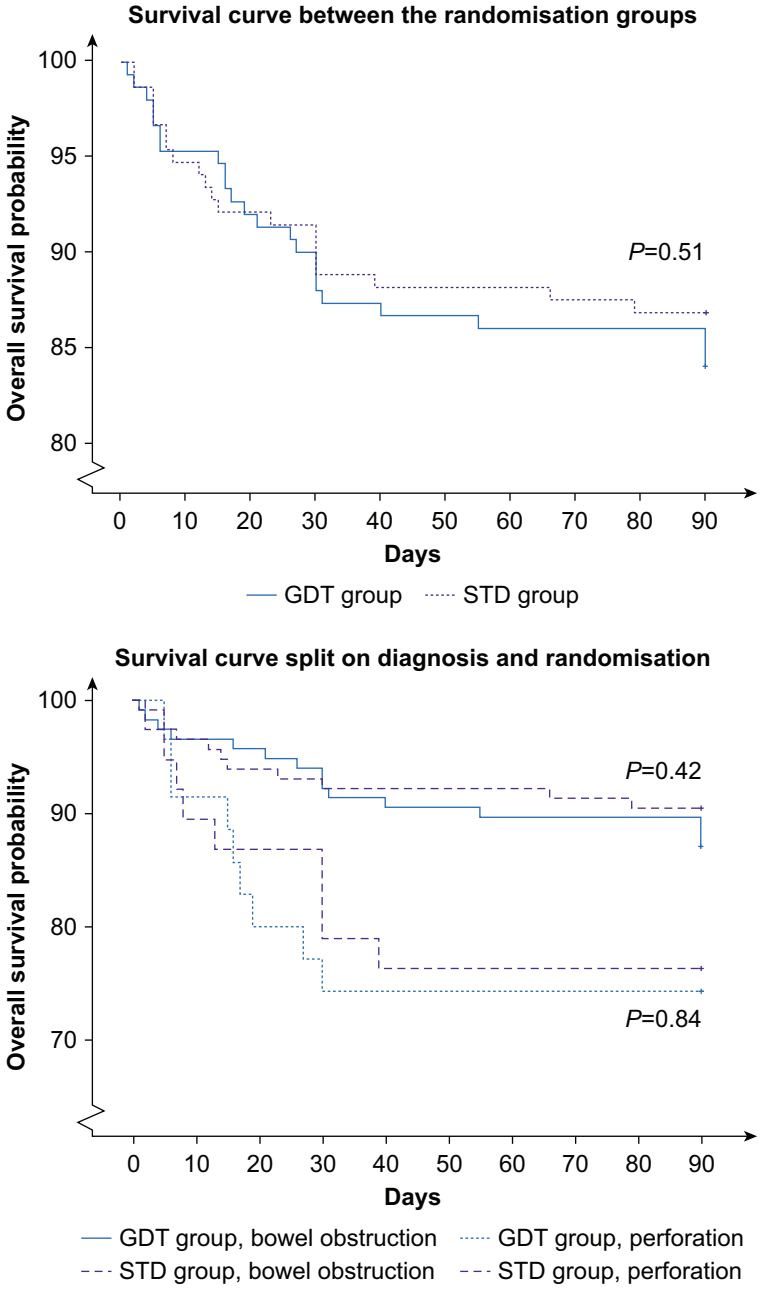

Fig 3. Kaplan–Meier curves displaying the survival probability (%) for the two randomised groups, and bowel obstruction or perforation subgroups. GDT, goal-directed fluid therapy.

we chose human albumin to achieve a near-maximal SV.[32–34] Thus, the GDT group received significantly more colloid than the STD group, and in any trial of SV monitoring, the timing, volume, and constituents of the fluid therapy used might affect the outcome.

In alignment with the previous trials of GDT-guided fluid optimisation, the fluid difference between our two groups was small.[28,35] Our results indicate that a median positive fluid balance of 500 ml does not comprise a risk of fluid overload leading to complications. We expected the fluid administration to be more liberal in the STD group, but a zero-balance fluid approach that avoids fluid overload seems to be the national standard even during emergency surgical procedures. Thus, our result is in accordance with a recent Cochrane review including elective surgical patients that showed no benefit of GDT-guided fluid therapy over restricted (zero-balance) fluid therapy.[19]

As expected, in the mortality analysis divided by diagnosis, we found that patients with GI perforation had a higher 90-day mortality (26%) compared with patients with obstructive

bowel disease (13%). According to the UK National Emergency Laparotomy Audit (NELA) report from 2019,[36] the mortality rate after emergency laparotomy including appendectomies was 9.3%. The mortality in our trial was 11.1% after 30 days. This highlights the problem when comparing results between trials of patients undergoing GI emergency surgery: minor surgeries (e.g. appendectomies) are often included in the cohort. However, the mortality in our trial might have been influenced by selection bias because it excluded patients who were too ill to give informed consent.

Our trial has strengths and weaknesses. The trial was not blinded because adequate i.v. fluid therapy is lifesaving and given by several providers at different wards. Instead, we imposed a blinded assessment of the primary outcome in an attempt to avoid bias. However, the blinded assessment of patient files might have led to the loss of relevant information; therefore, we opted to report both blinded and un-blinded results.

The fluid therapy given 'on the day of surgery' was calculated from the start of surgery to the end of the day of surgery. As this was a trial of emergency procedures, some patients were operated at 5 or 6 o'clock in the morning, causing variation in the length of day of surgery. Thus, it was not possible to define a number of postoperative hours as 'day of surgery'. The postoperative 0–2 L balance therapy might not be standard of care in many countries but was without difference between the groups and should not influence the outcome of the trial. Research on emergency surgical patients is difficult and requires a complex set-up. Attention from the local investigator at all times of the day is not possible, resulting in a risk of non-adherence to the protocol, selection bias, and long inclusion time. Most of the patients (65%) in this trial were included during the daytime (07.00 AM–7.00 PM), which might reflect a selection bias or might equally reflect the fact that in many patients with bowel obstruction, surgery can safely be postponed to daytime. In general, trials investigating fluid therapy suffer from difficult data collection, and we experienced missing preoperative and postoperative fluid data.

A strength of our trial is the multicentre set-up, which increased the heterogeneity of the patients and the treatments, and thus the generalisability of the results. Another strength is that the primary outcome is meaningful and easily collectable. In general, a composite endpoint needs to be carefully defined to avoid bias.

The outcomes in our study were well defined with diagnostic criteria and were thus minimally affected by subjective judgement and held equal importance.

In conclusion, this randomised multicentre trial of patients undergoing emergency surgery for obstructive bowel disease or GI perforation showed no superiority of a flow-guided (GDT) fluid regimen followed by zero fluid balance compared with a pressure-guided (STD) fluid regimen, for both complications and mortality.

Authors' contributions

Conception or design: AWV, BB, AMM
Data collection: AAA, AWV, NS, JK, EGH, EZ, KMJ, PT, AM, BB
Data analysis: AAA supervised by BB, AMM
Drafting the article: AAA supervised by BB, AMM
Revision of the article: AAA, AWV, NS, JK, EGH, EZ, KMJ, PT, AM, AMM, BB
Approval of the final version of the article: AAA, AWV, NS, JK, EGH, EZ, KMJ, PT, AM, AMM, BB

Acknowledgements

The authors thank the following doctors for including patients and other contributions to GAS-ART: Pernille Hadersley, Bodil Thorsager, Anne Axelsen, Panteha Khodadadeh, Søren Salomon, Søren Trap Andersen, Jakob Westergaard-Nielsen, Ole Mathiesen, Per Bo Larsen, Kim Wildgaard, Benedicte Ramsing, Klaus Marcussen, Frants Wegman, Kenneth Rütz, Assia Amal Bada, Niels Qvist, and secretary Pia Lykke Wiese. They thank the nursing staff at both the anaesthesiological and the surgical departments at all participating hospitals for collecting data for this trial. They are also grateful to Edwards Lifescience in Denmark for lending two monitors.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

Department of Surgery, Holbaek Hospital; Department of Anaesthesia, Holbaek Hospital; The Research fund for the Region of Zealand; The Research fund for the Regions of South Denmark and Zealand; Axel Muusfeldt's fund; Merchant Chr. Andersen and wife Ingeborg Andersen's fund founded by their daughter, Miss Lilli Ellen Andersen.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.06.031.

References

1. Møller MH, Vester-Andersen M, Thomsen RW. Long-term mortality following peptic ulcer perforation in the PULP trial. A nationwide follow-up study. *Scand J Gastroenterol* 2013; **48**: 168–75
2. Vester-Andersen M, Waldau T, Wetterslev J, et al. Randomized multicentre feasibility trial of intermediate care versus standard ward care after emergency abdominal surgery (InCare trial). *Br J Surg* 2015; **102**: 619–29
3. Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ, UK Emergency Laparotomy Network. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth* 2012; **109**: 368–75
4. Barrow E, Anderson ID, Varley S, et al. UK practice in emergency laparotomy. *Ann R Coll Surg Engl* 2013; **95**: 599–603
5. Watt DG, Wilson MSJ, Shapter OC, Patil P. 30-Day and 1-year mortality in emergency general surgery laparotomies: an area of concern and need for improvement? *Eur J Trauma Emerg Surg* 2015; **41**: 369–74
6. Jørgensen H. Danish clinical register of emergency surgery for peptic ulcer. Danish clinical register of emergency surgery for peptic ulcer. In: *Annual report 2015. Akut kir database*; 2016. Available from: https://www.rkkp.dk/om-rkkp/

de-kliniske-kvalitetsdatabaser/akut-kirurgidatabasen/. [Accessed 22 February 2017]
7. Harten J, Crozier JEM, McCreath B, et al. Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: a randomised controlled pilot study (ISRCTN 11799696). *Int J Surg* 2008; **6**: 197–204
8. Pavlovic G, Diaper J, Ellenberger C, et al. Impact of early haemodynamic goal-directed therapy in patients undergoing emergency surgery: an open prospective, randomised trial. *J Clin Monit Comput* 2016; **30**: 87–99
9. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* 2002; **89**: 622–32
10. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25–32
11. Piljic D, Petricevic M, Piljic D, Ksela J, Robic B, Klokocovnik T. Restrictive versus standard fluid regimen in elective minilaparotomy abdominal aortic repair—-prospective randomized controlled trial. *Thorac Cardiovasc Surg* 2015; **64**: 296–303
12. Marjanovic G, Villain C, Juettner E, et al. Impact of different crystalloid volume regimes on intestinal anastomotic stability. *Ann Surg* 2009; **249**: 181–5
13. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641–8
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. CONSORT. *Consort — Welcome to the CONSORT Website*. Medical Research Council; 2010. Available from: http://www.consort-statement.org/. [Accessed 12 January 2017]
16. Voldby AW, Aaen AA, Møller AM, Brandstrup B. Goal-directed fluid therapy in urgent GAstrointestinal Surgery—study protocol for a randomised multicentre trial: the GAS-ART trial. *BMJ Open* 2018; **8**, e022651
17. Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? *Br J Anaesth* 2012; **109**: 191–9
18. Team Rs. RStudio: integrated development environment for R. [cited 2018 Aug 17]. Available from: http://www.rstudio.com/.
19. Wrzosek A, Jakowicka-Wordliczek J, Zajaczkowska R, et al. Perioperative restrictive versus goal-directed fluid therapy for adults undergoing major non-cardiac surgery. *Cochrane Database Syst Rev* 2019; **12**: CD012767
20. Sandham JD, Hull RD, Frederick Brant R, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; **348**: 5–14
21. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; **57**: 845–9
22. Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS study (PeriOperative goal-directed thErapy in Major Abdominal Surgery. *Anesth Analg* 2014; **119**: 579–87
23. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output–guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery. *JAMA* 2014; **311**: 2181–90
24. Benes J, Chytra I, Altmann P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care* 2010; **14**: R118
25. Dalfino L, Giglio MT, Puntillo F, Marucci M, Brienza N. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. *Crit Care* 2011; **15**: R154
26. Tengberg LT, Bay-Nielsen M, Bisgaard T, Cihoric M, Lauritsen ML, Foss NB. Multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. *Br J Surg* 2017; **104**: 463–71
27. Huddart S, Peden CJ, Swart M, et al. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. *Br J Surg* 2015; **102**: 57–66
28. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; **93**: 1069–76
29. 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
30. Pucher PH, Carter NC, Knight BC, Toh SKC, Tucker V, Mercer SJ. Impact of laparoscopic approach in emergency major abdominal surgery: single-centre analysis of 748 consecutive cases. *Ann R Coll Surg Engl* 2018; **100**: 279–84
31. Verheij J, Van Lingen A, Beishuizen A, et al. Cardiac response is greater for colloid than saline fluid loading after cardiac or vascular surgery. *Intensive Care Med* 2006; **32**: 1030–8
32. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901–11
33. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2013; **2**: CD000567
34. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34
35. Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95**: 634–42
36. NELA Project Team. *Fifth Patient NELA report* 2019. Available from: https://rcoa.ac.uk/sites/default/files/documents/2020-11/TheSixthPatientReportoftheNELA2020—FINALNovember2020_0.pdf. [Accessed 13 March 2021]

Handling editor: Paul Myles