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Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery

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Editor's key points

- This study presents very interesting results of goal-directed therapy in patients undergoing colorectal surgery.
- The patients, aerobically fit or not, were randomized to receive goal-directed fluid therapy (GDT) vs standard fluid management therapy during surgery.
- GDT patients tended to have an increased length of stay and time to fitness for discharge.
- Contrary to the expectation, this study showed no advantage of GDT.

Background. Intraoperative fluid therapy regimens using oesophageal Doppler monitoring (ODM) to optimize stroke volume (SV) (goal-directed fluid therapy, GDT) have been associated with a reduction in length of stay (LOS) and complication rates after major surgery. We hypothesized that intraoperative GDT would reduce the time to surgical readiness for discharge (RfD) of patients having major elective colorectal surgery but that this effect might be less marked in aerobically fit patients.

Methods. In this double-blinded controlled trial, 179 patients undergoing major open or laparoscopic colorectal surgery were characterized as aerobically 'fit' ($n=123$) or 'unfit' ($n=56$) on the basis of their performance during a cardiopulmonary exercise test. Within these fitness strata, patients were randomized to receive a standard fluid regimen with or without ODM-guided intraoperative GDT.

Results. GDT patients received an average of 1360 ml of additional intraoperative colloid. The mean cardiac index and SV at skin closure were significantly higher in the GDT group than in controls. Times to RfD and LOS were longer in GDT than control patients but did not reach statistical significance (median 6.8 vs 4.9 days, $P=0.09$, and median 8.8 vs 6.7 days, $P=0.09$, respectively). Fit GDT patients had an increased RfD (median 7.0 vs 4.7 days; $P=0.01$) and LOS (median 8.8 vs 6.0 days; $P=0.01$) compared with controls.

Conclusions. Intraoperative SV optimization conferred no additional benefit over standard fluid therapy. In an aerobically fit subgroup of patients, GDT was associated with detrimental effects on the primary outcome.

Trial registry: UK NIHR CRN 7285, ISRCTN 14680495.

<http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=7285>.

Keywords: assessment; goal-directed therapy; patient outcomes, colorectal surgery, exercise test, fluid balance

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Perioperative fluid management for patients undergoing elective major surgery is controversial.¹ Surgery alters fluid balance,² generates a systemic inflammatory response which increases oxygen consumption, and is associated with an increase in cardiac output and oxygen delivery. An inability to meet the metabolic demands of recovery from surgery is associated with increased morbidity and mortality.³

Defining and attaining an adequate circulating volume is complex, and the fluid deficit before surgery varies among individuals.⁴ Recommended fluid administration strategies during major colorectal surgery include volume restriction^{5 6} and maintenance of an adequate circulating volume while avoiding fluid and salt overload.⁷

Goal-directed fluid therapy (GDT) aimed at optimizing cardiac output and oxygen delivery has been shown to improve outcome for high-risk surgical patients.^{8 9} Intraoperative colloid GDT guided by oesophageal Doppler monitoring (ODM) has been associated with significant reductions in the time to readiness for discharge (RfD) and rate of complications in elective intra-abdominal¹⁰ and colorectal surgery.^{11 12} Individualized GDT through stroke volume (SV) optimization has recently been recommended by the UK National Institute for Health and Clinical Excellence (NICE) as a standard of care during major surgery.¹³ Of note, the NICE guidelines were based predominantly on independent studies performed several years ago. Since these trials, the manufacturer of the Oesophageal Doppler Monitor has

simplified the recommended GDT algorithm, placing more emphasis on SV maximization.¹⁴

Cardiopulmonary Exercise Testing (CPET) is a non-invasive measure of cardiorespiratory function. It has a clear ability to quantify cardiorespiratory reserve in the non-surgical setting. Previous studies have suggested that it is capable of identifying patients with poor aerobic fitness who may be less able to maintain perioperative oxygen delivery and are at increased risk of mortality and clinically important complications after surgery.^{15–17}

We set out to validate the simplified GDT algorithm in patients undergoing elective colorectal surgery, hypothesizing that intraoperative GDT might reduce the time to RfD and complication rates as in previous studies. We further planned to investigate whether this would remain true in patients with good aerobic fitness.

Methods

This double-blind stratified randomized controlled trial (RCT) was approved by the Cornwall and Plymouth Research Ethics Committee (Ref: 08/H0203/159) and conducted at Derriford Hospital, Plymouth, UK, between March 2009 and April 2010 (UK NIHR CRN 7285, ISRCTN 14680495).

All patients undergoing major colorectal surgery underwent CPET on a stationary bicycle (Zan, nSpire, CO, USA) as part of their routine preoperative assessment. Anaerobic threshold (AT), determined by V slope and ventilatory equivalents, was used as the marker of aerobic fitness.

Individuals whose oxygen consumption at AT was undetectable or measured $< 8.0 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$ (considered too unfit to randomize) were excluded, as were those where CPET was not performed. Patients were provided with written information at the time of CPET and invited to consider their participation.

Written informed consent was obtained from all participants before randomization. They were risk-stratified as aerobically unfit (AT $8.0\text{--}10.9 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$) or aerobically fit (AT $> 11.0 \text{ ml O}_2 \text{ kg}^{-1} \text{ min}^{-1}$)^{15 16} and within these strata were allocated to the intervention, GDT or standard fluid management (control) groups by random block allocation using sequentially numbered opaque sealed envelopes (Fig. 1).

Perioperative management and masking

A comprehensive description of standard perioperative care and of the blinding procedure can be found in the Supplementary Appendix. Perioperative surgical care was conducted in line with enhanced recovery principles. The majority of patients came to an admission ward on the day of surgery. Bowel preparation was discouraged; those patients receiving bowel preparation were admitted for an i.v. infusion of 1–2 litre of Hartmann's solution in the 12 h preceding their arrival in the operating theatre, according to our previously reported protocol.¹⁸

Local consensus guidelines for perioperative anaesthetic care for bowel surgery were readily available. All participants

received general anaesthesia; for pragmatic reasons, the conduct of this was left to the discretion of the consultant anaesthetist. Local guidelines suggest supplementary thoracic epidural anaesthesia for open procedures and intrathecal morphine with local anaesthetic or local anaesthetic field blocks for laparoscopic operations. Intraoperative crystalloid, colloid, blood products, and inotropes/vasopressors were administered by the anaesthetist based on estimated maintenance fluid requirements, intraoperative losses, and the measurement of standard haemodynamic variables—aiming for a maintenance rate of $10 \text{ ml kg}^{-1} \text{ h}^{-1}$ Hartmann's solution. Invasive arterial and central venous pressure monitoring was undertaken in selected patients.

A medically qualified investigator inserted an Oesophageal Doppler probe (CardioQ™, Deltex Medical, Chichester, UK) immediately after induction of anaesthesia and recorded Doppler readings and haemodynamic variables every 15 min until the end of surgery. Patients allocated to GDT received supplementary colloid (Voluven™; Fresenius Kabi Ltd, Cheshire, UK) given by the investigator, aiming to maximize SV throughout the surgical procedure. Bolus doses of warmed colloid (200 ml) were given according to the algorithm provided by the manufacturer (Fig. 2). Group allocation, ODM readings, and algorithm-guided colloid administration were concealed from other staff in the operating theatre by screens.

The investigator had no involvement in perioperative decision-making or postoperative care.

Postoperative care

Standardized postoperative care was provided on a dedicated colorectal surgery ward. Admission to the critical care unit was at the discretion of the surgeon or anaesthetist. All patients were allowed free fluids, light diet, or both on the evening of surgery if tolerated. There was no formal protocol for postoperative fluid administration though local guidelines suggest a daily fluid intake of 2 litre. Early mobilization was encouraged, epidurals were discontinued at 48–72 h, and pain managed with oral analgesics at the earliest opportunity.

Postoperative outcomes were recorded by a researcher blinded to group allocation. The primary outcome measure was surgical RfD based on predefined criteria, that is, tolerance of oral diet, mobilization and self-support at an appropriate level, adequate pain control with simple oral analgesics, return of adequate lower gastrointestinal function, and adequate stoma care, where applicable.

Secondary outcomes included actual length of stay (LOS), critical care admission, 30 and 90 day mortality, and 30 day hospital readmission rates. Postoperative complications were categorized and graded on a five-point scale according to validated predefined criteria (Appendix 1).¹⁹

Safety monitoring

An independent safety committee reviewed all outcome data in a planned interim analysis which was not revealed to the research team. Adverse events were monitored by

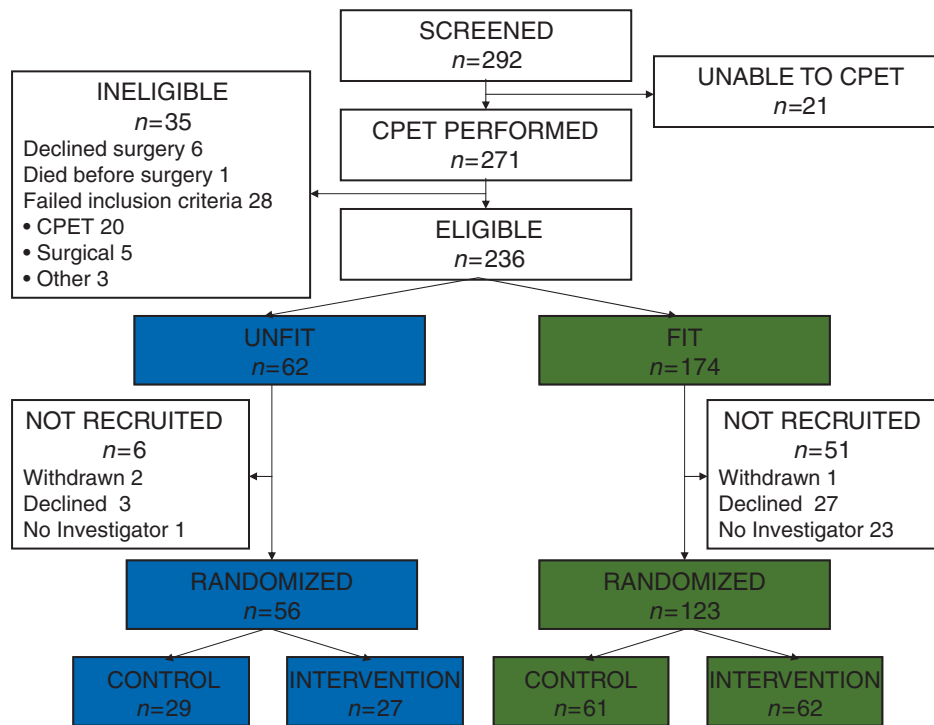


Fig 1 CONSORT diagram. CPET, Cardiopulmonary Exercise Test; CONSORT, Consolidated Standards of Reporting Trials.

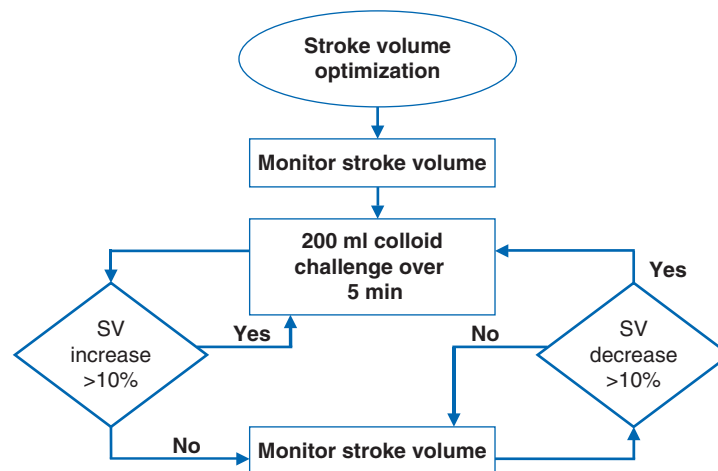


Fig 2 Algorithm for intraoperative GDT as recommended by Deltax, manufacturer of the Oesophageal Doppler Monitor. The user monitors the response of the cardiac SV to an initial colloid bolus.¹⁴ Where fluid responsiveness is present, a further bolus is administered. Where it is absent, the user tracks changes in SV, using a drop of more than 10% as the cue for a fluid challenge.

the local Research and Development service. Serious adverse events were additionally reported to the Ethical Committee.

Statistical analysis

Previous studies in elective colorectal surgery have demonstrated a reduction in time to RfD of 1.5¹¹ and 3 days.¹²

Our existing median LOS of 9 days indicated that a sample of 148 patients would be sufficient to detect a 2 day reduction in the time to RfD at a significance level of 0.05 and a power of 0.9.

We planned to compare the primary outcome within a subgroup of fit patients. At a significance level of 0.05 and

Table 1 Patient characteristics and operative details—overall: *data are mean (sd) or †median (IQR). Data were compared using Mann–Whitney *U*-test, Student's *t*-test or χ^2 test as appropriate. AT, anaerobic threshold. Additional patient characteristic and operative details are provided in Supplementary Table S1

	Control (n=90)	Goal-directed therapy (n=89)	P-value
Age (yr)*	65.9 (14.1)	66.0 (15.6)	
Male:female	48:42	54:35	
Diagnosis—carcinoma	68	65	
AT* (ml O ₂ kg ⁻¹ min ⁻¹)	13.0 (3.8)	13.0 (3.2)	
ASA			
I	11	11	
II	52	51	
III/IV	27	27	
Colonic:rectal resection	37:53	32:57	
Mechanical bowel preparation	35	30	
Preoperative crystalloid* (ml)	971 (570)	1273 (730)	
Thoracic epidural	48	54	
Laparoscopic surgery	37	28	
Stoma	34	38	
Duration (min)*	172 (68)	171 (69)	0.88
Blood loss (ml)†	250 (100–500)	500 (200–1000)	0.006
Transfused in OR	8	19	0.03
Fluids (ml)*			
Crystalloid	3593 (1398)	3479 (1181)	0.56
Colloid	336 (623)	358 (676)	0.82
Packed cells	81 (334)	112 (274)	0.49
Protocol colloid	—	1360 (446)	
Urine output (ml)*	388 (355)	655 (302)	<0.001
Measured fluid balance operative day*	4062 (1957)	4179 (1759)	0.675
Measured fluid balance first postoperative day*	2011 (1718)	2083 (1973)	0.794

a power of 0.8, 112 patients within this subgroup would be required. Pilot data suggested that approximately two-thirds of the patients tested were likely to be fit (AT > 11 ml O₂ kg⁻¹ min⁻¹)¹⁵ and the sample size was increased further to allow for dropouts.

For continuous data, the Kolmogorov–Smirnov tests were performed to assess normality and where appropriate the data were analysed with the two-tailed Student's *t*-test. Non-parametric data were analysed with the Mann–Whitney *U*-test. Categorical data were compared using χ^2 and Fisher's exact tests [PASW Statistics® 18.0 (IBM Corp., Somers, NY, USA) and Microsoft Excel 2007].

Results

Two hundred and ninety-two patients were screened during the study period (Fig. 1). One hundred and seventy-nine participants were randomized: 89 to GDT and 90 to standard fluid management (control). One hundred and twenty-three were risk-stratified as aerobically fit and 56 as unfit.

All randomized patients completed the study. Four had their ODM data revealed to the anaesthetist in the operating theatre. Three patients (one fit and one unfit GDT patient, and one unfit control patient) were unblinded after

intraoperative haemorrhage. One fit patient in the GDT group became haemodynamically unstable without apparent haemorrhage and the anaesthetist requested access to the ODM readings. No participants were lost to follow-up. All results were analysed on an intention-to-treat basis.

Overall, the patient characteristics and risk indices of the control and GDT groups were well matched (Table 1, Supplementary Table S1). There were imbalances between the groups with respect to operative details: more rectal and open procedures were performed in the GDT group and this was associated with a greater use of epidural anaesthesia. Approximately one-third of the patients in each group had bowel preparation. GDT patients received more preoperative i.v. fluid replacement after bowel preparation.

Within the 'fit' and 'unfit' risk categories, the control and GDT treatment groups were well matched in terms of patient characteristics and risk indices (Table 2; Supplementary Table S2 and S3). Unfit patients were older with a greater proportion of resections being performed for carcinoma.

Intraoperative data and fluid administration

There were no significant differences between the control and GDT groups in heart rate, arterial pressure, or ODM readings immediately after induction of anaesthesia (Table 3).

Table 2 Patient characteristics and operative details for aerobically fit patients—risk-stratified by AT >11.0 ml O₂ kg⁻¹ min⁻¹;¹⁵ *data are mean (sd) or †median (IQR). Data were compared using Mann–Whitney U-test, Student's t-test, or χ² test as appropriate. AT, anaerobic threshold. Additional patient characteristic and operative details are provided in Supplementary Table S2

	Control (n=61)	GDT (n=62)	P-value
Age (yr)*	63.7(15.7)	64.6 (16.3)	
Male:female	33:28	41:21	
Diagnosis—carcinoma	43	42	
AT* (ml O ₂ kg ⁻¹ min ⁻¹)	14.6 (3.6)	14.4 (2.8)	
Colonic:rectal resection	25:36	20:42	
Mechanical bowel preparation	22	21	
Preoperative crystalloid (ml)	909 (498)	1310 (818)	
Thoracic epidural	31	37	
Laparoscopic surgery	26	21	
Stoma	22	28	
Duration (min)*	176 (67)	178 (66)	0.87
Blood loss (ml)†	300 (100–500)	430 (250–970)	0.02
Number transfused in OR	6	9	0.45
Fluids (ml)*			
Crystalloid	3631 (1276)	3489 (1088)	0.51
Colloid	262 (480)	311 (592)	0.62
Packed cells	53 (177)	97 (288)	0.31
Protocol colloid	–	1442 (426)	
Urine output (ml)*	334 (253)	644 (421)	<0.001
Measured fluid balance operative day*	3887 (1631)	4298 (1744)	0.18
Measured fluid balance first postoperative day*	1851 (1728)	1954 (1976)	0.76

Table 3 Cardiovascular variables before skin incision and after skin closure—overall: values are mean (sd): MAP, mean arterial pressure; SV, stroke volume; FTc, corrected flow time; CI, cardiac index. Data compared using Student's t-test.

	Control (n=90)	Goal-directed therapy (n=89)	P-value
Pulse rate (bpm)			
Start	71.0 (17.8)	68.7 (15.0)	0.36
End	68.5 (11.5)	69.5 (12.7)	0.61
MAP (mm Hg)			
Start	73.8 (13.5)	77.4 (16.1)	0.11
End	78.3 (13.2)	78.7 (13.7)	0.86
SV (ml)			
Start	80.9 (22.2)	80.9 (21.6)	1
End	95.4 (23.5)	112.0 (22.9)	<0.001
FTc (ms)			
Start	347.6 (47.1)	355.9 (42.5)	0.22
End	364.8 (38.6)	388.8 (36.6)	<0.001
CI (litre min ⁻¹ m ⁻²)			
Start	2.9 (1.0)	3.0 (1.0)	0.52
End	3.4 (1.0)	4.2 (1.0)	<0.001

The attending consultant anaesthetist administered similar volumes of intraoperative fluids to GDT and control group patients (Table 1). This averaged 17 ml kg⁻¹ h⁻¹ of Hartmann's solution. A mean intraoperative positive fluid

balance of 3500 ml was evident in the control group. Patients in the GDT group received an average of 1360 ml of additional colloid from the investigator as per protocol (range 400–2200 ml).

GDT patients had statistically significantly more intraoperative blood loss and urine output than control and were more likely to receive a transfusion of packed cells in the operating theatre (Table 1). Four GDT patients (three fit and one unfit) and two control patients (both unfit) experienced significant intraoperative haemorrhage (brisk bleeding estimated at more than 3 litre).

Cardiac index (CI) increased throughout the operation in both groups, more so in the GDT patients. At skin closure, patients in the GDT group had significantly greater SV, corrected flow time (FTc), and CI than controls (Table 3). The intraoperative increase in SV among GDT patients was greater in the fit than in the unfit (Supplementary Table S4).

The mean measured fluid balance for both GDT and control groups was very similar for both the operative day and the first full postoperative day (Tables 1 and 2).

Patient outcomes

Patient outcomes are summarized in Tables 4 and 5 and Supplementary Tables S5 and S6. The overall median time to RfD was 5.8 days [inter-quartile range (IQR) 3.8–8.9], median LOS was 7.9 days (IQR 5.0–12.1), and 30 day mortality was 2.2%. Median times to RfD and LOS were around 2 days longer in

GDT than in control patients; however, these differences were not statistically significant (6.8 vs 4.9 days; $P=0.09$, and 8.8 vs 6.7 days; $P=0.09$, respectively). There were no significant differences between the groups in other outcome measures (Table 4; Supplementary Table S6).

Fit patients in the GDT group had a significantly increased median time to RfD (7.0 vs 4.7 days; $P=0.01$) and prolonged LOS (8.8 vs 6.0 days; $P=0.01$) (Table 5). Critical care admission was more common in the GDT group including three unplanned admissions after intraoperative haemorrhage. There were no significant differences in other outcome measures. There were two 30 day mortalities in the control group: one patient suffered an anastomotic leak requiring re-operation and died from multiorgan failure and one patient died from pneumonia. One patient in the GDT group died from pneumonia.

For unfit patients, time to RfD and LOS were similar between GDT and control groups (Supplementary Table S5). Unfit patients were more likely to be admitted to critical care than fit patients (22 of 56 vs 19 of 123, $P<0.001$). One postoperative death occurred within 30 days in the GDT group; this was from multiorgan failure after re-operation for anastomotic leak.

Discussion

Our intention was to evaluate whether supplementary colloid boluses guided by haemodynamic information provided by the ODM would enhance clinical outcomes in elective colorectal procedures. In contrast to previous studies, GDT did not improve RfD or LOS compared with standard care. Additionally in an aerobically 'fit' subgroup of patients, the

Table 4 Primary and secondary outcome measures—overall: data are median (IQR) and absolute number. Data were compared using Mann–Whitney U -test or χ^2 test.

	Control (n=90)	Goal-directed therapy (n=89)	Difference	P-value
Surgical readiness for discharge (days)	4.9 (3.7–8.8)	6.8 (4.0–9.8)	+1.9	0.09
Total postoperative stay (days)	6.7 (4.8–13.3)	8.8 (6.0–11.9)	+2.1	0.09
Flatus passed (days)	1.8 (0.8–2.8)	1.8 (0.9–2.9)	0	0.94
Bowel movement (days)	2.8 (1.3–3.9)	2.9 (1.6–4.7)	+0.1	0.53
Toleration of diet (days)	1.8 (0.8–2.8)	1.7 (0.8–3.0)	–0.1	0.81
Any deviation from normal postoperative course	60	63		0.46
Serious postoperative complication (Dindo grade 3–5) ¹⁹	13	10		0.47
Renal complications	13	20		0.17
Creatinine increase to >149% of baseline during first postoperative week	6	10		0.28
Critical care admission	17	24		0.26
Readmission <30 days	13	18		0.35
Mortality				
<30 days	2	2		1.0
<90 days	4	5		0.72

Table 5 Primary and secondary outcome measures in patients classed as aerobically fit: data are median (IQR) or absolute number. Data compared using Mann–Whitney U -test or χ^2 test.

	Control (n=61)	GDT (n=62)	Difference	P-value
Surgical readiness for discharge (days)	4.7 (3.0–7.8)	7.0 (4.7–9.6)	+2.3	0.01
Total postoperative stay (days)	6.0 (4.1–9.8)	8.8 (6.8–11.0)	+2.8	0.01
Flatus passed (days)	1.7 (0.7–2.8)	1.5 (0.7–2.6)	–0.2	0.59
Bowel movement (days)	2.7 (0.9–3.7)	2.9 (1.3–4.9)	+0.2	0.16
Toleration of diet (days)	1.6 (0.7–2.8)	1.7 (0.8–3.0)	+0.1	0.41
Any deviation from normal postoperative course	38	42		0.47
Serious postoperative complication (Dindo grade 3–5) ¹⁹	6	6		0.32
Critical care admission	5	14		0.03
Readmission <30 days	10	11		0.36
Mortality				
<30 days	2	1		0.46
<90 days	3	2		0.43

GDT regimen was associated with detrimental effects on the primary outcome measures of RfD and LOS.

We studied the impact of SV maximization on clinical outcomes and whether patients' aerobic fitness had a bearing. The extent to which we could explore this latter aim was limited by practical considerations. *Post hoc* power calculation suggests that a trial would have to recruit ~160 aerobically unfit participants to detect a 2 day difference in time to RfD in such patients.

The trial was not powered to compare outcomes between aerobically fit and unfit groups, nor were the clinical or research teams blinded to the CPET results. Hence, our discussion focuses primarily on why our overall findings are at odds with previous studies and on the surprising results for the fit subgroup.

This was a pragmatic study conducted in an unselected population of patients having major surgery in a single unit. Heterogeneity of clinical personnel may have impacted on study findings, although in this sense our study was 'real world'. Perioperative care broadly adhered to the principles of enhanced recovery²⁰ but was not strictly protocolized and it is clear that intraoperative fluid therapy practice varied widely between attending anaesthetists.

Limitations of outcome measures

Our short overall median LOS compares favourably with UK national averages²¹ but might attenuate differences attributable to any single intervention such as GDT.

Length of hospital stay is a relatively subjective marker of outcome, affected by systematic failures, patient motivation, and socioeconomic status.²² Our primary outcome measure, RfD by defined criteria, was designed to identify when participants were medically fit to go home. This was adjudicated by a blinded investigator in conjunction with surgical and nursing staff and was a median of 2 days earlier than actual discharge. Subjective elements such as deciding when a patient is ready to cope at home vary between surgeons; these blur the outcome measure and effectively reduce study power. Moreover, we used a previously validated scale (Appendix 1)¹⁹ which failed to discriminate well between serious and relatively minor complications. For example, the intestinal ileus is graded the same whether it is treated with pro-kinetic drugs or with total parenteral nutrition on the basis that both of these represent 'pharmacological treatment'. Importantly, the scale fails to convey the duration of adverse events and we were thus unable to determine whether a prolonged time to discharge readiness may have been due to persistent complications.

Putting this study into context

There is considerable evidence that individualized goal-directed therapy in the perioperative period improves outcome for high-risk surgical patients.^{9 23} Recent meta-analyses suggest that intraoperative ODM-guided haemodynamic management is associated with reduced LOS and complications in patients having major abdominal surgery.^{24 25} Our contrasting findings imply that control perioperative care or

our delivery of GDT was fundamentally different from that of those studies.

The 'ideal' intraoperative i.v. fluid regimen for major bowel surgery has previously been expressed conceptually as a 'J'-shaped curve,^{1 26} and previous studies with favourable results have suggested that the ODM enables the clinician to identify and maintain the optimal SV throughout surgery.¹⁰⁻¹² Interestingly, the cardiac index of control patients in our study rose progressively throughout surgery which has not been the case in previous colorectal GDT trials.^{11 12} This suggests to us that 'standard' pre- and intraoperative fluid management was different from these earlier studies, having perhaps been influenced by them. It is striking that at the conclusion of the procedure, our control group had Doppler readings very similar to those of the intervention groups in other trials (Supplementary Table S7).^{11 12}

Might 'standard care' in our institution be sufficiently good to neutralize the effects of GDT? The incidence of occult hypovolaemia during elective bowel surgery is affected by the duration of preoperative starvation, the use of bowel preparation, the magnitude of the physiological surgical stress response, and the degree of vasoparesis and venodilatation associated with neuraxial blockade. In the Enhanced Recovery era, advances in perioperative care may have attenuated these factors.

Set against this background, the average intraoperative fluid load ($17 \text{ ml kg}^{-1} \text{ h}^{-1}$) given to each patient by the attending anaesthetists represents a substantial increase on previous trials. However, RfD and LOS for our control group compare favourably (Supplementary Table S7).

In contrast to previous trials,^{10 12} augmentation of SV by the investigator added nothing, and in fit patients, it appeared to be detrimental. This may be partially attributable to the manufacturers' simplification of the GDT algorithm. Previous versions have incorporated additional parameters—typically, an increase in corrected flow time, Ftc,^{10 12} or an increase in central venous pressure¹¹ as a signal that the circulating blood volume is replete. Colloid boluses are then withheld even after an increase in SV. Under the new algorithm, each individual is titrated close to the top of their Starling curve. In our view, this is SV 'maximization' rather than optimization and the approach has not yet been validated in an intraoperative setting. A recent trial comparing ODM-guided GDT to standard fluid therapy during laparoscopic colonic resection reported a longer time to discharge in patients receiving starch boluses according to an algorithm similar to ours.²⁷

SV manipulation solely by fluid treatment may be an overly simplistic approach to the replenishment of intraoperative tissue oxygen debt. Several trials have shown benefit when individualized, targeted oxygen delivery algorithms incorporating both fluid resuscitation and vasoactive drugs are applied to high-risk surgical patients,^{9 23 28-30} although interestingly a recent study has suggested that a fixed-dose dopexamine regimen confers no additional benefit over colloid GDT for all comers having elective colorectal surgery.³¹

Finally, it is important to appreciate how trial methodology differs from real-world practice. In our study, every GDT patient received at least an initial 200 ml colloid bolus regardless of FTC; and the investigator was committed to complete each bolus once started, regardless of the contemporaneous actions of the attending anaesthetist.

There is a strong possibility that aerobically fit GDT patients received inappropriate additional fluids with end-operative SVs which were considerably higher than those of the intervention group in previous trials. This trend was less apparent in unfit individuals. Potentially, the fit individuals with relatively compliant vasculature continued to increase their SVs in response to fluid and were given excess. Three fit GDT group patients vs no fit controls experienced significant intraoperative haemorrhage which appeared to be due to coincidental surgical mishap, but the possibility that the fluid load distended pelvic capacitance vessels cannot be disregarded.

It is not clear what the mechanism for the prolonged stay of GDT vs control in fit patients may have been. We did not see a higher rate of measured postoperative complications in the GDT group.

An important consideration is whether harm could be attributed to the specific colloid used by the investigator for boluses. Typically, trials of GDT during colorectal surgery have used gelatin solutions,^{11 12} whereas we used 6% starch (Voluven). Starch solutions have been linked with coagulopathy and renal medullary damage,^{32–34} though such associations in patients with sepsis may not be applicable to the elective perioperative setting. There are a number of small studies implying that modern starches have an improved safety profile but the clinical usefulness of the solutions remains controversial.³⁴ In our study, there was increased average blood loss in GDT patients compared with controls, but we did not see more cases of acute renal impairment in the first postoperative week in that group (Table 4). No GDT patients received more than the maximum recommended daily dose of 6% starch (50 ml kg⁻¹) and there was no relationship between the volume of starch administered and the magnitude of postoperative creatinine increase or renal complications.

Small trials are vulnerable to type I error. Patients having colonic surgery have a shorter RfD than those undergoing rectal surgery [in our trial, median 4.8 days (IQR 3.0–7.3) vs 7.0 days (IQR 4.0–9.9), respectively ($P < 0.001$ MW test), which is in line with national findings].²¹

Disproportions of colonic vs rectal and open vs laparoscopic procedures between groups may be important. In this RCT, more GDT than control patients had rectal resections, which would be expected to increase RfD. In contrast, previous studies of GDT in colorectal surgery had an imbalance in the opposite direction with proportionately more colonic surgery in the GDT group.^{11 12}

Aerobic fitness and LOS

Previous GDT trials have not characterized the functional capacity of the participants. For this study, we used an AT threshold of 11 ml O₂ kg⁻¹ min⁻¹ to risk stratify patients

as 'fit' or 'unfit'.^{15 17} Functional capacity characterized in this way may have a bearing on RfD and LOS. Interestingly, on *post hoc* analysis, aerobically unfit patients having major rectal procedures tended to have a longer RfD and LOS than their fit counterparts but this association was lost in colonic surgery (fit vs unfit: 4.8 vs 4.5 and 6.0 vs 5.6 days, respectively). This is hypothesis-generating: the physiological stress of surgery may be lower in colonic than in rectal operations, such that the ability to increase oxygen delivery may be less important as a determinant of LOS in such patients. However, our study was not powered to address this.

Implications

GDT focusing on SV maximization may have important limitations including a risk of iatrogenic fluid overload which may be associated with prolonged hospital stay. Further studies are required to investigate whether alternative GDT algorithms may be of benefit. Recent NICE guidelines are in favour of intraoperative GDT during major surgery, but it is unclear whether the apparent benefits apply to all subgroups of patients. Future studies should seek to define the 'high-risk surgical patient' taking into account the planned surgical procedure (rectal vs colonic; open vs laparoscopic) and functional capacity, and evaluate the effects of GDT within these strata.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

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Appendix 1. Grading system for complications, modified from Dindo and colleagues¹⁹

Grade	Definition
1	Any deviation from normal postoperative course with no need for pharmacological treatment or surgical, endoscopic, or radiological intervention
2	Any deviation from normal postoperative course with need for pharmacological treatment
3	Any deviation from normal postoperative course requiring surgical, endoscopic, or radiological intervention
4	Life-threatening complication requiring HDU or ICU care
5	Death

References

- Bellamy MC. Wet, dry or something else? *Br J Anaesth* 2006; **97**: 755–7
- Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesth Analg* 2005; **100**: 1093–106
- Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure, sepsis and death in high risk surgical patients. *Chest* 1992; **102**: 208–15
- Bundgaard-Nielsen M, Jorgensen C, Secher N, Kehlet H. Functional intravascular volume deficit in patients before surgery. *Acta Anaesthesiol Scand* 2010; **54**: 464–9
- Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Danish Study Group on Perioperative Fluid Therapy: 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
- Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812–8
- Powell-Tuck J, Gosling P, Lobo D, et al. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients. BAPEN Medical 2008 NHS Evidence—National Library of Guidelines. Available from <http://www.library.nhs.uk/GuidelinesFinder/ViewResource.aspx?resID=299532> (accessed December 24, 2010)
- Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–86
- Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a metaanalysis of randomised controlled trials. *Br J Anaesth* 2009; **103**: 637–46
- 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
- Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens post-operative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95**: 634–42
- 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
- Available from <http://www.nice.org.uk/nicemedia/live/13312/52624/52624.pdf> (accessed April 1, 2011)
- Available from http://www.deltexmedical.com/downloads/clinical_educationguides/CQ_OR_QRG9051_5309_3.pdf (accessed March 17, 2011)
- Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischaemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; **104**: 701–4
- Snowden CP, Prentis JM, Anderson HL, et al. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Ann Surg* 2010; **251**: 535–41
- Wilson RJT, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010; **105**: 297–303
- Sanders G, Mercer SJ, Saeb-Parsey K, Akhavan MA, Hosie KB, Lambert AW. Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery. *Br J Surg* 2001; **88**: 1363–5
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13
- Kehlet H. Fast-track colorectal surgery. *Lancet* 2008; **371**: 791–3
- Faiz O, Kennedy RH, Warusavitarne J, et al. Laparoscopically-assisted vs open elective colonic and rectal resection: a comparison of outcomes in English NHS Trusts between 1996 and 2006. *Dis Colon Rectum* 2009; **52**: 1695–704
- Hollowell J, Grocott MPW, Hardy R, Haddad FS, Mythen MG, Raine R. Major elective joint replacement surgery: socioeconomic variations in surgical risk, postoperative morbidity and length of stay. *J Eval Clin Pract* 2010; **16**: 529–38
- Lees N, Hamilton M, Rhodes A. Clinical review: goal-directed therapy in high risk surgical patients. *Crit Care* 2009; **13**: 231
- Walsh SR, Tang T, Bass S, Gaunt ME. Doppler-guided intra-operative fluid management during major abdominal surgery: systematic review and metaanalysis. *Int J Clin Pract* 2008; **62**: 466–70
- Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia* 2008; **63**: 44–51
- Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs 'restrictive' perioperative fluid therapy—a critical assessment of the evidence. *Acta Anaesthesiol Scand* 2009; **53**: 843–51
- Senagore AJ, Emery T, Luchtefeld M, Kim D, Dujovny N, Hoedema R. Fluid management for laparoscopic colectomy: a prospective, randomized assessment of goal-directed administration of balanced salt solution or hetastarch coupled with an enhanced recovery program. *Dis Col Rect* 2009; **52**: 1935–40

- 28 Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care* 2005; **9**: R687–93
- 29 Futier E, Vallet B. Inotropes in goal-directed therapy: do we need 'goals'? *Crit Care* 2010; **14**: 1001
- 30 Roche AM, Miller TE. Goal-directed or goal-misdirected—how should we interpret the literature? *Crit Care* 2010; **14**: 129
- 31 Davies SJ, Yates D, Wilson RJ. Dopexamine has no additional benefit in high-risk patients receiving goal-directed fluid therapy undergoing major abdominal surgery. *Anesth Analg* 2011; **112**: 130–8
- 32 Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125–39
- 33 Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet* 2001; **357**: 911–6
- 34 Mills GH. Hydroxyethyl starch: does our choice of colloid prevent or add to renal impairment? *Br J Anaesth* 2007; **98**: 157–9