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Clinical Practice

Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness

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Abstract

Background: The benefits of stroke volume optimization during surgery are unclear, with recent data not replicating the positive effects of earlier studies.

Methods: This was a randomized controlled trial of standard fluid therapy with or without supplementary blinded intraoperative stroke volume optimization in 220 patients having major elective rectal resection or cystectomy with ileal conduit. All patients were treated using a contemporary enhanced recovery pathway. Interventional fluid challenges used Gelofusine (B Braun, Germany), guided by stoke volume variability measured by LiDCO*rapid* (LiDCO, UK). Participants were stratified by aerobic fitness (characterized by preoperative cardiopulmonary exercise test), surgical specialty, and intended surgical approach (open or laparoscopic). The primary outcome was the prevalence of moderate or severe complications on day 5 after surgery, defined using the postoperative morbidity survey (POMS) criteria.

Results: Patients received ~13 ml kg^{-1} h^{-1} of i.v. fluids during surgery. The intervention group received an additional mean (SD) 956 (896) ml Gelofusine. There were no statistically significant differences between groups in any primary or secondary end point. A positive POMS on postoperative day 5 was noted in 54 of 111 control subjects (48.6%) and 55 of 109 participants in the intervention group [50.5%; adjusted odds ratio 0.90 (95% confidence interval 0.52–1.57), P=0.717]. Mean (SD) hospital length of stay was 9.6 (6.8) days in the control group and 11.8 (11.5) days in the intervention group (adjusted difference −2.1 (−4.6 to 0.3) days, P=0.091). There was no statistical interaction between stroke volume optimization and aerobic fitness in terms of rate of complications or length of stay.

Conclusions: Algorithm-driven stroke volume optimization is of no benefit when superimposed on a liberal baseline fluid regimen in patients having elective major abdominal surgery, when stratified to minimize differences in fitness and surgical approach between groups.

Clinical trial registration: ISRCTN21597243.

Key words: colorectal surgery; exercise test; fluid therapy; haemodynamics; postoperative complications

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Editor's key points

- Perioperative goal-directed fluid therapy is considered beneficial, but recent data are conflicting; the benefits may depend on the type of surgery and individual physical fitness.
- This study examined the effects of stroke volume optimization in patients undergoing major colonic surgery or cystectomy, under an enhanced recovery care programme.
- Patients were stratified and allocated according to aerobic fitness and type and technique of surgery to minimize confounding factors.
- Fluid regimens in both groups were liberal, but there were no significant differences in postoperative complications or other outcomes.
- These data do not support the widespread routine use of intraoperative cardiac output monitoring in major elective surgery.

Over the past four decades, goal-directed fluid therapy (GDT) has largely been associated with improved clinical outcomes in high-risk perioperative patients.[1–4] Stroke volume optimization (SVO), defined as the endeavour to titrate i.v. fluids to achieve an ideal target stroke volume throughout surgery,[5] has shown few or no benefits in patients undergoing elective major abdominal surgery in more recent studies.[6–9] Contemporary perioperative management may have minimized the effect of SVO. Alternatively, benefits may apply only to patients who are genuinely 'high risk', such as on the basis of decreased aerobic fitness.

We previously reported a single-centre trial where patients having major elective colorectal surgery were randomized to intraoperative fluid therapy with or without supplementary SVO guided by oesophageal Doppler.[7] There was no evidence of a significant benefit of the intervention on patients' time to discharge readiness or length of hospital stay and some evidence of a detrimental effect on these outcomes in a prospectively defined subgroup of aerobically 'fit' patients. Our interpretation was that the intervention algorithm, based solely on a consideration of stroke volume with no stopping threshold to limit further fluid administration, was perhaps aimed at stroke volume maximization rather than optimization and may therefore have promoted a fluid excess, particularly in fit patients. Adverse outcomes may also have been associated with the use of starch-based colloid solutions for fluid challenges. Starch-based colloids have since been withdrawn from such use in the UK.[10]

Moreover, there is a high likelihood of confounding in small randomized trials. For example, in most of the prominent GDT studies in colorectal surgery to date[7 11 12] an imbalance between groups in the proportion of rectal resections (operations associated with a longer overall length of stay than colonic resections)[13] is apparent. This may contribute to seemingly inferior outcomes in one group, in a manner that has little to do with the fluid therapy intervention.

Likewise, most of these studies[6 7 9 11 12] used length of hospital stay or time to discharge readiness as their primary outcomes. These factors are reliant on subjective clinical judgements, patient motivation, and social factors, and are thus relatively weak as study end points. Complication rate is perhaps more clinically relevant.

The aim of this study was to investigate the effects of intraoperative SVO on postoperative outcomes in patients stratified according to aerobic fitness and type of surgery in order to minimize the effects of these factors between groups.

Methods

This was a prospective parallel-arm double-blind randomized controlled trial conducted at Derriford Hospital, Plymouth, UK. The clinical trial was approved by the Cornwall and Plymouth Research Ethics Committee (reference: 10/H0203/68), adopted by National Institute of Healthcare Research (UKCRN ID: 10093), and registered at http://www.isrctn.org (trial identifier: ISRCTN21597243).

Participant recruitment and randomization

All patients undergoing elective rectal resection and cystectomy at our hospital are routinely offered preoperative cardiopulmonary exercise testing (CPET) to facilitate informed consent about perioperative risk and to assist planning of perioperative care. Incremental submaximal workload CPET is performed on a stationary bicycle (Zan; nSpire, Longmont, CO, USA), according to a standard procedure as previously reported.[7]

Consecutive eligible patients were provided with written information at the time of CPET and invited to participate in the trial. Potential participants were risk stratified as aerobically fit or unfit primarily on the basis of weight-indexed oxygen consumption at anaerobic threshold >10.9 or <11.0 ml O_2 kg^{-1} min^{-1}, but ultimately depending on classification of fitness by an objective clinician experienced in interpreting CPET. Therefore, patients in whom anaerobic threshold could not be identified were also eligible for the trial and were included in the unfit group.[14]

Exclusion criteria were as follows: recent acute myocardial infarction, unstable angina, uncontrolled arrhythmias causing symptoms or haemodynamic compromise, syncope, active endocarditis, acute myocarditis or pericarditis, symptomatic severe aortic stenosis, uncontrolled heart failure, acute pulmonary embolus or pulmonary infarction, thrombosis of lower extremities, suspected dissecting aneurysm, uncontrolled asthma, pulmonary oedema, oxygen saturation <85% at rest, respiratory failure, or acute non-cardiopulmonary disorder that might affect exercise performance or be aggravated by exercise (e.g. infection, acute renal failure, thyrotoxicosis).

Written informed consent to participate in the trial was obtained at the time of admission for surgery. Participants were allocated via a secure Web-based dynamic randomization system, computer generated by the UK Clinical Research Collaboration-registered Peninsula Clinical Trials Unit (PenCTU) in conjunction with an independent statistician. They were allocated in a 1:1 ratio to either the control group or SVO group, using a minimization-based method including the stratification factors of aerobic fitness (fit or unfit), type of surgery (rectal or cystectomy), and planned surgical approach (open or laparoscopic). Apart from the investigator, all perioperative medical and nursing personnel were blinded to fluid therapy group allocation.

Perioperative care

Perioperative surgical care was conducted in line with an enhanced recovery pathway that has been in use at our hospital since 2009 (Supplementary data, Appendix S1). The majority of patients were admitted on the day of surgery; they received mechanical bowel preparation at the discretion of the surgeon. All patients received general anaesthesia, conducted at the discretion of the consultant anaesthetist. Likewise, thoracic

epidural anaesthesia or local anaesthetic field blocks were used where clinically appropriate as judged by the anaesthetist. All patients received mechanical ventilation whilst under general anaesthesia; tidal volume was not protocolized. The anaesthetist administered intraoperative crystalloid, colloid, blood products, and inotropes or vasopressors based on estimated patient requirements, losses, and standard haemodynamic variables. All participants had arterial line monitoring. Central venous pressure monitoring was permitted. Standard fluid therapy was not defined, but a general recommendation was made that perioperative fluid excess should be avoided, as per national consensus guidelines, and this was publicized through local presentations signposting available literature.[15]

Intervention

A medically qualified investigator monitored the patient throughout surgery with a LiDCO*rapid* (LiDCO, Cambridge, UK). This is an uncalibrated pulse power monitoring system, which interrogates the arterial blood pressure trace, converting the pressure signal into a nominal beat-to-beat estimate of cardiac stroke volume and other haemodynamic indices. Stroke volume variability (SVV), a dynamic flow index, characterizes the 'swing' in the arterial wave form caused by intermittent positive pressure ventilation. Previous work has suggested that in the presence of a regular heart rate an SVV of >10% is indicative of likely responsiveness to a fluid challenge.[16] The investigator, the LiDCO monitor screen, and the fluid administration lines/bags were all concealed from other staff in the operating room inside a screened 'tent'. Serial haemodynamic variables were recorded every 15 min until the end of surgery.

In the intervention (SVO) group, the concealed investigator administered warmed colloid fluid challenges with Gelofusine (B Braun, Melsungen, Germany) directed by an algorithm to achieve an SVV goal of less than 10% throughout surgery (Fig. 1).

When the condition for a regular heart rate was not met for part or all of the intraoperative period (such as when patients were in atrial fibrillation), the measurement of stroke volume response to a 200 ml fluid challenge was used instead to guide stroke volume optimization. The researcher carrying out the optimization was aware of all contemporaneous anaesthetic and surgical activity and could modulate their fluid challenges accordingly to between 50 and 200 ml per bolus. In the control group, sham boluses were administered in order to maintain blinding of clinicians. The investigator intermittently opened fluid bags to mimic the requisite auditory cues, occasionally also discarding prepared gelatin 'empties' from inside the tent.

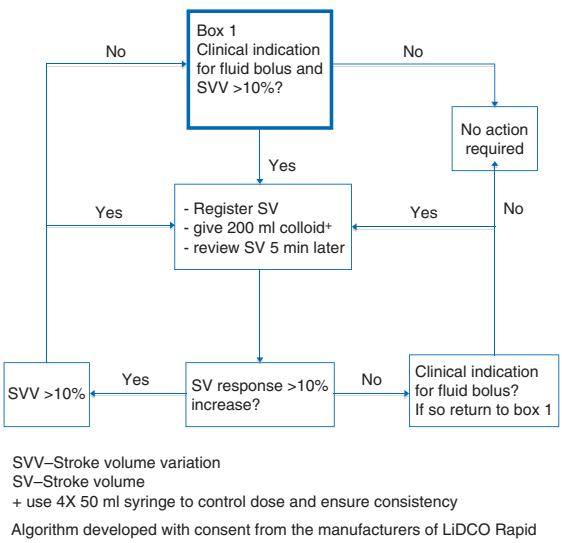

Fig 1 Algorithm developed with consent from the manufacturers of LiDCO*rapid*. SV, stroke volume; SVV, stroke volume variation; + use four times 50 ml syringe to control dose and ensure consistency.

Intraoperative measurements

Perioperative fluid administration by the anaesthetist and investigator was recorded. Haemodynamic measures relevant to fluid therapy were recorded at baseline, at surgical closure, and at quarter-hourly intervals throughout surgery. Global oxygen delivery index (D_{O_2}) was calculated at the start and conclusion of surgery using arterial measurements of haemoglobin (Hb) and oxygen saturation, and concurrent nominal cardiac index as characterized by LiDCO*rapid*. Arterial lactate was also measured at these time points.

Postoperative care

All patients received standard postoperative care on a dedicated colorectal surgery ward (Supplementary data, Appendix S1). In line with the enhanced recovery programme, all patients were allowed a light diet on the evening of surgery if tolerated. Postoperative i.v. fluid administration was at the discretion of the clinical team. In all participants, early mobilization was encouraged, epidurals were discontinued at 48–72 h, and use of opiates was minimized. The investigator was not involved in postoperative care.

Outcomes

A different researcher, blinded to group allocation, recorded all postoperative outcomes. The primary outcome measure was postoperative morbidity survey (POMS) score on postoperative day 5 (Appendix 1).[17] The POMS is an ordinal scoring system designed to record the incidence of clinically important complications; those with POMS of 1 or greater are likely to require continuation of their hospital admission, whereas those with a score of 0 are effectively medically ready for discharge.[18] Where patients had been discharged at the time of the assessment, a score of 0 was assumed. The POMS scores on days 3 and 8 were recorded as secondary end points. Other postoperative outcomes included time to passage of flatus and stool, establishment of oral intake, and time to surgical readiness for discharge as defined by five criteria (Supplementary data, Appendix 1), including the ability to cope independently with a stoma, where present.

Additional secondary end points were hospital length of stay, postoperative mortality at 30 and 90 days, reoperation (requirement for return to theatre for procedure under anaesthetic), readmission for at least an overnight stay within 30 days of initial surgery, acute kidney injury by RIFLE criteria,[19] and unplanned intensive care unit admission. Anastamotic leak was diagnosed radiologically or at laparotomy.

Statistical plan and analysis

Previous studies of patients undergoing major abdominal surgery have shown an incidence of positive POMS score (i.e. >0) at day 5 of up to 78%.[18] Based on these and our own observations of a trend towards benefit of SVO in more complex (i.e. rectal)

surgery patients in a previous trial,[7] we hypothesized that SVO might reduce moderate or severe complications by 20%. Sample size calculations suggested that 97 participants in each group (194 in total) would be required to detect a 20% reduction in the proportion of patients with complications (POMS >0) at day 5, based on 80% power and at the 5% significance level. We increased the recruitment target in each group to 110 participants (220 in total) to allow for dropouts.

Data were analysed based on intention-to-treat principles using SPSS® version 19 (SPSS, Chicago, IL, USA). The statistical significance was set at the 5% level, with 95% confidence intervals (CIs) produced for all appropriate between-group comparisons.

Categorical data were compared using χ^2 and Fisher's exact tests. Visual inspection of distribution plots was performed to assess for approximate normality of continuous data. Unadjusted between-group comparisons were made using the two-tailed Student's *t*-test or Mann–Whitney *U*-test as appropriate depending on distribution of the data. Adjusted analyses used logistic (categorical outcomes) or linear regression analysis (continuous data) as appropriate, to adjust for the three factors used in the allocation procedure, namely fitness group (aerobically fit or unfit), type of surgery (rectal or cystectomy), and intended surgical technique (open *vs* laparoscopic); the adjusted analyses were considered to be the primary analyses. Summary treatment effects and 95% CIs were estimated for all end points.

Results

Between March 2011 and April 2013, 380 patients were screened, of whom 311 were eligible to participate. Thirteen patients declined participation. For 77 further patients, no investigator was available. Some 220 unselected patients having elective rectal resections (*n*=208) or cystectomy and ileal conduit procedures (*n*=12) were recruited to the trial. One hundred and ten were randomized to receive SVO guided by LiDCO*rapid* in addition to standard intraoperative fluid therapy ('SVO' group); the remaining 111 participants were allocated to receive usual care ('control' group; Fig. 2). No participants were lost to follow-up; however,

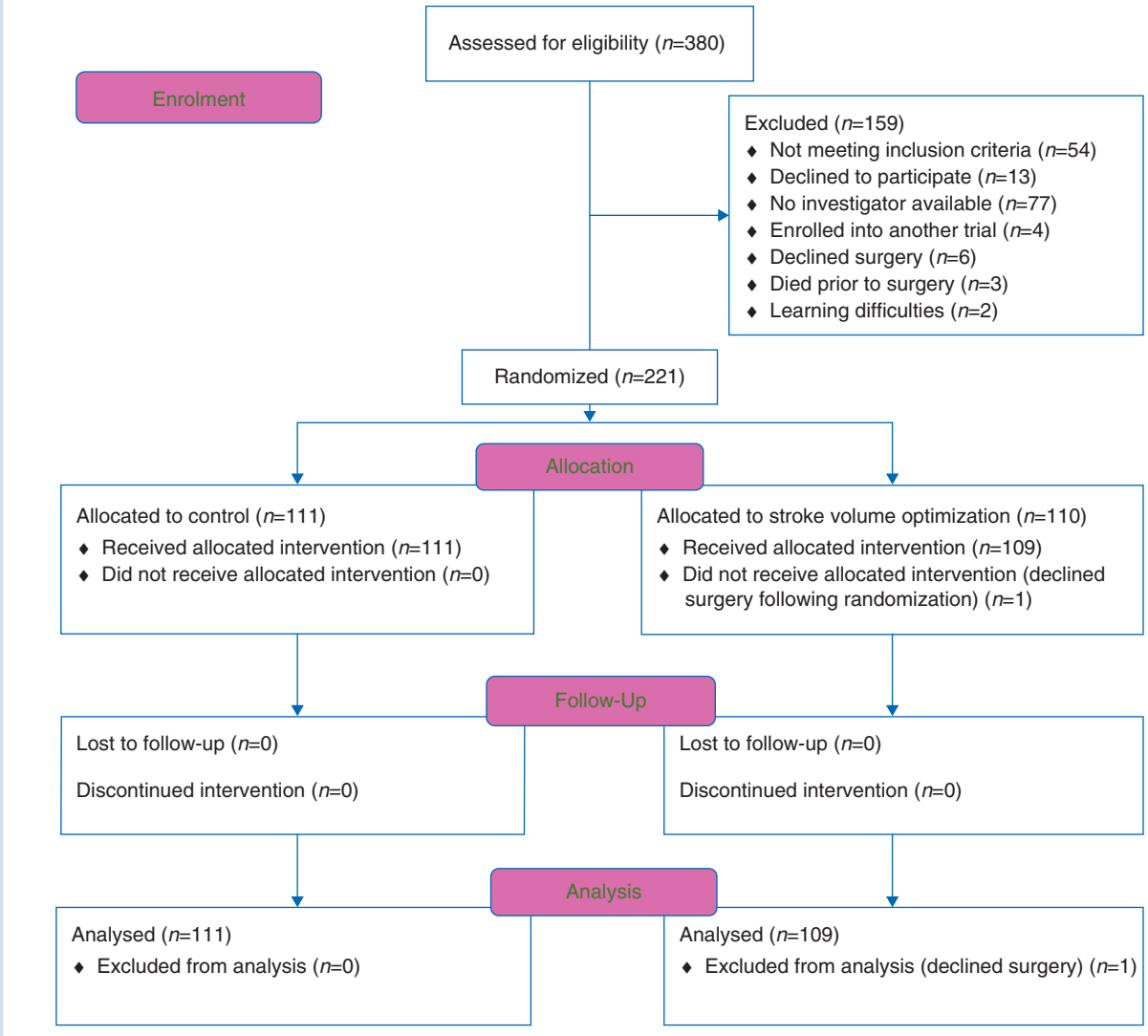

Fig 2 CONSORT 2010 flow diagram. Trial CONSORT diagram. CONSORT Consolidated Standards of Reporting Trials CPET Cardiopulmonary Exercise Test Not meeting inclusion criteria: No CPET 27 (14 Unable to perform; 11 Did not attempt; 2 Refused); Not having eligible surgery 23; Other 4.

arterial line placement failed in two participants allocated to the SVO group, negating the use of cardiac output monitoring. One patient who had been randomized then left the anaesthetic room and subsequently refused surgery. He had been allocated to the SVO group, although this was not known to the patient or perioperative team; his study number was declared null, and the subsequent participant received the next study number (and concealed allocation) in the sequence. Eleven patients (four control; seven SVO) were in atrial fibrillation for all or part of the procedure.

The dynamic allocation procedure to minimize differences between groups with respect to the main stratification factors worked successfully. Overall, patient characteristics in the control and SVO groups were well matched (Table 1; Supplementary Table S1). Twenty-three participants (11%) received neo-adjuvant radiotherapy or chemoradiotherapy before resection. After preoperative CPET, 164 participants (75%) were characterized as aerobically fit and 56 (25%) as unfit. In 72 patients (33%), the planned procedure was via laparoscopically assisted surgery, of which 12 were converted during surgery to an open procedure (17% conversion rate). In two further patients listed for laparoscopic resection, surgery was open from the start. For the purposes of regression analysis, these 14 patients were regarded as having had laparoscopic surgery, on an intention-to-treat basis. No participants allocated to the open group received laparoscopic surgery.

Two trial participants had abdominoperineal resections with part of the procedure carried out with the patient in the prone position (one control and one SVO). Use of the algorithm in the intervention group participant was associated with postoperative pulmonary oedema. The study data monitoring committee recommended that subsequent planned prone abdominoperineal resections were ineligible for inclusion.

Intraoperative and haemodynamic data

Operative and anaesthetic procedures were broadly well matched between groups (Table 2; Supplementary Table S2). Intraoperative data were complete for all but a small number of participants. Summary and comparative statistics are based on the available data (Table 3; Supplementary Table S3). Details of missing data are provided in Supplementary data, Appendix S2.

Seventy-seven participants (35%) received preoperative oral bowel preparation; a further 50 patients had an enema before surgery. Twenty-two (17%) had i.v. fluid replacement before theatre. Mean operative duration (incision to skin closure) was 197 min. Patients received slightly more than 4 litres of i.v. crystalloid and 380 ml of gelatin from the attending anaesthetist during surgery, an average of ~13 ml kg^{-1} h^{-1}. The intervention group received an additional 956 ml of Gelofusine during surgery from the investigator. Haemodynamic variables were similar between groups at all time points, apart from a greater mean SVV at baseline in the control group (Table 4; Supplementary Table S3). Nominal stroke volume tracked at 15 min intervals rose gradually throughout surgery in both groups (Fig. 3).

End-operative Hb was significantly lower in the SVO group [103 *vs* 112 g $litre^{-1}$, adjusted treatment effect 9 g $litre^{-1}$ reduction

Table 1 Patient data. BMI, body mass index; predicted CR-POSSUM, colorectal physiological and operative severity score for the enumeration of mortality and morbidity. – variables to calculate operative score were predicted before surgery; RCRI, revised cardiac risk index score. Values are expressed as *mean (SD) unless as number (%) or range where specified; †mean (SD) is reported for those patients where anaerobic threshold was detectable

Characteristic	Control (*n*=111)	Stroke volume optimization (*n*=109)	Total (*n*=220)
Age (yr)*	63.4 (15.1) (range 22–86)	62.5 (14.4) (range 22–93)	63.0 (15.0) (range 22–93)
BMI (kg m^{-2})*	28.2 (5.0) (range 19.0–46.0)	27.5 (4.5) (range 19.0–39.0)	27.8 (4.8) (range 19.0–46.0)
Male:female (%)	71:40 (64:36)	63:46 (58:42)	134:86 (61:39)
Diagnosis (%)			
Carcinoma	78 (70.3)	82 (75.2)	160 (72.7)
Diverticular	14 (12.6)	9 (8.3)	23 (10.5)
Inflammatory	14 (12.6)	14 (12.8)	28 (12.7)
Other	5 (4.5)	4 (3.7)	9 (4.1)
Anaerobic threshold (ml O_2 kg^{-1} min^{-1})*	14.0 (4.8) (*n*=105)†	12.8 (3.0) (*n*=107)†	13.4 (4.0) (*n*=212)†
ASA (%)			
I	14 (12.6)	15 (13.8)	29 (13.2)
II	77 (69.4)	76 (69.7)	153 (69.5)
III/IV	19 (17.1)	17 (15.6)	36 (16.4)
Lee RCRI (%)			
1	98 (88.3)	95 (87.2)	193 (87.7)
2	10 (9.0)	14 (12.8)	24 (10.9)
≥3	3 (2.7)	0	3 (1.4)
Predicted CR-POSSUM*			
Physiological score	8.5 (2.3)	8.4 (2.3)	8.4 (2.3)
Operative score	7.6 (1.1)	8.1 (1.8)	7.8 (1.6)
Percentage operative mortality	2.7 (3.2)	3.0 (3.9)	2.9 (3.6)
Fit:unfit (%)	83:28 (74.8:25.2)	81:28 (74.3:25.7)	164:56 (74.5:24.5)
Planned surgical technique			
Open rectal	69 (62.2)	66 (60.6)	135 (61.4)
Laparoscopic rectal	36 (35.1)	37 (33.9)	73 (33.2)
Open cystectomy (%)	6 (5.4)	6 (5.5)	12 (5.5)
Neo-adjuvant treatment (%)	9 (8.1)	14 (12.8)	23 (10.5)

Table 2 Perioperative surgical and anaesthetic data. CVP, central venous pressure; HDU, high-dependency unit; MBP, mechanical bowel preparation; SVO, stroke volume optimization; TAP, transversus abdominus plane block. *Mean (SD). †Student's *t*-test apart from proportion of patients receiving inotropes (χ^2). ‡Median (range). ¶Some patients received more than one regional technique or vasoactive drug. §Planned, arranged before surgery; unplanned, postoperative destination altered from surgical ward to HDU, arranged during surgery

Parameter	Control (*n*=111)	SVO (*n*=109)	*P*-value†
MBP (%)	35 (31.5)	42 (38.5)	
Preoperative crystalloids (ml)‡	1500 (800–2000)	1000 (200–1000)	
Analgesia technique (%)¶			
Thoracic epidural	54 (48.6)	59 (54.1)	
Spinal	18 (16.2)	14 (12.8)	
Regional (TAP/rectus sheath)	40 (36.0)	29 (26.6)	
Monitoring (%)			
CVP line	23 (20.7)	19 (17.4)	
Operation type (%)			
Open/conversion rectal	74 (66.7)	74 (67.9)	
Laparoscopic rectal	31 (27.9)	29 (26.6)	
Open cystectomy	6 (5.4)	6 (5.5)	
Stoma (%)	62 (55.9)	63 (57.8)	
Duration (min)*	196 (81.4)	200 (86.5)	0.66
Blood loss (ml)*	396 (354)	513 (622)	0.09
Blood transfusion (units)*	0.2 (0.8) (*n*=8)	0.3 (0.9) (*n*=12)	0.37
Intraoperative fluids (ml)*			
Crystalloid	4142 (1393)	4043 (1538)	0.59
Colloid	390 (655)	370 (700)	0.89
Investigator colloid	0	956 (896)	<0.001
Total intraoperative fluids (ml)*	4532 (1525)	5369 (2270)	0.001
Vasoactive drugs			
Proportion of patients (%)¶			
Metaraminol	96 (86)	92 (84)	0.96
Ephedrine	13(12)	11 (10)	0.9
Dose (mg)*			
Metaraminol	6.8 (5.7)	6.1 (5.3)	0.38
Ephedrine	1.3 (4.2)	1.3 (4.4)	0.96
Urine output (ml)*	542.4 (508.7)	535.6 (540.9)	0.97
HDU admission from theatre (%)§			
Planned	16 (14.4)	19 (17.4)	0.54
Unplanned	2 (1.8)	5 (4.6)	0.24
Postoperative fluids (ml)*			
Day 0			
Crystalloids	1274 (1057)	1182 (1079)	0.63
Colloids	104 (381)	71 (259)	0.19
Day 1			
Crystalloids	2182 (1124)	2264 (1264)	0.15
Colloids	61 (195)	37 (144)	0.3

(95% CI 4.3–13.6 g litre^{-1}), *P*<0.001; Table 5]. Stroke volume optimization was also associated with a trend to increased mean intraoperative blood loss (513 *vs* 396 ml, adjusted 95% CI −245–18 ml, *P*=0.090), although the proportion of participants receiving a red cell transfusion during surgery did not differ between groups. Five participants (4.5%) in the SVO group had major intraoperative bleeding (defined as more than 2 litres estimated loss) *vs* two (1.8%) in the control group. To investigate whether the lower mean Hb in the intervention group was attributable to greater blood loss, we performed a sensitivity analysis of postoperative Hb concentration with these seven patients removed (data not shown). The SVO group still had, on average, statistically significantly lower Hb, suggesting haemodilution as a mechanism.

The anaesthetist did not request access to the cardiac output monitoring data during surgery in any patients. Eighteen control and 24 SVO participants were admitted to high-dependency care after surgery. Twenty of these were classified as 'fit' before surgery; 11 of them were admitted 'for close monitoring after surgery' or to receive vasopressors to offset hypotension; in six the reason for admission was declared as 'co-morbidities' despite having reasonable aerobic fitness; and the remainder were admitted because of blood loss (two) or an ischaemic ECG (one).

Outcomes

Clinically important morbidity as captured by a positive POMS score on postoperative day 5 (primary outcome) was present in 109 participants (49.6%). Median length of hospital stay for the cohort was 7.9 days (mean 10.7 days). Median time to discharge readiness was 6.9 days (mean 9.8 days). Five patients died within 30 days of surgery (2.3%), two control (severe sepsis and myocardial infarction) and three SVO (bilateral pulmonary embolus, pulseless circulatory arrest with stroke, and metastatic carcinomatosis), compared with a predicted mortality by colorectal

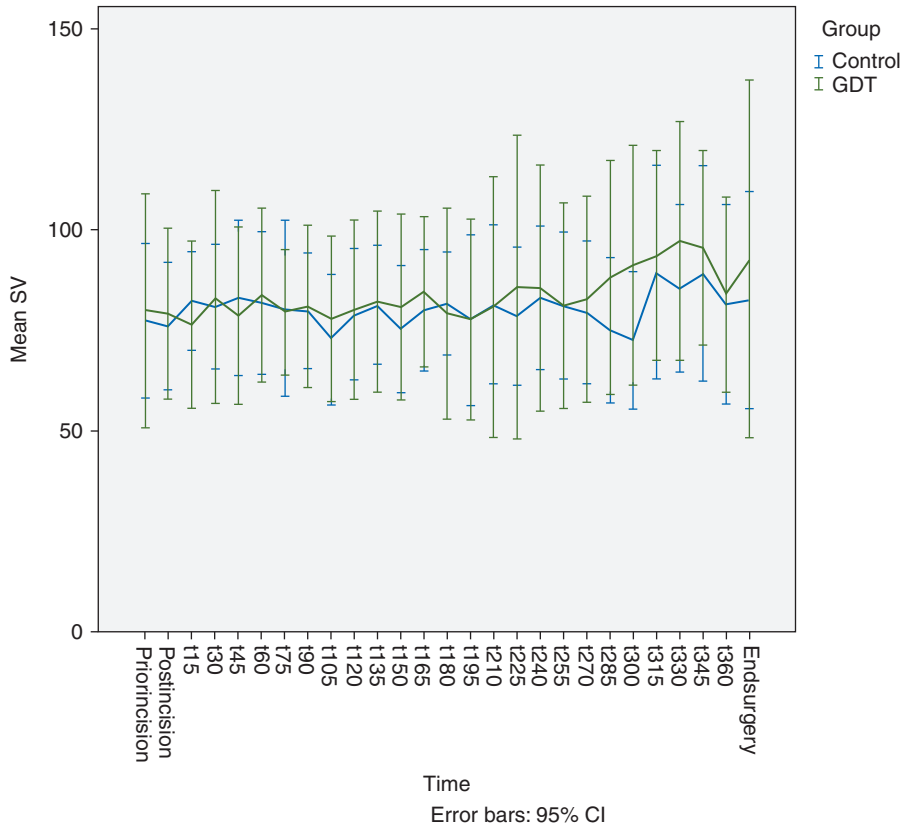

Fig 3. Stroke Volume through surgery. SV Stroke Volume. Time (minutes), SV (ml), 95% CI (95% confidence interval).

physiological and operative severity score for the enumeration of mortality and morbidity (CR-POSSUM) score of 2.9%.[20] A further control group patient died between 1 and 3 months after surgery, of metastatic carcinomatosis. Twenty-one participants (9.6%) suffered a radiologically confirmed postoperative anastamotic leak, of whom 18 returned to theatre for examination under anaesthesia, six having a re-exploration laparotomy and Hartmann's procedure.

No statistically significant difference was noted between allocated treatment groups in any end point. In the control group, 54 of 111 (48.6%) had a positive POMS on postoperative day 5 compared with 55 of 109 SVO participants (50.5%). Unadjusted and adjusted (for fitness group, operation type, and planned surgical approach) treatment effects (with 95% CIs) are presented for all outcomes and for selected intraoperative variables (Tables 3 and 5).

The study was not powered to compare outcomes within subgroups according to fitness; however, outcome data divided into prospectively defined fitness subgroups are provided (Supplementary data, Table S4). It is striking that the unfit group, despite having apparently inferior functional capacity on CPET, had outcomes comparable with their fitter counterparts.

Discussion

Stroke volume optimization guided predominantly by SVV in addition to standard intraoperative fluid therapy had no impact on postoperative complications or any other prospectively defined end point in a cohort of patients having major rectal surgery or cystecomy and ileal conduit.

To our knowledge, this is the only study of intraoperative GDT to date to have used several stratification factors to minimize confounding between treatment groups. We further confined recruitment only to patients having major or complex major elective abdominal surgeries, which might be expected to generate fluid shifts and an increased perioperative oxygen demand, a context where individualization of fluid therapy might be expected to make a clinical impact.[4]

Several previous trials have investigated the utility of intraoperative pulse contour monitoring, and the impact on clinical outcomes of fluid therapy algorithms based on dynamic flow indices, such as SVV.[21 22] However, we are aware of only one previous study, OPTIMISE, where perioperative fluid therapy was guided (as in our study) by uncalibrated pulse power monitoring.[2] In that multicentre randomized trial of 730 patients having major abdominal surgery, GDT had a strong trend towards benefit on the composite primary outcome of moderate or major postoperative complications within 30 days. However, in contrast to our study the intervention included a fixed dose dopexamine infusion. This drug may have important anti-inflammatory effects aside from its known haemodynamic ones.[23] A further key feature of OPTIMISE was that the intervention group received algorithm-directed haemodynamic management for 6 h after surgery, not necessarily the case for the control group. It may be that what affects clinical outcomes is care being closely applied and monitored by diligent personnel, rather than monitors and algorithms *per se*.

Table 3 Trial outcomes. AKI, acute kidney injury; ICU, intensive care unit; POMS, postoperative morbidity survey; RIFLE, renal risk, injury, failure, loss, and end-stage kidney disease criteria. *Mean (SD). †χ^2 test. ‡Student's t-test. ¶P-value from logistic or linear regression as appropriate

Parameter	Control (n=111)	Stroke volume optimization (n=109)	Unadjusted		Adjusted	
			Odds ratio (95% CI) apart from $difference (95% CI)	P-value	Odds ratio (95% CI) apart from $difference (95% CI)	P-value¶
Day 5 POMS (%)						
POMS =0	57 (51.4)	54 (49.5)	0.89 (0.53–1.52)	0.688†	0.90 (0.52–1.57)	0.717
POMS ≥1	54 (48.6)	55 (50.5)				
Day 3 POMS (%)						
POMS =0	30 (27.0)	20 (18.3)	0.61 (0.32–1.15)	0.125†	0.59 (0.29–1.17)	0.13
POMS ≥1	81 (73.0)	89 (81.7)				
Day 8 POMS (%)						
POMS =0	79 (71.2)	69 (63.3)	0.67 (0.38–1.18)	0.164†	0.66 (0.37–1.19)	0.165
POMS ≥1	32 (28.8)	40 (36.7)				
Time to discharge readiness (days)*	8.9 (6.7)	10.8 (11.0)	−1.7 (−4.2 to 0.7)$	0.161‡	−1.7 (−4.1 to 0.7)$	0.166
Length of hospital stay (days)*	9.6 (6.8)	11.8 (11.5)	−2.2 (−4.7 to 0.3)$	0.090‡	−2.1 (−4.6 to 0.3)$	0.091
30 day reoperation (%)	16 (14.4)	17 (15.6)	0.9 (0.4–1.9)	0.806†	0.9 (0.4–1.9)	0.817
30 day re-admission (%)	9 (8.1)	11 (10.1)	0.9 (0.3–2.2)	0.778†	0.9 (0.3–2.2)	0.781
Mortality (%)						
30 days	2 (1.8)	3 (2.8)	1.5 (0.3–9.4)	0.639	1.7 (0.3–10.5)	0.593
90 days	3 (2.7)	3 (2.8)	1.0 (0.2–5.2)	0.982	1.1 (0.2–5.9)	0.902
Anastomotic leak (%)	11 (9.9)	10 (9.2)	1.1 (0.4–2.7)	0.853†	1.1 (0.4–2.7)	0.886
AKI, by RIFLE criteria (%)	8 (7.2)	3 (2.8)	0.4 (0.1–1.4)	0.144	0.3 (0.1–1.4)	0.13
ICU admission from ward (%)	3 (2.7)	4 (3.7)	1.4 (0.3–6.3)	0.684	1.4 (0.3–6.3)	0.692

The clinical usefulness of minimally invasive monitoring to guide intraoperative fluid therapy is uncertain. For dynamic preload indicators certain conditions must be met, in particular a regular heart rate, absence of spontaneous respiratory efforts, and sufficiently large tidal volumes (<7 ml kg^{-1}), with intermittent positive pressure ventilation so as to generate a swing in arterial blood pressure.[16 24] We did not protocolize tidal volume during ventilation; in this sense, the study is representative of how clinicians might approach SVV-guided fluid therapy in their 'usual' clinical practice. This trial was performed before publication of a prominent study suggesting that low tidal volumes (~6 ml kg^{-1} ideal body weight) reduce the incidence of postoperative pulmonary complications.[25] Protective lung ventilation in this manner might reduce intrathoracic pressure swings below the threshold suggested for SVV to work as a predictor of fluid responsiveness. However, the same potential for attenuation of intrathoracic pressure may exist when the abdomen is opened to allow surgical access. Conversely, pneumoperitoneum during laparoscopic surgery in the head-down position might accentuate pressure swings. Most of the studies suggesting that dynamic flow indicators are useful to guide fluid therapy have been conducted predominantly in critically ill patients receiving intermittent positive pressure ventilation, conditions in which intra-abdominal pressure is likely to be less variable.[16 26] A subgroup analysis of 100 patients included in the intervention arm of the OPTIMISE study concurs with our choice of an SVV threshold of >10% as the optimal threshold value to predict fluid responsiveness during surgery in mechanically ventilated patients, but the association was only moderate.[27] Further studies are necessary. Likewise, the relevance of our data to urgent or emergency major surgery is unknown; the likelihood of fluid shifts and a variable degree of systemic inflammatory response in these settings make individualization of fluid therapy attractive, but for methodological reasons this is a difficult population to study.

Our study may provide translational insight into useful markers of oxygen delivery. Haemodynamic targets, such as stroke volume, are only surrogates.[28] Clinicians use continuous stroke volume optimization during surgery, believing that they are thus improving end-organ perfusion, particularly in the gut, compared with therapy based on standard haemodynamic information.[1 11] However, GDT trials have not typically measured intestinal perfusion directly during the intervention.

In our study, stroke volume and cardiac index increased as surgery progressed, marginally more so in the intervention group (Fig. 3; Supplementary data, Fig. S1). We further measured end-operative arterial Hb, oxygen saturation and cardiac index to calculate D_{O_2} at this time. It is apparent that any benefit in terms of maintaining stroke volume with fluid was offset by haemodilution, such that overall calculated oxygen delivery did not change (Table 4). A caveat is that we calculated D_{O_2} index by sampling from a radial arterial line, which does not necessarily mirror intestinal capillary blood. We also report end-operative arterial lactate as a marker of perfusion; these are very similar in the two allocated groups (Table 5).

Whilst no statistically significant effect was observed in the present trial, a trend towards greater blood loss (and product use) in the GDT group has been observed in this and previous studies.[2 7] This pattern is so often repeated that while it may result by chance, it is plausible that it is linked to mechanical distension of pelvic capacitance vessels, promoting haemorrhage during surgical dissection, to haemodilution, or to a pharmacological effect of the fluid used (colloid in all three studies). Whatever the mechanism, a driver towards allogenic blood transfusion is not necessarily in patients' best interests.[29]

Baseline fluid regimen and fluid challenge algorithm

A systematic review[30] and recent large randomized controlled trial demonstrate that liberal administration of fluid and salt may be deleterious compared with a more restrictive regimen.[31]

Many centres now recommend a baseline intraoperative crystalloid regimen of ~1.5 ml kg h^{-1}. Against this background, our trial may be criticized for an excessively liberal standard fluid regimen. Where baseline therapy is already excessive, the hope is that SVV monitoring will prevent the operator from giving additional excess of fluid, but there may be an important distinction to be made between stroke volume 'optimization' and 'maximization'. We rely on our algorithms to characterize individual patients' fluid responsiveness. The use of sequential 200 ml fluid challenges until fluid responsiveness ceases is likely to lead to maximization or perhaps excess (a fluid challenge that fails to increase stroke volume represents fluid that was not required). Using SVV monitoring, no such test bolus is required; intrathoracic pressure-induced alterations in stroke volume are in effect mini fluid challenges. But recent work on dynamic flow indices suggests that these variables have a 'grey zone', a range of values within which there is uncertainty about whether a patient will be fluid responsive or not,[21] whereas study algorithms, including our own, generally apply more rigid thresholds.

Our algorithm was responsive, allowing the investigator to take into account the contemporaneous actions of the consultant anaesthetist in deciding the volume of fluid challenges, but the aggregate fluid given may still represent a relative free water and salt excess. Overall outcomes for our cohort are within the expected range of UK national benchmarks,[32] but do not compare especially favourably with those reported recently by the Enhanced Recovery After Surgery (ERAS) group.[33] For example, our anastamotic leak rate was double the 4.1% reported. In retrospective analysis of the ERAS registry, administration of more than 3.5 litres of i.v. fluid on the day of surgery appeared to be a key factor associated with morbidity in rectal surgery patients.

Table 4 Intraoperative haemodynamic variables. D_{O_2}, calculated oxygen delivery index; GDT, goal-directed therapy; Hb, haemoglobin; MABP, mean arterial blood pressure. Values are expressed as mean (SD)

Parameter	Control (*n*=111)	GDT (*n*=109)
Heart rate (beats min^{-1})		
Awake	77 (14)	80 (18)
Before incision	61 (10)	62 (13)
End	68 (11)	69 (12)
MABP (mm Hg)		
Awake	102.8 (18.7)	101.5 (17.4)
Before incision	70.4 (15.0)	72.2 (13.8)
End	75.4 (13.1)	76.2 (12.9)
Stroke volume (ml)		
Awake	94.2 (22.7)	92.0 (28.5)
Before incision	75.9 (20.5)	75.6 (21.0)
End	76.7 (23.0)	77.8 (23.7)
Stroke volume variation (%)		
Before incision	10.1 (10.5)	7.4 (6.6)
End	9.0 (6.6)	7.9 (6.8)
Cardiac index (litres min^{-1})		
Awake	3.7 (1.0)	3.7 (1.3)
Before incision	2.4 (0.8)	2.5 (0.8)
End	2.8 (1.0)	2.8 (1.0)
D_{O_2} (ml O_2 min^{-1} m^{-2})		
Start	343.0 (174.0)	332.0 (179.0)
End	411.1 (149.6)	387.5 (154.2)
Lactate (mmol $litre^{-1}$)		
Start	1.6 (0.6)	1.5 (0.5)
End	1.8 (0.8)	1.7 (0.9)
Hb (g $litre^{-1}$)		
Start	120 (18)	120 (17)
End	112 (18)	103 (17)

Aerobic fitness

Stratification of fluid therapy trial participants into fit or unfit groups based on measurement of their functional capacity by cardiopulmonary exercise testing has been reported only once before, by ourselves.[7] Our rationale in repeating this was to allocate participants evenly to reduce confounding and to facilitate exploratory analysis into potential interactions between intraoperative fluid therapy and aerobic fitness. Regression analyses of the association between fluid regimen and complication rate (or length of stay), adjusted for fitness (Table 3) and for the two-way interaction of fitness and SVO (not shown), suggests that fitness had no effect on these end points. Supplementary data, Table S4 reports primary and secondary outcomes of control and SVO participants stratified by fitness. No statistically significant effects were apparent. Interestingly, a sensitivity analysis whereby particularly fit patients (oxygen consumption at anaerobic threshold 14.0 ml kg^{-1} min^{-1}) were excluded (Supplementary data, Table S5) suggests that the intervention is associated with harm in moderately fit patients; however, any such *post hoc* analysis must be treated with caution.

'High-risk' patients, however defined (co-morbidities, fitness, or magnitude of surgery), are likely to have a higher event rate than low-risk patients of adverse clinical end points, which allows for a lower sample size in clinical trials. Recent literature suggests that higher complication rates and longer hospital stays after major surgery are concentrated in patients with an

Table 5 Surrogate markers of end-operative organ perfusion. Values are expressed as mean (SD). CI, confidence interval; D_{O_2}, calculated oxygen delivery index; Hb, haemoglobin. Statistical analysis: unadjusted *Student's *t*-test; adjusted †linear regression

Parameter	Control (*n*=111)	Stroke volume optimization (*n*=109)	Unadjusted difference (95% CI)	P-value*	Adjusted difference (95% CI)	P-value†
D_{O_2} (ml O_2 min^{-1} m^{-2})	411.1 (149.6)	387.5 (154.2)	23.6 (−17.3 to 64.6)	0.257	24.4 (−16.8 to 65.5)	0.244
Hb (g $litre^{-1}$)	112 (18)	103 (17)	9.1 (4.4 to 14.0)	<0.001	9.0 (4.3 to 13.6)	<0.001
Lactate (mmol $litre^{-1}$)	1.8 (0.8)	1.7 (0.9)	0.1 (−0.2 to 0.3)	0.563	0.1 (−0.2 to 0.3)	0.502
Cardiac index (litres min^{-1} m^{-2})	2.8 (1.0)	2.8 (1.0)	−0.1 (−0.3 to 0.2)	0.705	−0.1 (−0.3 to 0.2)	0.729

oxygen consumption at anaerobic threshold less than 10.1 ml kg^{-1} min^{-1}.[34 35] Thirty-nine such participants were randomized in the present study. Eight of 19 control patients and 11 of 20 SVO patients had a positive POMS at postoperative day 5. Based on our data, an adequately powered trial in a so-defined 'unfit' cohort would have to randomize at least 228 such patients to explore the hypothesis that the intervention is associated with harm.

It is striking also that complications, including anastamotic leak and reoperation rates, were no more frequent in unfit than fit patients (Supplementary data, Table S4). Does this suggest that our characterization of aerobic fitness with CPET was incorrect? When CPET results are known to clinicians, they may have an influence on perioperative care, so-called confounding by indication.[35 36] Statistical adjustment for such effects, whether measurable or covert, is difficult.

We appreciate that clinical research may not accurately reflect 'real'-life practice, whereby clinicians may use cardiac output monitoring in a heuristic way, taking into account real-time changes in patient position, anaesthetic depth, vasomotor tone, analgesia, and recent fluid shifts, including haemorrhage, to influence their fluid administration at that moment. In 'real' life, minimally invasive measurement of stroke volume may justify not giving further crystalloid, whereas our study methodology did not permit the investigator to influence care in this way.

In contrast to OPTIMISE,[2] we made no attempt to regulate postoperative i.v. fluid therapy. Although overall postoperative fluid volumes infused were similar (Table 2, Supplementary data, Table S3), we do not have details about exact timing of fluid administration, and this may have offset the clinical effect of intraoperative therapy.

Ours is a relatively small trial and therefore susceptible to confounding from factors other than those for which we controlled. A related issue is the inclusion of 60 patients whose operations were conducted laparoscopically. Intraoperative haemodynamics during laparoscopic surgery are different from when the abdomen is open.[37] More work is required to define whether stroke volume optimization is useful in this setting.

Our choice of a categorical primary outcome measure may be flawed, particularly as we effectively used the scale as a binary measure. The POMS has been well validated in elective surgical settings, with good interobserver agreement and with the advantage that it should capture the presence on any given day of morbidity that is of sufficient severity to require continued hospital admission.[17 38] However, whilst POMS is a recognized way to quantify complications, it is possible that for rectal resections and cystectomies, day 5 is too early for the score to differentiate between those recovering well and not. It is notable that in two large cohorts of UK patients, a positive POMS on day 15 after surgery was predictive of an increased mortality risk during the next 3 yr, whereas a positive POMS at day 5 lacked similar discriminatory power.[39]

Conclusions

Our study suggests that in patients having elective bowel surgery, algorithm-driven SVO is of no benefit when superimposed on a liberal baseline fluid regimen. In the light of this, this study does not support current National Institute for Health and Care Excellence recommendations for intraoperative cardiac output monitoring during a wide array of elective major surgeries.[40] Many small efficacy studies have examined whether perioperative GDT produces important clinical benefit, with conflicting findings. Additional such studies are unlikely to advance our knowledge. What matters is whether GDT as used by clinicians in everyday practice makes a difference. A definitive, large effectiveness trial of SVO against usual practice is required.

Supplementary material

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

Authors' contributions

Patient recruitment, execution of the protocol, data collection, analysis, writing up of the first draft, revision of the paper: C.W.L.

Patient recruitment, execution of the protocol, data collection, analysis: T.S.

Study design, data analysis, writing up of the first draft, revision of the paper: S.C.

Study conception and design, data analysis: R.A.S.

Patient recruitment, execution of the protocol, data collection: P.D.E., D.P.Patient recruitment, execution of the protocol: N.M. Study design, data analysis: K.B.H.

Study design, data analysis, writing up of the first draft of the paper: J.R.S.

Study conception and design, patient recruitment, execution of the protocol, data collection; data analysis, writing up of the first draft, revision of the paper: G.M.

All authors approved the final draft of the manuscript before submission.

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Declaration of interest

G.M. is National Coordinator in the UK for the RELIEF study. G.M. received an honorarium from LiDCO, UK, to attend a 1 day update on perioperative fluid management in 2010 and attended a meal sponsored by Deltex, UK in 2013. R.A.S. has attended a meal hosted by Deltex, UK and one by Nihon Kohden, Japan within the past 5 yr. J.R.S. is an advisory Consultant to Maruishi, Japan and an ex-Board member of the *British Journal of Anaesthesia*. None of the funding sources had any role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Appendix 1: Postoperative morbidity score

The postoperative morbidity score (POMS) was recorded prospectively using a proforma on postoperative days 1, 5, and 8. For each of nine domains, a score of 1 is assigned if one of the criteria detailed below is met. A score of 1 or more indicates presence of morbidity within that domain. The POMS is not cumulative and does not reflect severity of morbidity.[17]
The POMS criteria are as follows:

- **Pulmonary** *De novo* requirement for supplemental oxygen or other respiratory support (e.g. mechanical ventilation or continuous positive airway pressure).
- **Infectious** Currently on antibiotics or temperature >38°C in the last 24 h.
- **Renal** Presence of oliguria (500 ml day^{-1}), increased serum creatinine (0.30% from preoperative value), or urinary catheter in place for a non-surgical reason.
- **Gastrointestinal** Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting, and abdominal distension.
- **Cardiovascular** Diagnostic tests or therapy within the last 24 h for any of the following: *de novo* myocardial infarction or ischaemia, hypotension (requiring pharmacological therapy or fluid therapy >200 ml h^{-1}), atrial or ventricular arrhythmias, or cardiogenic pulmonary oedema.
- **Neurological** Presence of a *de novo* focal deficit, coma, or confusion/delirium.
- **Wound complication** Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms.
- **Haematological** Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.
- **Pain** Surgical wound pain significant enough to require parenteral opioids or regional analgesia.

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