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Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery

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Background. Occult hypovolaemia is a key factor in the aetiology of postoperative morbidity and may not be detected by routine heart rate and arterial pressure measurements. Intraoperative gut hypoperfusion during major surgery is associated with increased morbidity and postoperative hospital stay. We assessed whether using intraoperative oesophageal Doppler guided fluid management to minimize hypovolaemia would reduce postoperative hospital stay and the time before return of gut function after colorectal surgery.

Methods. This single centre, blinded, prospective controlled trial randomized 128 consecutive consenting patients undergoing colorectal resection to oesophageal Doppler guided or central venous pressure (CVP)-based (conventional) intraoperative fluid management. The intervention group patients followed a dynamic oesophageal Doppler guided fluid protocol whereas control patients were managed using routine cardiovascular monitoring aiming for a CVP between 12 and 15 mm Hg.

Results. The median postoperative stay in the Doppler guided fluid group was 10 *vs* 11.5 days in the control group $P<0.05$. The median time to resuming full diet in the Doppler guided fluid group was 6 *vs* 7 for controls $P<0.001$. Doppler patients achieved significantly higher cardiac output, stroke volume, and oxygen delivery. Twenty-nine (45.3%) control patients suffered gastrointestinal morbidity compared with nine (14.1%) in the Doppler guided fluid group $P<0.001$, overall morbidity was also significantly higher in the control group $P=0.05$.

Conclusions. Intraoperative oesophageal Doppler guided fluid management was associated with a 1.5-day median reduction in postoperative hospital stay. Patients recovered gut function significantly faster and suffered significantly less gastrointestinal and overall morbidity.

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Occult hypovolaemia leading to poor organ perfusion is thought to be a major factor in determining postoperative morbidity after major surgery. 'Routine' cardiovascular measurements such as heart rate and arterial pressure remain relatively unchanged despite reduced blood flow to certain organs such as the gut and hence are insensitive indicators of hypovolaemia.[1] Intraoperative gut hypoperfusion has been identified in 63% of major surgery patients and was associated with increased morbidity and duration of hospital stay.[1]

Impressive improvements in patient outcome have been demonstrated where therapy has been targeted at optimizing oxygen delivery to tissues and avoiding hypovolaemia.[2–4] Such 'goal directed therapy' has been used in cardiac surgery where reductions in complications and postoperative hospital stay, as well as improved gut perfusion, were achieved by increased fluid administration alone.[5] Moreover, further studies have demonstrated improved patient outcomes in orthopaedic and major general, urological, and gynaecological surgery.[6 7] Conway and colleagues[8] investigated patients undergoing colorectal resection; they demonstrated an increased final cardiac output and reduction in critical care admissions and called for a larger study to

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investigate further the effect on postoperative hospital stay and mortality. In a survey of moderate risk elective surgery patients, gastrointestinal complications occurred in 22% of patients. Gastric hypoperfusion and arterial base deficit were among the strongest intraoperative predictors of these complications.[9]

Hypovolaemia following cardiopulmonary bypass,[10] major vascular surgery,[11] and in the critically ill[12] patient has been implicated in the development of poor intestinal perfusion and increased mucosal permeability. Intestinal permeability testing based on the differential absorption of non-metabolized oligosaccharides across the small intestine can be used as a non-invasive method of assessing gut mucosal barrier function. Menzies[13] demonstrated the concept of the differential urinary excretion of orally administered sugars and the differential urinary recovery of oral lactulose and mannitol is widely accepted as a measure of small intestinal permeability.[14] There are a number of conditions that are associated with increased permeability including burns, sepsis, and various drugs including non-steroidal anti-inflammatory drugs (NSAIDS), alcohol, and cytotoxic agents. This phenomenon has also been observed following the i.v. injection of endotoxin into humans.[15] Secondary outcome variables such as serial intestinal permeability and serum endotoxin were made in an attempt to provide evidence for the mechanism of intestinal mucosal barrier breakdown and bacterial translocation. Serial measurements of C-reactive protein (CRP) and interleukin-6 were made to assess the systemic inflammatory response and its possible modification by intraoperative Doppler guided fluid. Interleukin-6 is an integral cytokine mediator of the acute phase response to injury and infection. Prolonged excessive levels of interleukin-6 in patients after elective surgery have been associated with complications and mortality.[16]

In this study we assessed whether using intraoperative oesophageal Doppler guided fluid management to minimize hypovolaemia would reduce postoperative hospital stay and the time before return of gut function after colorectal surgery.

Methods

All patients requiring elective or semi-elective large bowel surgery under the care of two consultant colorectal surgeons between December 2001 and September 2003 were assessed for eligibility. Exclusion criteria were age under 18 yr, hepatic pathology, perforated viscus, oesophageal pathology, and coagulopathy. Written, informed consent was obtained from all patients by the research nurse before participation in the study, which was approved by the local research ethics committee.

The study was a single centre, blinded, prospective randomized controlled trial carried out in a District General Hospital setting. Only the anaesthetist and research nurse were aware of individual patients' allocation. The surgical teams, nursing staff and patients themselves were blinded. Each operation was carried out or closely supervised by the investigating consultant surgeons. A common, patient-led postoperative care pathway was followed for all patients. The anaesthetist and research nurse had no influence over postoperative care and management.

Patients were randomized and allocated according to the sequentially numbered, sealed opaque envelope technique. There were no restrictions or stratification in the randomization process. The allocation envelope was opened immediately before the induction of anaesthesia by the research nurse who then assigned the patient to the control or Doppler guided group.

All patients were given bowel preparation using two doses of Fleet (De Witt, Runcorn, UK) on the afternoon before surgery. They were encouraged to drink water until midnight and then given 1000–2000 ml Hartmann's solution i.v. overnight to minimize dehydration before surgery.

Anaesthesia was induced with propofol and was maintained with a balanced technique incorporating nitrous oxide, isoflurane, and oxygen with vecuronium or rocuronium providing muscle relaxation. Fentanyl and morphine were used for analgesia with postoperative epidural analgesia at the anaesthetist's discretion. Patients were intubated and ventilated to normocapnia throughout the operation. Standard monitoring included ECG, pulse oximetry, capnography, and non-invasive arterial pressure. After induction of anaesthesia, a central venous line was inserted for monitoring of central venous pressure (CVP) and vascular access. The oesophageal Doppler probe was then inserted orally and positioned approximately 35–40 cm from the teeth. The CardioQ (Deltex Medical, Chichester, UK) oesophageal Doppler monitor measures the velocity of blood flow in the descending thoracic aorta. Integrating the velocity–time curve gives the distance travelled by the blood following cardiac systole and multiplying this by the cross-sectional area (estimated by a nomogram) derives stroke volume and cardiac output. These measurements were taken, by the research nurse, before the operation, immediately after laparotomy, and at the end of the operation in the control group, and continuously in the Doppler guided fluid group.

In control group, patients were managed using routine cardiovascular monitoring and CVP measurements. The CVP was used to guide i.v. fluid administration and was kept between 12 and 15 mm Hg. The anaesthetist was blinded to the oesophageal Doppler measurements made by the research assistant in this group.

In Doppler guided fluid therapy group, in addition to the routine fluid management, the patients received 250 ml boluses of colloid solution, Haemaccel (Hoechst Marion Roussel, Uxbridge, UK) or Gelofusine® (Braun, Sheffield, UK). If the stroke volume increased by 10% or more but the CVP did not rise by 3 mm Hg or more, the fluid challenge was repeated. The fluid challenges of 250 ml were repeated until the stroke volume failed to rise by 10% and/or the CVP rose by 3 mm Hg or more. No further colloid fluid boluses were given until a 10% decrease in stroke volume occurred.

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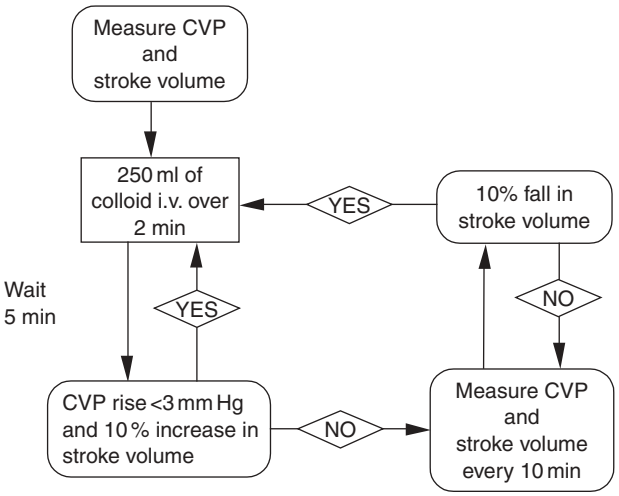

Fig 1 SVO fluid algorithm.

This fluid protocol started immediately after probe placement and continued until the surgeons began to close the abdomen (Fig. 1).

Patients followed a common recovery pathway during the postoperative recovery phase. On day 1 all nasogastric tubes were removed unless there was continued nausea or vomiting or drainage exceeded 300 ml. Water was given orally at 30–60 ml h^{-1} as tolerated and the patients were mobilized to sitting in the chair if able. On day 2, free oral fluids were given if tolerated and patients were mobilized to the chair or bathroom if able. From day 3 onwards patients continued free oral fluids and progressed to soft diet if tolerated. I.V. fluids were discontinued when oral intake exceeded 1500 ml in the previous 24 h and there was no nausea or vomiting. Mobilization continued as the patients were able. From day 4, patients could progress to full unrestricted diet if tolerated. The discharge criteria were resumption of normal diet without nausea or vomiting, ability to self care and mobilize independently or be able to be cared for and mobilized by existing home arrangements. Pain had to be controlled with oral analgesics and patients must have opened their bowels before discharge.

The primary outcome measure was the duration of postoperative hospital stay. The postoperative time until the patients were declared medically fit for discharge from hospital was measured to exclude social factors delaying discharge. The secondary outcome measure was the time taken until the patient was able to tolerate a full diet. Patient characteristics, past history, current diagnosis, and POSSUM scores[17] were recorded at baseline. Oxygen delivery was calculated from the cardiac output, the haemoglobin and the oxygen saturation at the beginning and end of operation. Intraoperative administration of crystalloid and colloid i.v. fluids were recorded along with fluid balance for the first 3 days, first appearance of bowel sounds, passing flatus, and opening of bowels.

Central venous blood gas samples were taken immediately after the induction of anaesthesia as baseline and at the end of operation. Blood tests including full blood count, biochemistry, serum albumin, and CRP were recorded before the operation and were repeated after the operation on alternate days from day 1 through to day 7.

A validated Quality of Recovery score was completed by the patients on days 3, 5, and 7[18] and complications were recorded using a previously published and validated postoperative morbidity survey.[8] In addition, quality of life questionnaires from the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR38 were completed 4–6 weeks after surgery.

Measurement of intestinal permeability and systemic endotoxin

Intestinal permeability was assessed by administering oral mannitol and lactulose as probe molecules, which were then assayed in urine using high-pressure liquid chromatography and pulsed amperometric detection.[19] Mannitol, the smaller molecule is absorbed by the transcellular route, lactulose by the paracellular route. Both probes are rapidly excreted in the urine. The test solution contained 5 g lactulose and 2 g mannitol in 100 ml water. Patients were fasted overnight excepting water before each test whilst avoiding NSAIDs and alcohol. The solution was given to the patients and all urine was collected for 6 h in containers containing thiomersal 1%. The collection volume was then recorded and a 20-ml aliquot taken and stored at −20°C until analysed. Tests were performed before surgery, and on days 1 and 5 after surgery. Free fluids were allowed 1 h after the test solution had been given and food after 2 h if appropriate.

Blood for endotoxin measurement was taken in endotoxin-free vacuum tubes (Endotubes, Quadratech, Ltd) at the start of surgery, end of surgery, and on day 1. The samples were frozen until analysed by a kinetic microplate modification of a chromogenic limulus amoebocyte lysate test kit (Coatest-ET, KabiVitrum Diagnostica). Interleukin-6 was measured using a quantitative sandwich enzyme immunoassay technique (Quantikine®, R&D Systems, Abingdon, UK) before the operation and on postoperative days 1 and 3.

Statistical analysis

For the primary outcome measure with reference to pilot[20] data, we calculated a study size of 58 patients in each group to demonstrate a reduction in postoperative hospital stay of 2 days knowing the mean (SD) postoperative hospital stay was 11 (3.79) days following standard anaesthetic management. For the secondary outcome measure with reference to previous data, we calculated a study size of 64 patients in each group to demonstrate a 2-day reduction in the time taken to tolerate full diet knowing that the mean (SD) number of postoperative days before tolerating full diet was 5.0 (4.0) after major abdominal surgery with standard anaesthetic management.[7] Sample sizes were calculated for two-tailed tests allowing for a type I error of 5% and a type II error of

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20%. Data were analysed using SPSS for Windows version 11.5. Data were tested for normality using the Kolmogorov–Smirnoff test with Lilliefors significance correction and Levene's test of variance. Parametric data were analysed using appropriate ANOVA or Student's *t*-test and non-parametric data were analysed using the Mann–Whitney *U*-test. Sequential measurements were analysed using ANCOVA. Pearson's correlation coefficient (*r*) was used to assess for associations between duration of hospital stay and the following factors: age, formation of stoma, POSSUM scores, biochemistry results, blood loss, and lactulose/mannitol ratio. The relative risk of developing a gastrointestinal complication between the two groups was also calculated.

Results

Figure 2 shows the trial profile of the study. Of 178 patients who were assessed for eligibility, 25 refused to participate and eight did not meet the inclusion criteria. A further 11 patients were not included, in six of these an anaesthetist with suitable oesophageal Doppler experience was unavailable, three patients were identified too late for reasonable informed consent to be offered, and two had already given consent to another trial when approached. Three patients were withdrawn after randomization in the Doppler guided fluid group, two of these had inoperable disease and consequently had no surgery to the bowel, and in one patient it was impossible to site a central venous line and therefore follow either fluid regimen. Three patients were withdrawn from the control group because of inoperable disease. There were no other discontinuations, exclusions or patients lost to follow up.

There were no differences between the groups with regard to age, ASA grade, BMI, physiological or operative POSSUM score, surgery type or duration, blood loss or postoperative haematology, and serum biochemistry (Table 1). The primary outcome measure, the median postoperative hospital stay, was 10 days in the Doppler guided fluid group compared with 11.5 days in the control group ($P<0.05$, Mann–Whitney *U*-test; see Table 2). There was a significant correlation between increased postoperative hospital stay and advancing age (Pearson correlation two-tailed 0.217, $P<0.05$), and the formation of a stoma (Pearson correlation two-tailed 0.216, $P<0.05$). There was no significant correlation with postoperative hospital stay for POSSUM scores, serum biochemistry, blood loss, or intestinal permeability. The secondary outcome measure, the median time to tolerating full diet, was 6 days in the Doppler guided fluid group compared with 7 days in the control group ($P<0.001$, Mann–Whitney *U*-test). In addition, for the patients in the Doppler guided fluid group bowel opening occurred after a median of 4 days compared with 5 days in the control group ($P<0.05$, Mann–Whitney *U*-test).

Patients in the Doppler guided fluid group were given a significantly greater volume of intravenous colloid than controls (median 2000 *vs* 1500 ml, $P<0.01$, Mann–Whitney *U*-test); however, the range of colloid given in the treatment group was large, that is 500–5000 ml. Both groups received a median volume of crystalloid of 3000 ml. Patients in the Doppler guided fluid group achieved significantly higher cardiac outputs and stroke volumes at the end of operation than the control group (Table 3). Oxygen delivery was higher at the end of surgery in the Doppler guided fluid group than in the control group (median 535 *vs* 445 ml min^{-1} m^{-2}, $P<0.05$, Mann–Whitney *U*-test). The CVP measurements were similar in the two groups, the median control group CVP was 13 mm Hg compared with 14 mm Hg in the Doppler guided fluid group ($P=0.287$, Mann–Whitney

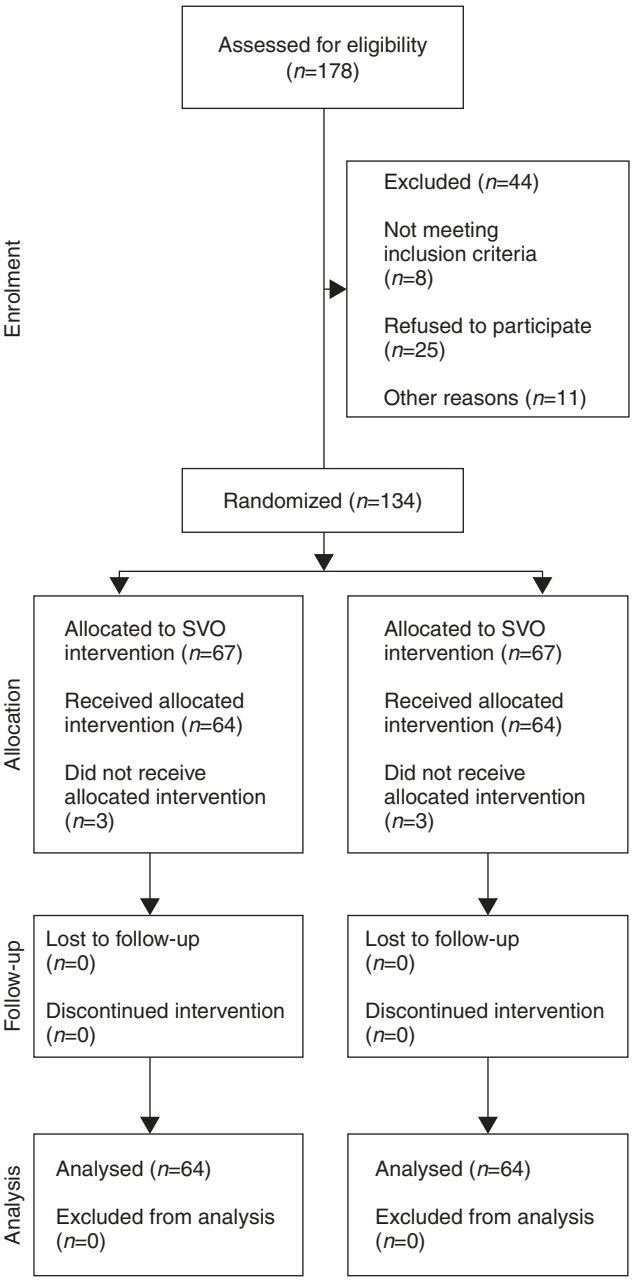

Fig 2 Study flow diagram.

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Table 1 Patient characteristics and operation details. IQR, interquartile range

	Control group Median (IQR)	Optimization group Median (IQR)
Patient characteristics		
Age (yr)	69.6 (10.2)	69.1 (12.3)
BMI (kg m^{-2})	26 (7.25)	24.5 (6.75)
ASA score	2 (1)	2 (1)
Physiological POSSUM	18 (7)	17 (6.5)
Gender M:F	34:30	38:26
Operation details		
Anterior and AP resections (*n*)	33	31
Left hemi- and sigmoid colectomy (*n*)	15	15
Right hemicolectomy (*n*)	9	15
Sub-total colectomy (*n*)	4	0
Reversal of Hartmann's (*n*)	2	3
Crohn's resection (*n*)	1	0
Operative POSSUM	16 (9)	15.5 (7)
Operative duration (min)	157 (68)	149 (65)
Estimated blood loss (ml)	500 (975)	500 (700)
Stoma sited (*n*)	27	23
Epidural sited (*n*)	11	11

Table 2 Postoperative hospitalization and recovery of gut funtion. IQR, interquartile range; MWU, Mann–Whitney *U*-test

	Control group Median (IQR)	SVO group	*P*-value (test)
Postoperative hospitalization (days)	11.5 (4.75)	10 (5.75)	0.031 MWU
Time until fit for discharge (days)	11 (4.0)	9.5 (5)	0.012 MWU
Bowel recovery (days)			
Flatus	4 (2)	3 (2)	0.085 MWU
Bowels opening	5 (2)	4 (3)	0.014 MWU
Full diet	7 (2)	6 (2)	<0.001 MWU

U-test), and at the end of operation the median CVP was 13 mm Hg in both groups. Venous blood gases at the end of surgery are shown in Table 3.

Twenty-nine patients in the control group suffered gastrointestinal morbidity compared with nine in the Doppler guided fluid group ($P<0.001$, χ^2-test). The relative risk (95% CI) of suffering gastrointestinal complications was 2.035 (1.474–2.810) in the control group compared with 0.379 (0.209–0.686) in the Doppler guided fluid group. This represents a risk ratio of 5.3:1.

Two patients in the control group and one in the Doppler guided fluid group had an anastamotic leak whereas five control group patients had a high output stoma compared with only one in the Doppler guided fluid group ($P=0.094$, χ^2-test). Overall morbidity was also significantly higher in the control group ($P=0.013$, χ^2-test) (Table 4). Five patients recorded urinary complications, four had urinary retention, and one had an episode of oliguria. Pulmonary complications were recorded in eight Doppler guided fluid patients group and three control group patients ($P=0.121$, χ^2-test). Nine of these patients had chest infections requiring antibiotics, one had a pulmonary embolus, and one a *de novo* requirement for additional oxygen because of a cardiac arrhythmia. Cardiovascular complications were recorded in 17 patients divided evenly between the Doppler guided fluid and control groups. There were 10 episodes of hypotension, five cases of atrial fibrillation, and five episodes of new coronary ischaemia. One patient (in the Doppler guided fluid group) developed pulmonary oedema following an intraoperative ischaemic cardiac event early into the operation, the fluid protocol was not followed further but the data were analysed according to intention to treat.

Table 3 Haemodynamic and blood gas data. MWU, Mann–Whitney *U*-test; ANCOVA, analysis of covariance; VBGs, central venous blood gases; IQR, interquartile range

Variable	Control group Median (IQR)	SVO group Median (IQR)	*P*-value (test)
Cardiac output (litre min^{-1})			
Pre-incision	4.80 (2.40)	5.20 (2.63)	0.19 (MWU)
After laparotomy	5.40 (2.10)	5.20 (2.10	0.47 (MWU)
End of surgery	5.60 (3.05)	7.25 (2.38)	0.02 (MWU)
CVP mm Hg (median)	13 (5)	14 (4)	0.287 (MWU)
CVP mm Hg (end of operation)	13 (5.5)	13 (4.5)	0.580 (MWU)
Stroke volume (ml)			
Pre-incision	72.0 (33.0)	82.0 (40.0)	0.074 (MWU)
After laparotomy	74.0 (26.0)	79.0 (31.3)	0.38 (MWU)
End of operation	77.0 (26.0)	99.5 (43.5)	<0.001 (MWU)
Oxygen delivery (ml min^{-1} m^{-2})			
Pre-incision	403.0 (175.5)	420 (250.3)	0.275 (MWU)
End of operation	453.0 (202.5)	535.0 (229.5)	0.003 (MWU)
End of surgery VBGs			
Base excess	−3.60 (3.20)	−5.10 (3.48)	0.079 (ANCOVA)
Chloride (mmol $litre^{-1}$)	110.0 (4.0)	110.0 (4.00)	0.139 (ANCOVA)
pH	7.28 (0.008)	7.26 (0.07)	0.146 (ANCOVA)
Lactate (mmol $litre^{-1}$)	1.20 (0.50)	1.25 (0.050)	0.163 (ANCOVA)
Bicarbonate (mmol $litre^{-1}$)	23.05 (2.78)	20.05 (2.85)	0.048 (ANCOVA)

Table 4 Data from quality of recovery scoring[18] and morbidity scoring.[9] IQR, interquartile range; MWU, Mann–Whitney *U*-test

Quality of recovery score[18]	Control group Median (IQR)	SVO group Median (IQR)	*P*-value (MWU)
Day 3	11 (4)	12 (3)	0.56
Day 5	13 (4)	15 (3.5)	<0.001
Day 7	15 (2)	17 (4)	0.007
Morbidity score:[9] Complication type	**Control group (*n*, %)**	**SVO group (*n*, %)**	***P*** **(χ^2)**
Pulmonary/thrombotic	3 (4.68)	8 (12.5)	0.121
Infectious	11 (17.1)	14 (21.8)	0.532
Renal	2 (3.13)	3 (4.68)	0.661
Gastrointestinal	29 (45.3)	9 (14.1)	<0.001
Cardiovascular	9 (14.1)	8 (12.5)	0.768
Neurological	4 (6.25)	2 (3.13)	0.392
Wound	4 (6.25)	5 (7.81)	0.748
Haematological	2 (3.13)	3 (4.68)	0.661
Pain	1 (1.56)	1 (1.56)	0.991
Social	1 (1.56)	1 (1.56)	0.991
Total number of patients with complications	38 (59.3)	24 (37.5)	0.013

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Table 5 Lactulose/mannitol, endotoxin and inflammatory marker results. IQR, interquartile range; MWU, Mann–Whitney *U*-test

	Control group Median (IQR)	SVO group Median (IQR)	*P*-value (test)
Baseline	0.0180 (0.020)	0.0190 (0.016)	0.273 MWU
Day 1	0.0475 (0.077)	0.046 (0.16)	0.309 ANCOVA
Day 5	0.0395 (0.051)	0.030 (0.029)	0.690 ANCOVA
Endotoxin			
Baseline	0.46 (5.29)	0.70 (6.45)	0.261 MWU
End of surgery	4.79 (20.5)	7.62 (22.7)	0.367 ANCOVA
Day 1	0.73 (6.32)	1.65 (7.91)	0.291 ANCOVA
CRP (iu litre^{-1})			
Pre-op	8.0 (23)	6.0 (9.0)	0.629 MWU
Day 1	145 (68.5)	123 (67)	0.359 ANCOVA
Day 3	140 (78.8)	150 (85.0)	0.289 ANCOVA
Day 5	75 (68)	53 (55)	0.259 ANCOVA
Day 7	46.5 (61)	35 (30)	0.312 ANCOVA
Interleukin-6 (iu ml^{-1})			
Pre-op	5 (0)	5 (1.45)	0.90 MWU
Day 1	53.5 (54.5)	47.9 (54.05)	0.905 ANCOVA
Day 3	10.4 (19.3)	11.9 (14.0)	0.729 ANCOVA

There were no differences between the groups with regard to lactulose/mannitol measurements of intestinal permeability. Permeability was significantly higher on day 1 compared with baseline in both groups but the measurements were no different from baseline at day 5 (Table 5). In both groups endotoxin measurements were significantly higher than baseline at the end of operation but were not significantly different from baseline on day 1. There were no differences between the groups in the systemic inflammatory markers interleukin-6 and CRP at any time.

There were no differences between the groups with regard to blood transfusion requirement. No patients died within 30 days of surgery, one patient died in the control group within 60 days. The validated Quality of Recovery score[18] indicated more rapid recovery in the Doppler guided fluid group, which was significant on both days 5 and 7 (Table 2). However, the EORTC QLQ C-30 and QLQ CR38 quality of life questionnaires completed 4–6 weeks after surgery showed no differences between the groups. The control group occupied hospital beds for a total of 840 days compared with 770 days for the Doppler guided fluid group.

Discussion

The median duration of hospital stay in the Doppler guided fluid group was 10 days compared with 11.5 days in the control group, $P<0.05$. This 13.0% reduction in median postoperative stay is of a similar magnitude to other studies.[5–7] The application of oesophageal Doppler guided fluid management has produced a similar improvement in recovery in patients undergoing very different surgical operations, which implies that the mechanism of action and resulting benefits are independent of operation type. In this study the control group received fluid management, which was a generous, although pressure-based, target CVP of 12–15 mm Hg. Despite this, a significant improvement in recovery and reduction in bed stay was observed in the Doppler guided fluid group. The oesophageal Doppler protocol is an example of dynamic goal directed fluid therapy in that a bolus of i.v. colloid is administered and changes in stroke volume or CVP are measured before deciding on further fluid management. Venn and colleagues[21] showed that a central venous line could be used dynamically by measuring CVP changes after a colloid bolus. This dynamic use of the CVP improved patient outcome compared with controls. In contrast absolute pressure-based CVP target on the other hand does not appear to improve outcome in the same way. This is because there is no correlation between blood volume and absolute CVP measurements.[22]

Patients in the Doppler guided fluid group were given a greater volume of i.v. colloid solution. The observed median difference in colloid fluid administration (500 ml) and the large range, 500–5000 ml, is very similar to that seen in other studies.[5–7] Parker and colleagues[23] randomized patients to receive 500 ml additional colloid before surgery but no outcome advantage was observed over patients not receiving the additional fluid. This is not surprising considering the enormous range of colloid we found was required to achieve the individualized maximum stroke volumes.

The patient characteristics between the two groups were remarkably similar overall, but as with any randomized study there are subtle differences that need to be discounted as causing major contributions to the results found. The control group patients had a slightly lower median physiological POSSUM score but the range was large and the median ASA scores were identical, consequently it is very unlikely that preoperative factors made a significant contribution to the difference in outcome. Although the distribution of operative procedures between the two groups was not significantly different, the reader may be concerned that the Doppler guided fluid group had a slightly higher number of generally easier right hemicolectomy patients and a slightly lower number of stoma sited. However, the operative POSSUM scores were virtually identical indicating an even overall distribution of operative difficulty. Only advancing age and stoma creation were correlated with increased postoperative hospital stay; the median patient age was virtually identical in both the groups, and only four additional stoma were sited in the Doppler guided fluid group. It is therefore very unlikely that patient characteristic variables influenced the results of the study significantly.

Patients in the Doppler guided fluid group achieved significantly higher cardiac output, stroke volume measurements at the end of operation than the control group. Calculated oxygen delivery was higher at the end of surgery in the Doppler guided fluid group than in the control group (median 535 *vs* 445 ml min^{-1} m^{-2}, $P<0.05$). The oxygen delivery in the Doppler guided fluid group therefore approached the supranormal value of 600 ml min^{-1} m^{-2} advocated by Shoemaker.[2] The control group oxygen

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delivery median was closer to 390 ml min^{-1} m^{-2} where tissue oxygenation may become physiologically inadequate in high-risk patients.[24] Interestingly the venous blood gas measurements showed possibly worse base deficit (median 5.1 *vs* 3.6, P=0.079) and standard bicarbonate levels (23.05 *vs* 20.05 mmol $litre^{-1}$, P=0.048) in the Doppler guided fluid group. As there were no differences in the lactate or chloride, it may be that a strong ion within the colloid solution may have been responsible for the differences seen.

The secondary outcome measure, the median time to tolerating full diet in the treatment group was 6 days compared with 7 days in the control group (P<0.001). Patients in the Doppler guided fluid group opened their bowels significantly earlier (median day 4 *vs* day 5) and significantly fewer (45.3 *vs* 14.0%) suffered gastrointestinal morbidity (P<0.001). Indices of tissue perfusion such as arterial base deficit and gastric intramucosal pH (pHi, a measurement of gut blood supply) are amongst the strongest predictors of postoperative gastrointestinal morbidity.[8] So that a better intraoperative splanchnic blood supply may have contributed to the quicker recovery of gut function and reduction in gastrointestinal complications in the Doppler guided fluid group.

Improved perioperative cardiac output has been associated with improved gut perfusion as measured by gastric tonometry or pHi.[5] Gut hypoperfusion may lead to increased intestinal permeability and bacterial translocation. We hypothesized that the Doppler guided fluid group would have a favourable outcome because improved gut perfusion may lead to a smaller rise in permeability and less endotoxaemia. Intestinal permeability was significantly higher than baseline on day 1 in both groups. Although improved cardiac output, oxygen delivery, and reduction in gastrointestinal complications were demonstrated in the Doppler guided fluid group there was no associated effect on intestinal permeability. It is possible that intestinal permeability measurement is not sensitive enough to detect changes in splanchnic hypoperfusion or that poor perfusion of the small intestinal mucosa may not be the only factor involved. An extraperitoneal compared with a trans-peritoneal approach reduces intestinal permeability after elective abdominal aneurysm repair.[25] This suggests that small intestinal manipulation *per se* may influence intestinal mucosal function. Similarly, there were no differences between the groups at any time interval with respect to serum endotoxin levels. Levels were significantly higher at the end of surgery compared with baseline, but were not significantly different from baseline on day 1. It is not known whether increased intestinal permeability correlates with an increased potential for bacterial translocation in humans.[26] The endotoxinaemia observed is likely to be a direct complication of the operation as endotoxin levels had returned to baseline by day 1 when intestinal permeability was high.

The systemic inflammatory markers interleukin-6 and CRP were measured as raised levels are associated with gastric hypoperfusion and poorer outcome after major operations.[27 28] We observed no differences between the groups at any time.

Brandstrup and colleagues[29] conducted a study on patients undergoing colorectal surgery, which showed benefit from restricting i.v. fluid administration in the perioperative period. It would seem at first glance that this is in contradiction to the findings in the current study. However, there are a number of differences between the studies. The fundamental difference is that the current study used an oesophageal Doppler guided, goal-directed approach to fluid management. This identified and treated hypovolaemia on an individualized basis and was sensitive to changing requirements over the course of the surgery. Brandstrup and colleagues used an arbitrary, non-individualized fluid protocol, which administered normal saline to patients whether or not it was required. Secondly unlike the current study, the patients in Brandstrup's series did not receive any bowel preparation, and did not therefore have the associated unpredictable fluid deficit. Despite the fluid-depleting effect of bowel preparation in the current study the median targeted intraoperative i.v. fluid administration was 5000 ml in the Doppler guided fluid group compared with 4000 ml in Brandstrup's restricted fluid group and over 6000 ml in their standard treatment group who had not had bowel preparation. It is very likely that some patients in Brandstrup's study were overloaded, particularly as normal saline was continued in the postoperative phase alongside enteral nutrition.

The exclusion criteria used in the two studies were very different. Brandstrup effectively excluded all but the very healthiest patients whereas we did not exclude patients on physiological status. Consequently, only three of Brandstrup's 141 patients were ASA III and none were ASA IV whereas 23 were ASA III and six were ASA IV in the current study's 128 patients. Lower mortality would be anticipated in the study with the fittest patients; however, the converse was found; the current study had a 30-day mortality of zero compared with 4.7% found by Brandstrup and colleagues. This implies that Brandstrup's standard fluid regimen was actually causing patients harm. This is further evidenced by the pulmonary oedema reported in ASA I and II patients in addition to the reported mortality in these patients. The patients in the restricted fluid group were protected from this fluid overloading. The administration of large volumes of normal saline is also associated with metabolic acidosis and poorer outcome.[30]

The validated Quality of Recovery score[23] indicated more rapid recovery in the Doppler guided fluid groups, which was significant on both days 5 and 7, these findings are in keeping with those of lower gastrointestinal and overall morbidity in the Doppler guided fluid group (P<0.05). The 30-day mortality was zero but the P-POSSUM predicted mortality[31] using the median physiology and operation severity scores was 3.3% for this cohort of 128 patients. The EORTC QLQ C-30 and QLQ CR38 quality of life questionnaires completed 4–6 weeks after surgery showed

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no differences between the groups. It is unsurprising that there were no differences found at this late stage. There were no differences between the groups with regard to blood transfusion requirement, this was important to note as the pilot study[20] had indicated a reduction in blood product requirement, a finding that can now be discounted.

The control group occupied hospital beds for a total of 840 days compared with 770 days for the Doppler guided fluid group, the 70-bed day difference following the treatment of 64 patients represents a more efficient use of hospital beds and a cost saving for this institution. At £400 per hospital bed-day, the cost saving is approximately £25 000 after taking account the costs of extra fluid (approximately £4.00 per patient) and CardioQ DP6 oesophageal Doppler probes at £45 per patient.

Finally, we have shown that the use of oesophageal Doppler guided fluid during large bowel surgery was associated with a significantly reduced postoperative hospital stay. In addition, patients recovered gut function significantly faster, suffered significantly less gastrointestinal and overall morbidity and had higher quality of recovery scores at days 5 and 7. The median bed stay was reduced by 1.5 days representing cost savings of approximately £25 000 for the 64 patients in the Doppler guided fluid group.

This study supports the hypothesis that intraoperative hypovolaemia is common and that the outcome from major surgery can be improved by following a simple dynamic oesophageal Doppler guided fluid algorithm.

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