British Journal of Anaesthesia **112** (2): 281–9 (2014)
Advance Access publication 20 September 2013 · doi:10.1093/bja/aet307

BJA

Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery

D. R. A. Yates*, S. J. Davies, H. E. Milner and R. J. T. Wilson

Department of Anaesthesia, York Teaching Hospital NHS Foundation Trust, York, UK

* Corresponding author. E-mail: drdavidyates@gmail.com

Editor's key points

- This study showed no clinical benefit from using hydroxyethyl starch (HES) for routine haemodynamic optimization in the perioperative period compared with crystalloid using a goal-directed fluid protocol.
- These data do not support the hypothesis that the use of HES maintains the splanchnic circulation more effectively and thus reduces inflammation.
- No actual coagulopathy was induced with the administration of HES and no increase in thrombotic events was seen in the crystalloid group.
- Despite HES patients requiring less fluid than those in the crystalloid group, there was no clinical benefit.

Background. Goal-directed fluid therapy has been shown to improve outcomes after colorectal surgery, but the optimal type of i.v. fluid to use is yet to be established. Theoretical advantages of using hydroxyethyl starch (HES) for goal-directed therapy include a reduction in the total volume of fluid required, resulting in less tissue oedema. Recent work has demonstrated that new generations of HES have a good safety profile, but their routine use in the perioperative setting has not been demonstrated to confer outcome benefit.

Methods. We randomly assigned 202 medium to high-risk patients undergoing elective colorectal surgery to receive either balanced 6% HES (130/0.4, Volulyte) or balanced crystalloid (Hartmann's solution) as haemodynamic optimization fluid. The primary outcome measure was the incidence of gastrointestinal (GI) morbidity on postoperative day 5. Secondary outcome measures included the incidence of postoperative complications, hospital length of stay, and the effect of trial fluids on coagulation and inflammation.

Results. No difference was seen in the number of patients who suffered GI morbidity on postoperative day 5 [30% in the HES group *vs* 32% in the crystalloid group; adjusted odds ratio=0.96 (0.52–1.77)]. Subjects in the crystalloid group received more fluid [median (inter-quartile ranges) 3175 (2000–3700) *vs* 1875 (1500–3000) ml, $P<0.001$] and had a higher 24 h fluid balance [+4226 (3251–5779) *vs* +3610 (2443–4519) ml, $P<0.001$]. No difference in the incidence of postoperative complications was seen between the groups.

Conclusions. Goal-directed fluid therapy is possible with either crystalloid or HES. There is no evidence of a benefit in using HES over crystalloid, despite its use resulting in a lower 24 h fluid balance.

Clinical trial registration. ISRCTN41882213 and EudraCT-2009-013872-29.

Keywords: complications; fluid therapy; plasma expanders; surgery, gastrointestinal; thromboelastography

Accepted for publication: 15 July 2013

All patients undergoing colorectal surgery receive i.v. fluid. The use of minimally invasive cardiac output monitors to guide the administration of fluid by optimizing stroke volume and cardiac output has been demonstrated to reduce postoperative complications.[1] The optimum type of fluid to use when performing this intervention, however, has yet to be determined. There is a theoretical advantage to using colloids in the perioperative period as lower volumes are needed to achieve similar haemodynamic endpoints, resulting in reduced tissue oedema and greater anastamotic integrity.[2] Several studies have demonstrated that excess volumes of crystalloid solution in the perioperative period, and the associated positive fluid balance, are detrimental to recovery.[3 4]

Colloids have not been shown to have a beneficial effect over crystalloids when used for fluid resuscitation in critical illness and the use of older generations of hydroxyethyl starch (HES) solutions with higher molecular weights and higher substitution ratios was associated with increased complications, including blood coagulation disorders and renal dysfunction.[5 6] The newer generations of HES certainly seem to have an improved safety profile as evidenced by two recent analyses,[7 8] but no clinical outcome benefit has been shown for their use in the perioperative period: indeed, a recent Cochrane review has recommended their use be limited to randomized controlled trials.[9]

We performed a double-blind, randomized controlled trial to assess whether a balanced HES solution reduced morbidity

© The Author [2013]. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved.
For Permissions, please email: journals.permissions@oup.com

after colorectal surgery compared with a balanced crystalloid solution, when both products were given within a goal-directed protocol.

Methods

Study oversight

This trial was a double-blind, randomized controlled trial conducted in a single-centre hospital in the UK. The trial protocol was written by the investigators and approved by the Leeds (West) Research Ethics Committee (09/H1307/77) and the Medicines and Healthcare products Regulatory Agency. The trial was registered with Current Controlled Trials (ISRCTN41882213) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT-2009-013872-29).

Written informed consent was obtained from all participants before randomization. Data and tissue samples were collected by trained research nurses or the investigators. The trial was conducted in accordance with GCP and monitored by an external agency.

Data management and statistical analysis plans were authorized by the sponsor before any data analysis or unblinding. The investigators remained blinded to group allocation until data had been validated and the database locked. The investigators performed all statistical analysis in accordance with the plan, and attest to the integrity of the data and the manuscript.

Financial support was in the form of an unrestricted grant from Fresenius Kabi who also supplied the study fluids free of charge. Fresenius Kabi had no input into the conduct of the trial, data analysis, or decision to submit the manuscript. The trial was adopted onto the National Institute for Health Research Clinical Research Network Portfolio.

No interim analysis was performed for this trial.

Screening and consent

Patients were screened for eligibility at a surgical pre-assessment clinic where they underwent cardiopulmonary exercise testing (CPET) as part of their standard preoperative investigations to assess their functional status, and therefore perioperative risk. Patients more than 55 yr of age were eligible for the trial if their oxygen consumption at anaerobic threshold was <14 ml kg^{-1} min^{-1}, thereby excluding the lowest risk patients. Inclusion and exclusion criteria are provided in Supplementary Table S1. Randomization was performed using a 'block of 4' technique, and stratified according to whether the patient was deemed to be moderate or high risk on the basis of CPET. Patients were randomized to receive either 6% HES (130/0.4) in a balanced salt solution (Volulyte 6%, Fresenius Kabi, Bad Homburg, Germany) or balanced salt solution alone (Hartmann's, Fresenius Kabi) as their haemodynamic optimization fluid (HOF). Trial fluids were blinded to investigators by pharmacy staff placing an opaque, black wrapper over the 500 ml bag leaving the identical administration ports free.

Haemodynamic optimization protocol

Before induction of anaesthesia, patients had an i.v. cannula inserted into a forearm vein for administration of study fluid, and an arterial line sited in a radial artery. Haemodynamic variables were measured via a LiDCO Rapid monitor (LiDCO, Cambridge, UK). A 250 ml bolus of HOF was administered using a 50 ml syringe and the stroke volume response recorded. If the stroke volume increased by more than 10%, the bolus was repeated. No further bolus was given once the stroke volume failed to increase by more than 10%. After induction of anaesthesia, further boluses of HOF were administered during surgery to maintain a stroke volume variation (SVV) $<10\%$. For patients with dysrhythmias, the stroke volume was used to guide HOF administration in the same manner as the pre-induction protocol (Supplementary Fig. S1).

HOF was administered up to a maximum of 50 ml kg^{-1} (the maximum daily dose of Volulyte) or 5000 ml which ever was the lesser amount, at which point an open-label balanced gelatin (Geloplasma, Fresenius Kabi) was administered if further boluses were required. In addition, all patients received an i.v. infusion of Hartmann's solution at a rate of 1.5 ml kg^{-1} h^{-1} from the start of the trial period and this continued for 24 h.

After surgery, if the urine output decreased below 0.5 ml kg^{-1} h^{-1} for 2 consecutive hours, a 250 ml bolus of HOF was administered. This continued for a 24 h period from the start of surgery.

Anaesthesia and postoperative management

Anaesthesia was induced with fentanyl (1–3 μg kg^{-1}) and propofol (1–3 mg kg^{-1}) and maintained with isoflurane or desflurane in oxygen-enriched air. Postoperative analgesia was provided with either a thoracic epidural or patient-controlled morphine boluses and discontinued at the discretion of the hospital Acute Pain Team. Dopexamine was started intraoperatively if there was evidence of tissue hypoperfusion (elevated lactate or base deficit) and if commenced was continued for 24 h after operation.

Postoperative fluid management beyond the first 24 h was at the discretion of the clinical team. The commencement of enteral diet was also at the discretion of the clinical teams with all surgeons using the principles of enhanced recovery.

Perioperative monitoring

Patient haemodynamic status was monitored and recorded continuously throughout the intraoperative period and for 3 h after surgery. Arterial blood gas monitoring was performed at predefined intervals and systemic oxygen delivery calculated.

Thromboelastography subgroup

A subgroup of 37 consecutive patients had thromboelastography (TEG) performed (Haemonetics, Thromboelastograph, Haemostasis System, Middlesex, UK) to assess the effect of trial fluids on coagulation. Samples were obtained at baseline, 1 h into surgery, end of surgery, and 3 h after surgery.

Inflammatory marker subgroup

A subgroup of 48 consecutive patients had serum inflammatory markers measured. Interleukin-6 (IL-6) and Interleukin-10 (IL-10) were measured before operation and at 1, 3, 6, and 24 h after operation (Luminex IS, Bio-Rad, Herts, UK). C-reactive protein (CRP) was measured before operation and on days 1, 3, 5, and 7 after operation (Cobas c501, Roche Diagnostics, West Sussex, UK).

Outcome measures

The primary outcome measure was the presence of gastrointestinal (GI) morbidity at day 5 after operation. This was defined as the inability to tolerate a full enteral diet either by mouth or via a feeding tube for any reason, including nausea, vomiting, abdominal distension, or ileus. This measure was recorded by blinded researchers using direct patient questioning and observing fluid balance charts, treatment charts, and the medical records. See Supplementary Table S2 for details of the Post-Operative Morbidity Survey (POMS).

Secondary outcome measures included the incidence of predefined major and minor complications during hospital admission, postoperative recovery as measured by the POMS, hospital length of stay, perioperative haemodynamic variables, use of additional inotropic support, measures of tissue perfusion (lactate and base deficit), the use of additional open-label gelatine, changes in inflammatory markers, and changes in coagulation.

Statistical analysis

We determined that 202 patients were needed to detect a reduction in the incidence of GI morbidity on postoperative day 5 from 50% to 30% with a one-tailed power of 90% assuming an α-level of 0.05.

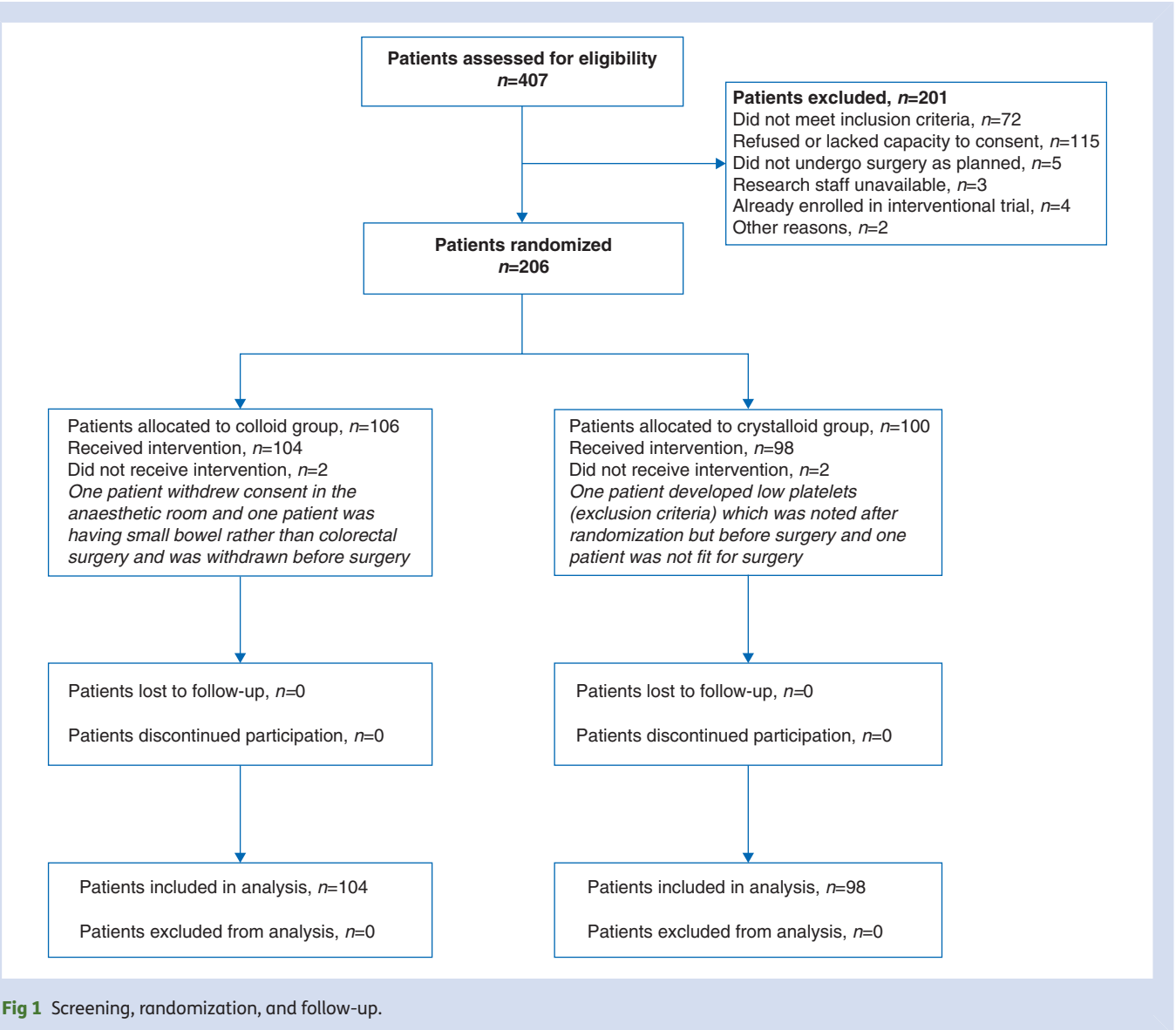

Fig 1 Screening, randomization, and follow-up.

In addition, 30 patients were needed to detect a 30% increase in reaction time (r time) on TEG with a power of 80% and an α-level of 0.05.

All data were analysed on an intention-to-treat basis. Missing data were coded as such—no imputations were used. Continuous data were analysed using mean differences and *t*-tests. Non-parametric data were analysed using the Mann–Whitney *U*-test.

Binary outcomes were compared using the χ^2 tests or logistic regression. Odds ratios (ORs) and 95% confidence intervals were calculated when appropriate. The length of hospital stay was analysed using log-rank tests and the Kaplan–Meier curves.

Areas under the curve were calculated for each patient for the temporal changes in inflammatory markers and compared with *t*-tests.

Results

A total of 206 patients were recruited from February 2010 to August 2012 (Fig. 1).

Functional capacity, and therefore perioperative risk,[10 11] as determined by CPET was similar between the two groups. There were no differences in other baseline characteristics (Tables 1 and 2).

Baseline oxygen delivery (DO_2) was higher in the crystalloid group [554 (167) *vs* 496 (153) ml kg^{-1} min^{-1}, P=0.01, Supplementary Table S3]. Given reported relationships between perioperative DO_2 and postoperative morbidity, outcomes are presented after adjustment for baseline DO_2.

Compliance with the haemodynamic optimization protocol was good. Deviations are reported in Supplementary Table S4. Patients in the crystalloid group received more trial fluid during surgery and were more likely to require Geloplasma [OR=4.44 (2.12–9.30)]. Subjects in the HES group received more fluid in the postoperative period, and when they did require Geloplasma, a greater volume was needed. Total fluid administered within the 24 h period was greater in the crystalloid group.

Table 1 Patient characteristics at baseline

	HES group (n=104)	Crystalloid group (n=98)
Patient characteristics		
Age (median, range)	72 (56–88)	70 (56–87)
Male sex [no. (%)]	63 (61)	54 (55)
Weight (kg) [mean (SD)]	77.9 (17.3)	79.0 (13.9)
Body mass index (kg m^{-2}) [mean (SD)]	27.3 (4.7)	27.9 (4.5)
Cardiopulmonary exercise test data		
Anaerobic threshold (ml kg^{-1} min^{-1}) [mean (SD)]	10.8 (1.7)	10.8 (1.7)
Ventilatory equivalent for CO_2 [mean (SD)]	34 (6)	33 (5)
High risk/moderate risk (no.)	28/76	24/74
ASA grade (I/II/III/IV) (no.)	8/63/32/1	12/56/30/0
Co-morbidities [no. (%)]		
Myocardial infarction	10 (10)	5 (5)
Angina	12 (12)	4 (4)
CABG	1 (1)	2 (2)
Heart failure	1 (1)	0 (0)
Cerebrovascular disease	6 (6)	4 (4)
Renal insufficiency/failure	1 (1)	1 (1)
Diabetes	22 (21)	13 (13)
Atrial fibrillation	11 (11)	4 (4)
Chronic obstructive pulmonary disease	8 (8)	3 (3)
Medications [no. (%)]		
β-Blocker	29 (28)	20 (20)
Aspirin	15 (14)	16 (16)
Statin	44 (42)	32 (33)
ACEI	26 (25)	30 (31)
Angiotensin II receptor blocker	9 (9)	6 (6)
Calcium channel blocker	18 (17)	20 (20)
Diuretic therapy	17 (16)	11 (11)
Insulin	4 (4)	4 (4)
Oral hypoglycaemic agents	14 (13)	12 (12)
Oral anticoagulation	7 (7)	5 (5)
Lee's revised cardiac risk index class II/III/IV	71 (68%)/29 (28%)/4 (4%)	80 (82%)/16 (16%)/2 (2%)

Table 2 Surgical and perioperative details

	HES group ($n=104$)	Crystalloid group ($n=98$)
Surgical procedure (no.)		
Anterior resection of rectum	35	41
Abdomino-perineal resection	7	6
Hartmann's procedure	7	6
Pan proctocolectomy	1	3
Reversal of Hartmann's procedure	1	3
Left hemicolectomy/ sigmoid colectomy	7	11
Right hemicolectomy	37	27
Other	9	1
POSSUM data [mean (SD)]		
Physiology score	20.0 (4)	19.0 (5)
Operative score	12.0 (3)	12.0 (4.0)
POSSUM-predicted morbidity (%)	38 (19)	37 (22)
POSSUM-predicted mortality (%)	8 (7)	9 (9)
P-POSSUM predicted mortality (%)	3 (4)	4 (5)
Other interventions		
Epidural analgesia	92%	91%
Laparoscopic procedure	24%	17%
Drains *in situ* after surgery	46%	56%
Dopexamine infusion	5%	3%

After adjustment for DO_2, there was no significant difference between the groups in the odds of a patient requiring a blood transfusion either intraoperatively [adjusted OR for the HES group=2.74 (0.94–8.01)] or in the entire trial period [adjusted OR=2.03 (0.88–4.68)]. There was no difference between the groups in the volumes of blood transfused within the trial period.

The overall fluid balance 24 h from the start of surgery was greater in the crystalloid group (Table 3).

There was no significant difference in the number of patients who required vasopressors to maintain arterial pressure during surgery, or in the doses required (Supplementary Table S5).

After the initial bolus of trial fluid, the haemoglobin level in the HES group was lower than that in the crystalloid group. There were no other significant differences in the haemodynamic variables between the two groups (Supplementary Table S3).

Primary outcome

The number of subjects unable to tolerate a full enteral diet on postoperative day 5 was 30% in the HES group and 32% in the crystalloid group [adjusted OR=0.96 (0.52–1.77)]. The mean time to oral diet was 2.8 days in both groups ($P=0.61$). The time to first bowel movement was also similar between the groups—3.7 days in the crystalloid group and 4.0 days in the colloid group ($P=0.62$).

No significant differences were seen between the treatment groups in the number of patients who developed postoperative complications (Table 4, definitions of complications—Supplementary Table S6).

Characteristics of patients in whom complications occurred compared with those in whom they did not are shown in Supplementary Table S7. No difference in postoperative morbidity was seen between the groups at any point (Supplementary Fig. S2). There were no significant outcome differences between the groups when analysed according to the risk group (Supplementary Table S8).

Five patients in the HES group and two patients in the crystalloid group died [adjusted OR=1.99 (0.37–10.78)]. There was little difference in hospital length of stay between the groups—a median of 8 days in the crystalloid group and 9 days in the HES group (log-rank test, $P=0.74$) (Supplementary Fig. S3).

There were no significant differences between the groups in measured inflammatory markers at any point, nor was there any difference in IL-6 between those patients who suffered complications and those who did not (Supplementary Fig. S4).

No changes were seen in coagulation with HES therapy except a reduction in the maximum amplitude (MA) at the end of surgery and at 3 h after operation when compared with baseline. MA values did not fall outside the normal range. Evidence of increased coagulation (from baseline) was seen in the crystalloid group in all the variables with the exception of MA which remained unchanged (Supplementary Fig. S5).

Discussion

In this double-blind randomized controlled trial, no clinical benefit was seen from using HES for routine haemodynamic optimization in the perioperative period compared with crystalloid. This is in concordance with recently published data which demonstrated either no benefit or harm in the routine use of similar products in patients with established critical illness.[12 13] Critically ill patients may have damaged vascular endothelium and colloid may redistribute into the interstitium causing harm.[14] The use of HES in elective surgical patients whose vascular endothelium is intact may therefore have benefits in terms of restricting the volume of fluid needed to achieve haemodynamic optimization. Despite HES patients requiring less fluid than those in the crystalloid group, there was no clinical benefit.

We chose the GI domain of the POMS as our primary outcome as it is a reliable and easily measured outcome parameter and relevant to the surgical population being studied. Rates for GI morbidity at day 5 after operation have previously been reported ranging from 26% to 65%.[15–17] Inter-observer reliability is good in this domain of the POMS with good agreement in both validation studies published to date, $\kappa=0.66$ and $\kappa=0.71$. In one of these studies, by Grocott and colleagues,[16] there was a mean increase in hospital length of stay of 4.3 days ($P=0.002$) in those patients with GI morbidity at day 5 after operation (65.3% of the cohort). Davies and colleagues,[17]

Table 3 Perioperative fluid administration and balance. Data presented as medians (IQRs). *$P<0.05$, **$P<0.01$, ***$P<0.001$

	HES group ($n=104$)	Crystalloid group ($n=98$)
Blinded trial fluid (ml)		
Pre-induction period	250 (250–250)	250 (250–250)
Intraoperative period	1000 (750–1500)	1750 (1250–2750)***
Postoperative period	500 (250–1250)	500 (0–1000)*
Total input in first 24 h		
Blinded trial fluid (ml)	1875 (1500–3000)	3175 (2000–3700)***
Hartmann's (maintenance fluid) (ml)	2592 (2377–3215)	2701 (2448–3120)
Geloplasma required, yes/no	12/92 (12%)	37/61 (38%)***
If yes, volume (ml)	1000 (500–1500)	750 (500–1625)
Blood, yes/no	20/84	10/88
If yes, volume (ml)	582 (564–1081)	565 (302–587)
Other blood products, yes/no	3/101	1/97
Oral fluids (ml)	288 (90–588)	175 (0–500)
Total fluid input (ml)	5398 (4498–6401)	6375 (5198–7535)**
Fluid output in first 24 h (including surgery)		
Blood loss (ml)	250 (50–700)	200 (100–620)
Urine output (ml)	1266 (943–1687)	1293 (918–1839)
Other measured losses (drains, etc.)	240 (131–592)	200 (125–450)
Nasogastric aspirate/vomit	0 (0–0)	0 (0–0)
Total fluid output	1755 (1281–2586)	1985 (1431–2538)
Fluid balance (ml)		
Total fluid balance for 24 h from the start of surgery (ml)	3610 (2443–4519)	4226 (3251–5779)***

in another POMS validation study performed at our institution, demonstrated a 5 day increase in length of stay ($P<0.001$) in the 32% of patients unable to tolerate an enteral diet at day 5. Two trials performed at our institution demonstrated significantly different GI morbidity rates at day 5 after operation after major intra-abdominal surgery (63% *vs* 26%). Different fluid therapy regimes were used; in the study by Davies and colleagues,[15] a quicker return of GI function was observed after the administration of goal-directed HES intraoperatively, without any additional crystalloid therapy, whereas in the study by Stone and colleagues,[18] a similar volume of colloid was administered but patients also received an additional 2000 ml of crystalloid during surgery. We hypothesized that this extra volume of crystalloid may have been responsible for the increase in morbidity. Kimberger and colleagues[2] demonstrated a higher tissue oxygen tension and perfusion at the colonic anastomoses in a porcine model receiving goal-directed colloid rather than goal-directed crystalloid and work by both Brandstrup and colleagues[3] and Nisanevich and colleagues[4] demonstrated worse postoperative outcomes as the administered perioperative fluid volumes increased, and in particular as the crystalloid volume increased. Both these studies were unblinded and the results of our study do not support this hypothesis. While patients in the crystalloid group received significantly more fluid, and had a greater 24 h fluid balance, it does not seem to have had any detrimental effect on postoperative outcomes.

Only one previous study has compared colloid with crystalloid in the elective perioperative setting;[19] however, numbers were small, and the trial lacked power to detect differences in complications between the groups. This is the first trial demonstrating that crystalloid alone given in a goal-directed manner is safe even in relatively large volumes.

We used SVV as measured by the LiDCO Rapid to guide fluid therapy. This parameter has been used in our institution for several years with good outcomes for both routine clinical practice and as part of a previous study.[15] While the bulk of the evidence supporting haemodynamic optimization in the perioperative setting has used oesophageal Doppler-based algorithms, emerging evidence would suggest that the use of SVV is a valid and beneficial option.[20–23]

Traditionally, clinicians have been taught that crystalloid solutions distribute across the extracellular compartment but that colloids are maintained intravascularly due to their molecular size. This led to a perception that three times more crystalloid as colloid would be required to achieve similar haemodynamic effects.

In this trial, administration of colloid to crystalloid was in a ratio of 1:1.6 implying that significantly smaller volumes of crystalloid are needed to optimize the circulation than the three-fold increase that was previously proposed. James and colleagues[24] investigated the role of crystalloids and colloids in trauma resuscitation and found a ratio of colloid to crystalloid of 1:1.5 and similarly, the SAFE study[25] demonstrated a

Table 4 Postoperative complications (ORs adjusted for baseline oxygen delivery)

Major complications	HES group ($n=104$)	Crystalloid group ($n=98$)
Anastomotic leakage	5	6
Leakage of the rectum	1	3
Peritonitis without leakage	3	2
Sepsis	13	8
Necrosis of stoma	1	0
Wound dehiscence	4	3
Intestinal obstruction	1	3
Bleeding	10	5
Stroke	0	0
Pulmonary embolism	1	1
Pulmonary oedema	5	2
Acute coronary syndrome	11	4
Ventricular arrhythmias	0	0
Bradycardia	4	2
Renal failure	4	0
Lesion of the ureter	0	0
Minor complications		
Superficial wound infection, haematoma, or dehiscence.	13	15
Paralytic ileus	14	11
Pneumonia	14	8
Pleural effusion	1	1
Minor cardiac dysrhythmia	19	8
Cystitis	9	4
Confusion	17	8
Number of patients with minor complications (%)	46 (44%)	33 (34%) Adjusted OR 1.58 (0.88–2.76)
Number of patients with major complications (%)	26 (25%)	19 (19%) Adjusted OR 1.35 (0.68–2.67)
Number of patients with any complication (%)	48 (46%)	37 (38%) Adjusted OR 1.40 (0.79–2.48)

ratio of 1:1.4 when resuscitating with albumin. It appears that the concept of the 1:3 replacement ratio in hypovolaemic patients is obsolete.

Patients in the HES group required significantly more fluid in the postoperative period. It is possible that the initial 'oncotic benefit' of using HES to keep fluid within the vasculature may be offset by a requirement to give more fluid later as the HES is degraded and fluid redistributes throughout the extracellular compartment.

The magnitude of the systemic inflammatory response after surgery has been shown to be related to the severity of surgical insult.[26] IL-6 is an inflammatory cytokine released predominantly from the colonic circulation at the time of surgery and elevated levels have been associated with worse outcomes.[27] In this study, we did not show any difference between the circulating levels of IL-6, IL-10, or CRP between the two groups. While the administration of i.v. fluid in a goal-directed manner has been demonstrated to reduce the peak inflammatory cytokine levels,[28] it does not appear to matter whether crystalloid or HES is used to achieve these goals.

We undertook this part of the study with reference to work that has since been retracted from the literature that demonstrated a reduction in pro-inflammatory cytokines with HES administration.[29] Our data do not support the hypothesis that the use of HES maintains the splanchnic circulation more effectively and thus reduces inflammation.

Several studies to date have demonstrated both *in vitro* and *in vivo* enhancement of coagulation with crystalloid administration.[30 31] In keeping with this literature, we demonstrated an increase in clot formation time and the MA (a measure of platelet function) that was not apparent in the HES group. No actual coagulopathy was induced with the administration of HES and no increase in thrombotic events was seen in the crystalloid group. It has been suggested that rapid haemodilution causes an enhancement of coagulation *per se* but that this enhancement in the HES group is offset by the inhibition of platelet aggregation by starch molecules.[32]

The strengths of this trial include its low risk of bias. Blinding was maintained throughout and all other perioperative variables were tightly controlled in an attempt to reduce confounding. We

studied a homogenous population of high to moderate-risk patients in an attempt to minimize 'noise' that would be generated by the inclusion of low-risk patients who suffer little postoperative morbidity. The fact that the group was so homogenous means that the results should be extrapolated to other surgical specialities with caution.

In summary, we have demonstrated that HES confers no benefit over crystalloids when used for routine haemodynamic optimization within a goal-directed protocol in the moderate to high-risk colorectal surgical patient. Lower volumes may be required to reach haemodynamic endpoints with HES, but targeted crystalloid administration would appear to be an effective alternative.

Supplementary material

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

Authors' contributions

D.R.A.Y., R.J.T.W., and S.J.D. devised and wrote the protocol. D.R.A.Y., S.J.D., R.J.T.W., and H.E.M. carried out the study and contributed to the data analysis and production of the final manuscript.

Declaration of interest

D.R.A.Y. has received an honorarium from Fresenius Kabi and expenses for lecturing for Fresenius Kabi and LiDCO. H.E.M.: none declared. S.J.D. has received a travel grant from LiDCO. R.J.T.W. has received honoraria and expenses for lecturing for Fresenius Kabi and LiDCO.

Funding

Unrestricted research grant from Fresenius Kabi.

References

1 Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; **112**: 1392–402

2 Kimberger O, Arnberger M, Brandt S, *et al.* Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. *Anesthesiology* 2009; **110**: 496–504

3 Brandstrup B, Tønnesen H, Beier-Holgersen R, *et al.* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens. *Ann Surg* 2003; **238**: 641–8

4 Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Mtot I. Effect of intraoperative fluid management on outcome after intra-abdominal surgery. *Anesthesiology* 2005; **103**: 25–32

5 Treib J, Haass A, Pindur G. Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 1997; **78**: 974

6 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

7 Martin C, Jacob M, Vicaut E, Guidet B, Von Aken H, Kurz A. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology* 2013; **118**: 387–94

8 Van Der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. *Anesth Analg* 2013; **116**: 35–48

9 Perel P, Roberts I, Pearson M. Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review). *Cochrane Database Syst Rev* 2007, Issue 4. Art. No.: CD000567

10 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

11 Snowden CP, Prentis J, Jacques B, *et al.* Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg* 2013; **257**: 999–1004

12 Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34

13 Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901–11

14 Steppan J, Hofer S, Funke B, *et al.* Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalyx. *J Surg Res* 2011; **165**: 136–41

15 Davies SJ, Yates DRA, Wilson RJT. Dopexamine has no additional benefit in high-risk patients receiving goal-directed fluid therapy undergoing major abdominal surgery. *Anesth Analg* 2011; **112**: 130–8

16 Grocott MPW, Browne JP, Van der Meulen J, *et al.* The Post-Operative Morbidity Survey was validated and used to describe morbidity following major surgery. *J Clin Epidemiol* 2007; **60**: 919–28

17 Davies SJ, Francis J, Dilley J, *et al.* Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. *Periop Med* 2013; **2**: 1

18 Stone MD, Wilson RJ, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; **91**: 619–24

19 Senagore AJ, Emery T, Luchtefeld M, Kim D, Duchovny 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 Colon Rectum* 2009; **52**: 1935–40

20 Benes J, Chytra I, Altmann P, *et al.* Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care* 2010; **14**: R118

21 Mayer J, Boldt J, Mengistu AM, Rohm KD, Suttner S. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care* 2010; **14**: R18

22 Cecconi M, Fasano N, Langiano N, *et al.* Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care* 2011; **15**: R132

23 Ping W, Hong-Wei W, Tai-Di Z. Effect of stroke volume variability-guided intraoperative fluid restriction on gastrointestinal functional recovery. *Hepato-Gastroenterology* 2012; **59**: 2457–60

24 James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth* 2011; **107**: 693–702

25 Finfer S, Bellomo R, Boyce N, *et al.* A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247–56

26 Lin E, Calvano S, Lowry S. Inflammatory cytokines and cell response in surgery. *Surgery* 2000; **127**: 117–26

27 Baigrie R, Lamont P, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; **79**: 757–60

28 Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Colorectal Dis* 2005; **7**(Suppl. 1): 144–51

29 Lang K, Suttner S, Boldt J, Kumble B, Nagel D. Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. *Can J Anaesth* 2003; **50**: 1009–16 (Retracted)

30 Ruttman TG, James MF, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–4

31 Ruttman TG, James MF, Finlayson J. Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. *Br J Anaesth* 2002; **89**: 226–30

32 Ruttman TG, James MF, Aronson I. In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998; **80**: 612–6

Handling editor: M. M. R. F. Struys