

Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery

N. N. Rahbari¹, J. B. Zimmermann², T. Schmidt¹, M. Koch¹, M. A. Weigand² and J. Weitz¹

Departments of ¹Surgery and ²Anaesthesiology, University of Heidelberg, Heidelberg, Germany

Correspondence to: J. Weitz, Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

(e-mail: nuh.rahbari@med.uni-heidelberg.de)

Background: Optimal fluid therapy for colorectal surgery remains uncertain.

Methods: A simple model was applied to define standard, restrictive and supplemental fluid administration. These definitions enabled pooling of data from different trials. Randomized controlled trials on fluid amount (standard *versus* restrictive or supplemental amount) and on guidance for fluid administration (goal-directed fluid therapy by oesophageal Doppler-derived variables *versus* conventional haemodynamic variables) in patients with colorectal resection were eligible for inclusion. The primary outcome measure was postoperative morbidity. Secondary endpoints were mortality, cardiopulmonary morbidity, wound infection, anastomotic failure, recovery of bowel function and hospital stay. A random-effects model was applied.

Results: Nine randomized controlled trials were included. Restrictive fluid amount (odds ratio (OR) 0.41 (95 per cent confidence interval (c.i.) 0.22 to 0.77); $P = 0.005$) and goal-directed fluid therapy by means of oesophageal Doppler-derived variables (OR 0.43 (95 per cent c.i. 0.26 to 0.71); $P = 0.001$) significantly reduced overall morbidity. There were no significant differences in the secondary endpoints analysed.

Conclusion: Using standardized definitions, this meta-analysis suggests that restrictive rather than standard fluid amount according to current textbook opinion, and goal-directed fluid therapy rather than fluid therapy guided by conventional haemodynamic variables, reduce morbidity after colorectal resection.

Paper accepted 28 November 2008

Published online in Wiley InterScience (www.bjcs.co.uk). DOI: 10.1002/bjcs.6552

Introduction

In the late 1990s, Henrik Kehlet introduced a comprehensive concept of perioperative care¹. This approach, subsequently referred to as 'enhanced recovery after surgery' (ERAS) or just 'fast track', aimed to lower surgery-related physical and psychological stress. This would be expected to reduce complications which, in turn, should result in a shorter hospital stay. Indeed, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) has demonstrated ERAS programmes in colonic surgery to be safe and efficient in reducing hospital stay².

There is, however, ongoing debate about certain components of this multimodal approach. Optimal perioperative fluid therapy for patients undergoing abdominal surgery and colorectal surgery, in particular, remains controversial. This might in part reflect the known

impact of fluid imbalances on postoperative outcome^{3–5}. Fluid excess may compromise cardiac and pulmonary function, prolong recovery of bowel function, and impair tissue oxygenation, which might ultimately impair wound healing including healing of the anastomosis^{6,7}. Conversely, hypovolaemia may cause microcirculatory disturbances that, in turn, might result in tissue damage and organ dysfunction^{8–10}. There is disagreement about the optimal amount of fluid to be administered as well as the strategy of fluid administration (fluid therapy guided by conventional cardiovascular parameters such as blood pressure and heart rate *versus* goal-directed therapy guided by means of oesophageal Doppler-derived variables aiming for maximum stroke volume).

Current recommendations on perioperative fluid therapy are based on single trials and refer to major general

abdominal surgery rather than to individual procedures, such as colorectal resection^{4,5,7}. Moreover, the disagreement about optimal perioperative fluid therapy for patients undergoing colorectal surgery might, in part, be exacerbated by the lack of uniform definitions of the terms standard, restrictive and supplemental fluid administration. This, in turn, hinders comparisons of published studies¹¹.

On the basis of current guidelines, definitions of the terms standard, restrictive and supplemental fluid administration were generated. Using this standardized nomenclature, a meta-analysis of RCTs was performed to evaluate the impact of infused fluid amount, and guidance by oesophageal Doppler, on outcome after colorectal resection. This allowed procedure-specific recommendations.

Methods

Definitions of the terms standard, restrictive and supplemental fluid administration

Current recommendations for perioperative fluid administration were applied to standardize the terms standard, restrictive and supplemental fluid administration. This enabled the meta-analysis to be performed. *Miller's Anaesthesia*¹² is probably the most highly regarded textbook of anaesthesiology available. It is considered a reference textbook of current knowledge in the field of anaesthesiology¹³. In its latest edition (2005) it recommends fluid administration for patients undergoing major surgery in terms of millilitres per kilogram bodyweight per hour. Consequently, it was decided to derive a reference ('standard') fluid therapy from the textbook on this basis. The book recommends administration of up to 2000 ml fluid to compensate for α 1- and β -blockade, that is predominantly venodilatation (internal loss) caused by neuraxial anaesthesia (preblock hydration). It recommends administration of 5–7 ml per kg bodyweight of balanced salt solution to compensate for the venodilatation and cardiac depression caused by general anaesthesia (compensatory intravascular volume expansion). It recommends administration of 4 ml per kg bodyweight per h for the first 10 kg of bodyweight, 2 ml per kg bodyweight per h for the second 10 kg of bodyweight, and another 1 ml per kg bodyweight per h for every kilogram of bodyweight exceeding 20 kg for every hour of fasting (deficit) and for every hour of surgery (maintenance).

The infusion rate is to be set to deliver three to four times the hourly need until the deficit is replaced. It recommends administration of 4–6 ml per kg bodyweight per h for every hour of surgery for loss to the so-called third space for major bowel resections. Finally,

it recommends administration of 3 ml of balanced salt solution or saline solution for every millilitre of blood lost (external loss) or administration of 1 ml of any colloidal fluid preparation. The recommendation for administration of up to 2000 ml fluid for preblock hydration is based on literature dating back to 2001 recommending either the administration of 250–2000 ml of any crystalloid solution or the administration of at least 500 ml of any colloidal fluid preparation, with a tendency towards the latter¹⁴.

Taking biophysical and biochemical properties of both body fluids and different fluid preparations into account, as well as the tendency towards recommendation of administration of colloidal fluid preparations for preblock hydration and the features of the different regimens applied to the patients treated within the studies included in the subsequent meta-analysis, standard fluid therapy for patients undergoing major bowel resections was considered to consist of the following: administration of 10 ml per kg bodyweight of any colloidal fluid preparation for preblock hydration where applicable; administration of 5–7 ml of any crystalloid solution for compensatory intravascular volume expansion; administration of 4 ml per kg per h for the first 10 kg, 2 ml per kg per h for the second 10 kg and 1 ml per h for each additional kilogram bodyweight for deficit and maintenance; administration of 4–6 ml per kg bodyweight per h for loss to the so-called third space; and administration of either 3 ml of any crystalloid solution or 1 ml of any colloidal solution for every millilitre of blood lost.

Standard fluid therapy for patients undergoing large bowel resection is summarized in *Table 1*. An additional 10 per cent of the calculated mean is added to the calculated ranges for possible measurement inaccuracies regarding amount of blood lost and fluid administered. Any approach to perioperative fluid therapy resulting in larger amounts of fluid administered, that is larger than the calculated ranges plus 10 per cent, is considered supplemental. Any approach to perioperative fluid therapy resulting in smaller amounts of fluid administered, that is smaller than the calculated ranges minus 10 per cent, is considered restrictive.

Systematic literature search

A systematic literature search of Medline (1966 to November 2007 via Ovid), Embase (1974 to November 2007 via Ovid) and The Cochrane Library (2007, issue 3) was conducted using validated methods of The Cochrane Collaboration¹⁵ and the QUOROM statement¹⁶. The search strategy consisted of a highly sensitive filter for detection of RCTs and the following keywords without any language restriction: major surgery, abdom* surgery,

Table 1 Fluid management according to current textbook opinion¹²

	Crystalloid solutions
Compensatory intravascular volume expansion (with epidural anaesthesia) (ml)	Bodyweight (kg) × 10 (ml/kg)
Compensatory intravascular volume expansion (without epidural anaesthesia) (ml)	Bodyweight (kg) × 5–7 (ml/kg)
Deficit (ml/h)	(Bodyweight + 40) (kg) × 1 (ml/kg/h)
Maintenance (ml/h)	(Bodyweight + 40) (kg) × 1 (ml/kg/h)
Third space (ml/h)	Bodyweight (kg) × 4–6 (ml/kg/h)
Blood loss (ml)	3:1 (volume: volume)*

*1:1 (volume: volume) for colloidal solutions.

colon resect*, colon* surgery, rect* resect*, rect* surgery, colorect* resect*, colorect* surgery, crystall* fluid, cristall* fluid, colloid* fluid, colloid* administration, crystall* administration, fluid restrict*, restrict* fluid management, volume replacement, fluid titration, Doppler, liberal fluid administration. Reference lists of relevant articles were screened for additional trials. In addition, investigators and experts in the field of colonic surgery and anaesthesiology were contacted.

Study selection, data extraction and quality assessment

Published and unpublished studies that met the following criteria were eligible for inclusion: (1) RCT, (2) evaluation of different fluid amounts administered during and after surgery (standard fluid amount compared with restrictive and supplemental fluid), (3) evaluation of fluid administration strategies guided by conventional haemodynamic variables compared with goal-directed fluid therapy by means of oesophageal Doppler-derived variables, (4) at least 50 per cent of the study population underwent elective surgery of the colon and/or rectum. Paediatric trials and studies comparing endoscopic or laparoscopic techniques alone or against each other were excluded.

Two reviewers (N.N.R., T.S.) independently screened the search findings for potentially relevant studies. In situations of uncertainty full papers were obtained. Selected articles were assessed independently for detailed evaluation. Any disagreements regarding selected articles and extracted data were resolved by discussion with two additional authors (J.B.Z., J.W.). Authors of the primary studies were contacted if information was missing or unclear.

Quality assessment of included trials was carried out using a modification of a previously applied scoring system^{17,18}, which meets international recommendations^{19,20}.

The following items were evaluated: sample size calculation, generation of allocation sequence, allocation concealment, efficacy of randomization, blinding, and description of protocol deviations, withdrawals and dropouts.

Definition of study groups and outcome parameters

Trials were grouped into two categories: RCTs assessing the amount of fluid substitution and those assessing the fluid administration strategy (conventional haemodynamic guidance *versus* goal-directed fluid therapy by means of oesophageal Doppler-derived variables) in patients undergoing colorectal resection. The first category was further subdivided into trials comparing standard fluid amount with restrictive amount and those comparing standard amount with supplemental fluid. Based on the algorithm detailed above, the 'standard' fluid volume for each study group was calculated separately. Depending on the volume actually administered, each study group was classified using the proposed definitions for restrictive and supplemental fluid. Meta-analyses were carried out for studies comparing standard with restrictive fluid administration and those comparing standard with supplemental fluid administration.

The primary outcome measure was postoperative morbidity, defined as the number of patients who developed at least one complication after surgery. Secondary outcomes were in-hospital mortality (death in hospital from any cause), recovery of bowel function (time to first flatus and time to first bowel movement) and hospital stay. To obtain a more precise estimate of the underlying causes of morbidity, cardiac (cardiac failure, myocardial infarction and arrhythmia) and pulmonary (respiratory failure, pulmonary oedema, pneumonia and pleural effusion) complications, incidence of (clinically apparent) anastomotic leakage and wound infections were analysed separately.

Data analysis

Meta-analyses were carried out using Review Manager, version 4.2 for Windows® (The Cochrane Collaboration, Oxford, UK) and a random-effects model for more conservative estimates^{21,22}. The measures of effect were odds ratio (OR) for dichotomous data and weighted mean difference for continuous data, both with 95 per cent confidence intervals (c.i.s). Data presented as median (range) were not included in meta-analyses, as methods for meta-analysing skewed data are not available at present and calculation of c.i.s on the basis of ranges is discouraged¹⁵. All results were checked for clinical and statistical heterogeneity. Inconsistent or missing information on study interventions, concomitant care and study populations were considered as sources of clinical heterogeneity. Statistical heterogeneity was evaluated using I^2 statistics, with I^2 values up to 25 per cent, up to 50 per cent and above 50 per cent indicating low, moderate and high levels of heterogeneity²³. The following *a priori* sensitivity analyses were considered to assess the effect of trial quality on effect size: allocation concealment (concealed *versus* unconcealed), blinding technique (blinded *versus* unblinded) and patient population (mixed *versus* selected colorectal patients). Analyses for studies assessing amount of fluid administration were stratified for time of study intervention (intraoperative, intraoperative and postoperative, and postoperative period).

Publication bias was evaluated with funnel plot analyses where the treatment effect (OR) is plotted against the standard error. This approach is based on the assumption that the precision of the effect estimate increases with the sample size. So effect estimates from small studies scatter more widely at the bottom of the graph, whereas those from large studies taper at the top. If there is no publication bias, the plot resembles an inverted funnel. The validity of this analysis is limited; if the corresponding meta-analysis includes a small number of studies with small sample size the remaining risk of bias should be considered²⁴.

Calculation of the number of patients needed to treat (NNT with 95 per cent c.i.) in order to prevent one patient with complications was carried out using the formula $NNT = 1/(RRR \times CER)$ where RRR is the summary relative risk reduction and CER the control event rate for all trials.

Results

Nine randomized controlled trials with a total of 971 patients met the eligibility criteria (Fig. 1). Six trials investigated amount^{25–30} (Appendix 1 and Appendix 2, supporting

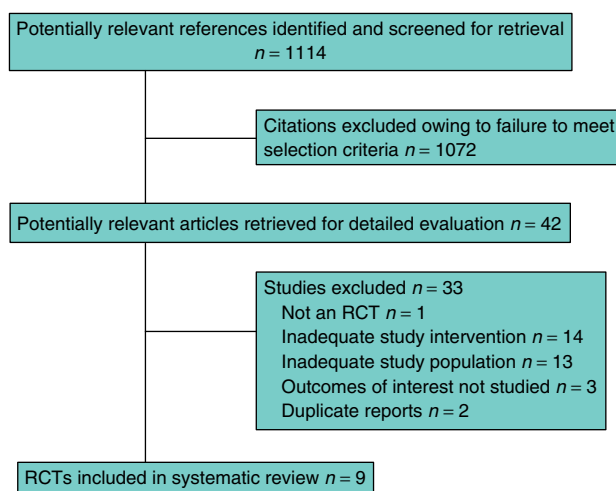


Fig. 1 Number of abstracts and articles identified and evaluated during the review process (modified flow chart according to QUOROM)¹⁶. RCT, randomized controlled trial

information) and three trials goal-directed fluid therapy by means of oesophageal Doppler-derived variables^{31–33} (Appendix 3, supporting information). Quality assessment revealed moderate to high quality of included studies (quality score range 8–10) (Appendix 4, supporting information).

Based on the predefined criteria three of the four trials investigating intraoperative fluid therapy were reclassified (Tables 2 and 3, Fig. 2). In the trial of Brandstrup and colleagues²⁶ the treatment groups had been classified and denoted in agreement with the proposed definitions. In the trial of Nisanevich and co-workers²⁷ the treatment groups had been denoted as 'restrictive protocol group' and 'liberal protocol group', whereas 'restrictive' and 'standard' would have met the definitions. In the trial of Kabon *et al.*²⁸ the treatment groups were denoted as 'small volume' and 'large volume', whereas 'standard' and 'supplemental' would have met the definitions. The greatest deviation between the authors' denotation and the proposed definitions was noted for the trial of Holte and colleagues³⁰. In this trial the treatment groups had been named 'restrictive fluid' and 'liberal fluid', whereas 'standard' and 'supplemental' would have agreed with the definitions.

The trial by Nisanevich and co-workers²⁷ included patients undergoing elective abdominal surgery. The remaining eight trials included patients with colorectal resections only. Identified studies were conducted in different countries (Denmark, Israel, Italy and the UK) and were published between 2002 and 2007. All studies reported power calculations, though using different primary endpoints. Thus, the sample size varied

Table 2 Raw data from individual studies assessing intraoperative fluid amount used for calculation of fluid administration according to current textbook opinion¹²

	Bodyweight (kg)	Duration of fasting and fluid substitution	Duration of anaesthesia (min)	Duration of surgery (min)	Blood loss (ml)	Comments
Brandstrup <i>et al.</i> ²⁶	70†	8 h‡				Bowel preparation unclear All epidural
Restrictive fluid		Substituted for by 500 ml 5 per cent glucose in water i.v.	240§	180 (90–360)*	400 (0–4530)*	
Standard fluid		Substituted for by 500 ml NS i.v.	240§	180 (120–390)*	500 (0–1600)*	
Nisanevich <i>et al.</i> ²⁷		Midnight to start of surgery (8 h‡)				Bowel preparation All epidural (not used during surgery)
Restrictive fluid	71.5(14.6)	Substituted for by 1000 ml 5 per cent dextrose in 0.45 per cent NS i.v. in both groups	328§	268(112)	400 (50–2100)*	
Liberal fluid	68.2(3.5)		311§	251(91)	440 (50–1800)*	
Kabon <i>et al.</i> ²⁸		At least 8 h				Bowel preparation No epidural (postoperative PCA)
Small volume	77(18)	Substituted for by 2 ml/kg/h i.v. in both groups	216§	156(66)	333(349)	
Large volume	78(17)		216§	156(60)	322(331)	
Holte <i>et al.</i> ³⁰		Midnight to start of surgery (8 h‡)				No bowel preparation All epidural
Restrictive fluid	73.3 (47–98)*	Substituted for in both groups by glucose drink (400 ml in the evening and 400 ml in the morning)	166 (116–262)*	119 (77–198)*	200 (10–980)*	
Liberal fluid	69.7 (49–90)*		174 (142–228)*	121 (88–182)*	305 (0–1600)*	

Values are mean(s.d.) unless indicated otherwise; *values are median (range). †If not available, 70 kg assumed; ‡if not available, 8 h assumed; §if not available, 60 min in addition to duration of surgery assumed. i.v., Intravenous; NS, normal saline; PCA, patient-controlled anaesthesia.

considerably within assessed comparisons (20²⁵ to 253²⁸ patients among studies on fluid amount and 57³¹ to 128³² patients among studies on guidance by means of oesophageal Doppler-derived variables). Seven trials reported standardized perioperative treatment^{26–30,32,33}. Postoperative management was at the discretion of the care providers in the trials by Lobo *et al.*²⁵ and Conway and co-workers³¹, with commencement of solid food intake representing an outcome variable. Funnel plot analyses did not indicate any relevant publication bias (*Appendix 5*, supporting information).

Standard versus restrictive fluid administration

Three of the four trials assessing restrictive fluid administration exclusively recruited patients undergoing colorectal resections^{25,26,29}. One study evaluated restrictive fluid administration for the intraoperative and postoperative period²⁶, whereas the remaining studies did so only for the intraoperative²⁷ or postoperative^{25,29} period.

Data on overall morbidity, the primary endpoint of this systematic review, were available for all four trials adding up to a total sample size of 393 patients. Meta-analysis of these trials yielded a statistically significant reduction of postoperative morbidity in favour of restrictive fluid administration (OR 0.41 (95 per cent c.i. 0.22 to 0.77); $P = 0.005$; $I^2 = 36.8$ per cent). Six patients (NNT 6 (95 per cent c.i. 4 to 17)) would have had to receive restrictive fluid administration in order to prevent one patient with complications. Sensitivity analyses revealed moderate heterogeneity to be caused by one trial²⁵. Excluding the data from this trial removed the heterogeneity (OR 0.45 (95 per cent c.i. 0.28 to 0.72); $P < 0.001$; $I^2 = 0$ per cent).

Stratified analysis for time of study intervention confirmed the positive effect of restrictive fluid administration if the treatment included the intraoperative period (intraoperative or intraoperative and postoperative fluid restriction). There was no statistically significant reduction in overall morbidity if fluid restriction was withheld until the

Table 3 Calculation of fluid administration according to current textbook opinion

	Deficit/maintenance (duration of fasting + duration of anaesthesia) (ml)*	Compensatory intravascular volume expansion (with epidural anaesthesia)(ml)	Compensatory intravascular volume expansion (without epidural anaesthesia)(ml)	Third space (duration of surgery) (ml)	Blood loss (ml)	Fluid management according to textbook opinion
Brandstrup <i>et al.</i> ²⁶						
Restrictive fluid	CrF 1320	CrF 700		CrF 840–1260	CrF 1200 CoF 400	Mixed 3260–3680
Standard fluid	CrF 1320	CrF 700		CrF 840–1260	CrF 1500 CoF 500	Mixed 4360–4780
Nisanevich <i>et al.</i> ²⁷						
Restrictive fluid	CrF 1502	CrF 715		CrF 1278–1916	CrF 1200 CoF 400	CrF 4694–5333
Liberal fluid	CrF 1426	CrF 682		CrF 1141–1712	CrF 1320 CoF 440	CrF 4570–5140
Kabon <i>et al.</i> ²⁸						
Small volume	CrF 1357		CrF 385–539	CrF 801–1201	CrF 999 CoF 333	CrF 3542–4096
Large volume	CrF 1369		CrF 390–546	CrF 811–1217	CrF 966 CoF 322	CrF 3536–4098
Holte <i>et al.</i> ³⁰						
Restrictive fluid	CrF 1220	CrF 733		CrF 582–872	CrF 600 CoF 200	Mixed 2734–3025
Liberal fluid	CrF 1196	CrF 697		CrF 562–843	CrF 915 CoF 305	Mixed 2760–3041

Data are presented as mean or median for each treatment group depending on the data available in the original report. Calculation is based on the proposal for standard fluid therapy (Table 1) and on the data extracted from the original reports (Table 2). *Administration of 4 ml per kg bodyweight for the first 10 kg, 2 ml/kg for the second 10 kg and 1 ml for each additional kilogram in patients weighing more than 20 kg (summing up to bodyweight in millilitres + 40 ml). Individual components (columns 2–6) add up to fluid management according to textbook opinion (column 7). CrF, crystalloid solutions; CoF, colloidal solutions. Holte *et al.* did not report on replacement of blood loss; it was assumed that colloidal fluid preparations were administered for replacement of blood loss.

postoperative period. The *a priori* defined sensitivity analyses were not feasible because the quality of the included studies did not differ significantly.

Meta-analysis of data on postoperative mortality from all four trials yielded no statistically significant difference, neither for the aforementioned subgroups, nor for the combined meta-analysis of all four trials (0.50 (95 per cent c.i. 0.09 to 2.65); $P = 0.42$; $I^2 = 0$ per cent). The summarized effect estimate indicated no difference in incidence of anastomotic leakage between patients receiving standard and restrictive fluid administration (OR 0.88 (95 per cent c.i. 0.31 to 2.55); $P = 0.82$; $I^2 = 0$ per cent). Data on cardiopulmonary complications and wound infections could not be summarized within meta-analyses, as they were available only as total number of events (not provided as number of patients with either complication). Measures of bowel function recovery (time to first flatus and time to first bowel movement) were presented as median (range) and so not suitable for pooled analyses. Two trials^{25,27} reported significantly earlier bowel function recovery in patients receiving restrictive fluid therapy, whereas another study²⁹ found

no statistically significant difference in these measures. Mackay and co-workers²⁹ reported no statistically significant difference in hospital stay between study groups, whereas Nisanevich *et al.*²⁷ reported a significantly shorter hospital stay for patients treated with restrictive fluid administration. Table 4 summarizes the results of the meta-analyses.

Standard versus supplemental fluid administration

Both trials evaluating supplemental fluid administration enrolled patients undergoing colorectal resection only. Data on overall morbidity were only available for one trial³⁰ indicating no statistically significant difference between study groups (OR 0.11 (95 per cent c.i. 0.01 to 1.07); $P = 0.06$). Kabon *et al.*²⁸ provided no data on any of the predefined outcome parameters apart from in-hospital mortality, wound infection rates and hospital stay. Pooled analysis of wound infection rates yielded no statistically significant difference between study groups (OR 0.70 (95 per cent c.i. 0.31 to 1.56); $P = 0.38$; $I^2 = 0$ per cent).

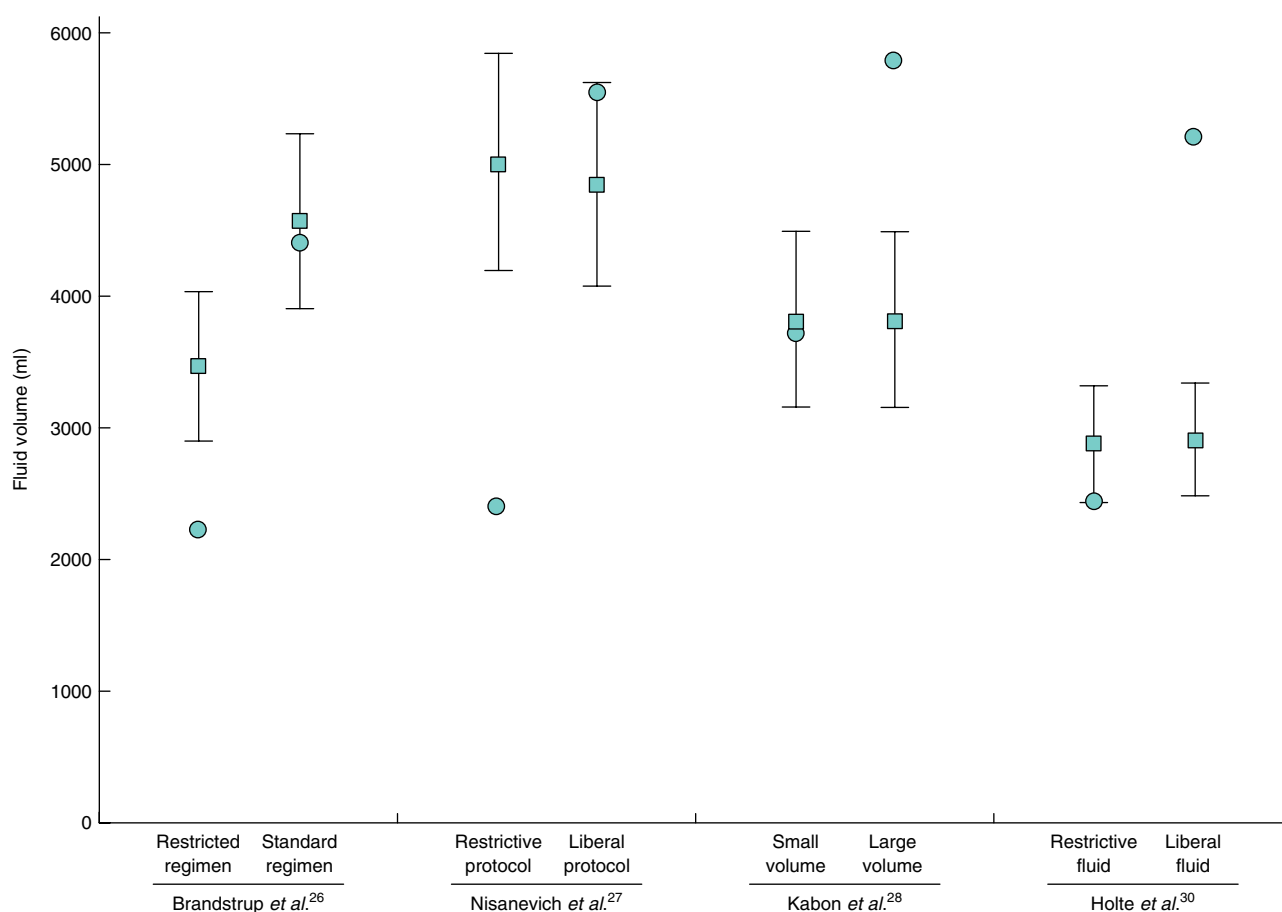


Fig. 2 Calculated fluid amounts compared with actual amount administered in trials evaluating amount of fluid administered until the end of surgery. Squares indicate calculated standard amount of fluid according to current textbook opinion, with error bars representing range. Circles represent actual amount of fluid administered. Differences in calculated fluid amounts between the two study groups in the trial by Brandstrup and colleagues²⁶ are explained by different strategies for replacement of blood loss. Study groups are named as in original publication

Conventional guidance *versus* goal-directed fluid therapy

The three trials on goal-directed fluid therapy by means of oesophageal Doppler-derived variables in patients undergoing elective colorectal resection used a fluid challenge algorithm consisting of repeated boluses of a colloidal fluid preparation until the stroke volume failed to rise by at least 10 per cent. Data on postoperative morbidity were extracted from all three trials adding up to a total sample size of 288 patients. Pooled analysis of these results revealed a statistically significant reduction in postoperative morbidity in favour of oesophageal Doppler guidance (OR 0.43 (95 per cent c.i. 0.26 to 0.71); $P = 0.001$; $I^2 = 0$ per cent). Five patients (NNT 6 (95 per cent c.i. 4 to 12)) would have had to receive goal-directed fluid therapy by

means of oesophageal Doppler-derived variables in order to prevent one patient with complications.

There was no statistically significant difference in in-hospital mortality between groups (OR 0.32 (95 per cent c.i. 0.03 to 3.17); $P = 0.33$; $I^2 = 0$ per cent). Anastomotic failure was reported in two trials and the pooled analysis indicated no statistically significant difference (OR 0.35 (95 per cent c.i. 0.05 to 2.31) $P = 0.27$; $I^2 = 0$ per cent). Data on cardiac and pulmonary complications as well as wound infections were available for the trial by Wakeling and co-workers³² only as total number of events. Data on time to first postoperative flatus and time to first bowel movement could not be summarized within meta-analyses, as they were available only as median values. Data on hospital stay were also reported as median values. Two trials^{32,33} reported a significantly shorter hospital stay for

Table 4 Pooled effect estimates of studies assessing fluid amount and strategy of fluid administration for patients undergoing colorectal resection

	Odds ratio	P	I ²
Restrictive <i>versus</i> standard fluid amount according to current textbook opinion			
Any restriction			
Overall morbidity	0.41 (0.22, 0.77)	0.005	36.8
Overall mortality	0.50 (0.09, 2.65)	0.42	0
Anastomotic leakage	0.88 (0.31, 2.55)	0.82	0
Perioperative restriction			
Overall morbidity	0.35 (0.18, 0.70)	0.003	n.a.
Overall mortality	0.11 (0.01, 2.07)	0.14	n.a.
Anastomotic leakage	0.50 (0.12, 2.08)	0.34	n.a.
Intraoperative restriction			
Overall morbidity	0.46 (0.21, 0.99)	0.05	n.a.
Overall mortality	—		
Anastomotic leakage	1.48 (0.24, 9.12)	0.67	n.a.
Postoperative restriction			
Overall morbidity	0.24 (0.02, 3.81)	0.32	76.7
Overall mortality	1.03 (0.14, 7.78)	0.98	0
Anastomotic leakage	3.23 (0.13, 81.79)	0.48	n.a.
Supplemental <i>versus</i> standard fluid amount according to current textbook opinion			
Overall morbidity	0.11 (0.01, 1.07)	0.06	n.a.
Overall mortality	—		
Anastomotic leakage	0.29 (0.03, 3.13)	0.31	n.a.
Wound infection	0.70 (0.31, 1.56)	0.38	0
Goal-directed therapy <i>versus</i> fluid administration guided by conventional cardiovascular parameters			
Overall morbidity	0.43 (0.26, 0.71)	0.001	0
Overall mortality	0.32 (0.03, 3.17)	0.33	0
Anastomotic leakage	0.35 (0.05, 2.31)	0.27	0

Values in parentheses are 95 per cent confidence intervals. I^2 indicates degree of statistical heterogeneity. n.a., Not applicable.

patients treated with goal-directed fluid therapy by means of oesophageal Doppler-derived variables, whereas the third study³¹ showed no statistically significant difference in hospital stay between the two groups.

Discussion

The interdisciplinary issue of optimal perioperative fluid therapy has been investigated for decades. Debate has increased with the introduction of the fast-track concept in the 1990s^{5,34,35}. The present paper has proposed standardized definitions for the terms standard, restrictive and supplemental fluid therapy for the first time. To provide procedure-specific recommendations, meta-analyses of RCTs assessing the amount and strategy of fluid administration for patients undergoing colorectal resection were performed using the proposed definitions. The results suggest that restrictive rather than standard fluid therapy reduces morbidity following colorectal surgery. Similarly, goal-directed fluid therapy by means of oesophageal Doppler-derived variables reduces morbidity compared with guidance by conventional haemodynamic parameters.

In the early 1960s Shires and colleagues³⁴ suggested that surgical trauma reduces functional extracellular volume (ECV) via internal redistribution, and that crystalloid solutions should be infused in order to compensate for these losses to the so-called 'third space'. Their recommendations have had a sustained influence on the daily practice of fluid therapy. Third-space losses are replaced on a millilitre per kilogram bodyweight per hour basis and this has resulted in large volumes being administered to patients undergoing elective surgery. A recent systematic review concluded that the existing evidence for perioperative ECV alterations (reduced ECV) is of low quality and potentially flawed³⁶. The authors suggested that currently administered fluid amounts are in excess to actual needs. The present data do not allow for any statements regarding ECV alterations associated with surgery, yet they provide quantitative evidence that restrictive fluid administration favourably affects outcome after elective colorectal resection. Based on the present results, replacement of fluid loss to the third space with as little fluid volume as possible (if any) seems advisable. Filling up the third space with large amounts of crystalloid

solution in order to prevent this loss seems unwise. It is worthy of note that the favourable effects of restrictive fluid administration seem to occur only if fluid restriction includes the intraoperative period. Prevention of fluid sequestration to the interstitial space and subsequent oedema might serve as a contributing mechanism, although the analyses do not allow any robust statement on this.

Fluid therapy according to rigid rules, such as the fixed regimens for standard, restrictive and supplemental fluid administration, is not adapted to the individual's age, sex, body composition, co-morbidities and hydration status. For this reason, goal-directed fluid therapy by means of oesophageal Doppler-derived variables has been proposed. The results of the individual randomized studies conducted so far, as well as the pooled analysis, consistently reveal this approach to result in a statistically significant reduction in overall morbidity after colorectal resection. These data may well confirm common haemodynamic variables (such as blood pressure, heart rate and central venous pressure) as poor indicators of hydration status³⁷. Moreover, they stress the importance of detecting and correcting fluid deficits early, and hence the relevance of timing of fluid administration, as the actual amount of fluid administered did not differ significantly between treatment groups. This finding is consistent with earlier work showing that volume effects of intravenous fluids are dependent on a patient's intravascular filling status^{38,39}. Previous studies on patients undergoing coronary artery bypass grafting indicated an association between improved perioperative cardiac output and increased gut perfusion⁴⁰. However, there was no statistically significant difference in anastomotic leakage rates between treatment groups. Even though invasive and considered by some as unsuitable for clinical routine use⁴¹, Doppler-guided fluid administration is popular in certain hospitals⁴².

The present results confirm that a fluid challenge strategy guided by oesophageal Doppler-derived variables is justified in patients undergoing colorectal resection. Whether this approach is superior to restrictive fluid administration has not been investigated so far. It needs to be addressed in future studies. As the amount of fluid administered in the treatment groups of the studies on goal-directed fluid therapy did not differ greatly, it seems probable that fluid restriction and goal-directed fluid administration reduce morbidity by separate pathophysiological mechanisms. These remain to be elucidated. Further research is also needed to identify more reliable non-invasive measures to guide fluid therapy.

Meta-analysis has inherent limitations, although it is considered the best available tool for summarizing existing evidence. This study provides a statistical aggregation of

results from RCTs assessing fluid therapy for patients undergoing elective colorectal resection. This was made possible by defining a standard of care to determine definitions of restrictive as well as supplemental fluid therapy. Amount and strategy of fluid therapy were analysed separately. The model of standardized definitions dispenses with the many terms that have been used arbitrarily in the past to refer to different amounts of intravenous fluid therapy; for example the term 'liberal' in the trial of Nisanevich *et al.*²⁷ refers to standard fluid amount, whereas the same term in the trial of Holte and colleagues³⁰ refers to supplemental fluids. If the notations used in the original publications had been adopted, the trials by Brandstrup and colleagues²⁶ (restricted *versus* standard regimen), Nisanevich and co-workers²⁷ (restrictive *versus* liberal), Lobo *et al.*²⁵ (restricted *versus* standard) and MacKay and colleagues²⁹ (restricted *versus* standard) would have been pooled together with the trial by Holte and co-workers³⁰ (restrictive *versus* liberal). Such analysis does not show a statistically significant advantage in overall morbidity for the restrictive fluid group (OR 0.54 (95 per cent c.i. 0.22 to 1.30); $P = 0.17$). Remarkably, inclusion of the Holte trial increased statistical heterogeneity substantially ($I^2 = 65.4$ per cent), potentially indicating that this trial's interventions are less congruent with those of the previously enrolled studies.

Standard intravenous fluid therapy defined in the present paper is derived from a reference textbook and resembles reference intravenous fluid therapy used in common practice. Moreover, a substantial number of the available trials used fixed algorithms based on millilitre per kilogram bodyweight per hour and it appeared justified to follow suit. Although the model may not properly depict the actual need for fluid in the individual patient, it does provide standard recommendations and by this means may be used to define the terms standard, restrictive and supplemental fluid administration. Taking possible measurement inaccuracies regarding amount of blood lost and fluid administered into account, an extra 10 per cent of the calculated mean should be added to the calculated ranges according to current textbook opinion. Although the definitions derived from the algorithm provided in *Miller's Anaesthesia* may not comply with all other textbooks or with all other institutional standards, one specific and generally accepted algorithm has to be chosen and the most renowned textbook was followed. Moreover, the algorithm within this textbook is consistent with the fluid management protocol at the authors' institution.

The decision to set a cut-off value for the proportion of patients who had colorectal surgery in each trial represents a compromise between the following two aims.

First, it was intended to formulate procedure-specific recommendations for patients undergoing colorectal surgery, as opposed to previous articles that dealt with major abdominal procedures in general. Second, available evidence on the topic of perioperative fluid management in colorectal surgery should not be missed or neglected. Based on the selection criteria only one additional study was included²⁷. The proportion of patients who had colorectal resection in this study accounted for 66 per cent in the restrictive and 69 per cent in the standard fluid group. Therefore, inclusion of this study did not distort the results of the analyses and still justifies procedure-specific recommendations for fluid management in colorectal surgery.

Although the proposed definitions refer to fluid administered during surgery, studies focusing on the intraoperative *and* the postoperative period were included deliberately. The rationale was to assess potential benefits of standard, restrictive and supplemental fluid administration as different but integral approaches to perioperative care. However, owing to the potential heterogeneity associated with this strategy the analyses were stratified for the timing of fluid restriction. This revealed that restrictive intravenous fluid administration is beneficial for patients only if fluid restriction is started during surgery. The decision to include the two studies on fluid restriction in the postoperative period^{25,29} in the meta-analyses was supported by the following. First, the intervention and control treatments (administration of a maximum of 2 litres of water and 77 mmol sodium *versus* at least 3 litres of water and 154 mmol sodium) in these two studies were almost identical. Second, the applied treatments are in accordance with postoperative fluid amounts considered restrictive and standard at the authors' institution. Stratified analyses of studies on fluid amount were carried out for timing of study intervention to further reduce clinical heterogeneity. Analyses of the strategy of fluid administration revealed very low heterogeneity supporting robustness of the results.

In summary, the present meta-analysis suggests that, in patients undergoing colorectal resection, restrictive rather than standard fluid substitution reduces postoperative morbidity. Moreover, goal-directed therapy with Doppler-guided fluid challenge rather than conventional haemodynamic guidance similarly results in reduced postoperative morbidity. Neither of these two beneficial strategies appears to influence mortality or incidence of anastomotic failure. The comparison of restrictive and Doppler-guided fluid management appears tempting in the spirit of 'compare the winners'.

Acknowledgements

Supporting information may be found in the online version of this article. The authors thank Dr M. K. Diener for critically reviewing the manuscript. The authors declare no conflict of interest. Drs N. N. Rahbari, J. B. Zimmermann and T. Schmidt contributed equally to this article.

References

- 1 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–617.
- 2 Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT *et al*. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800–809.
- 3 Lobo DN, Macafee DA, Allison SP. How perioperative fluid balance influences postoperative outcomes. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 439–455.
- 4 Boldt J. Fluid management of patients undergoing abdominal surgery – more questions than answers. *Eur J Anaesthesiol* 2006; **23**: 631–640.
- 5 Holte K, Kehlet H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *J Am Coll Surg* 2006; **202**: 971–989.
- 6 Lang K, Boldt J, Suttner S, Haisch G. Colloids *versus* crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 2001; **93**: 405–409.
- 7 Holte K, Kehlet H. Compensatory fluid administration for preoperative dehydration – does it improve outcome? *Acta Anaesthesiol Scand* 2002; **46**: 1089–1093.
- 8 Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Med* 1994; **20**: 99–104.
- 9 Sear JW. Kidney dysfunction in the postoperative period. *Br J Anaesth* 2005; **95**: 20–32.
- 10 Boyd O, Bennett ED. Achieving the goal. *Crit Care Med* 1999; **27**: 2298–2299.
- 11 Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–740.
- 12 Miller RD (ed.). *Miller's Anesthesia* (6th edn). Elsevier Churchill Livingstone: Philadelphia, 2005.
- 13 Teheng R. Books and multimedia of interest. *AANA Journal* 2005; **73**: 417–418.
- 14 Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology* 2001; **94**: 888–906.
- 15 Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0-0* [updated February 2008]. The Cochrane Collaboration, 2008; (<http://www.cochrane-handbook.org>) [accessed 30 May 2007].
- 16 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses

- of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999; **354**: 1896–1900.
- 17 Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003; **37**: 429–442.
 - 18 Rahbari NN, Wente MN, Schemmer P, Diener MK, Hoffmann K, Motschall E *et al.* Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. *Br J Surg* 2008; **95**: 424–432.
 - 19 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
 - 20 Boutron I, Moher D, Tugwell P, Giraudeau B, Poiraudeau S, Nizard R *et al.* A checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) was developed using consensus. *J Clin Epidemiol* 2005; **58**: 1233–1240.
 - 21 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
 - 22 Demets DL. Methods for combining randomized clinical trials: strengths and limitations. *Stat Med* 1987; **6**: 341–350.
 - 23 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
 - 24 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
 - 25 Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; **359**: 1812–1818.
 - 26 Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ørding H, Lindorff-Larsen K *et al.* Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641–648.
 - 27 Nisanevich V, Felsenstein I, Almog G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25–32.
 - 28 Kabon B, Akca O, Taguchi A, Nagele A, Jebadurai R, Arkilic CF *et al.* Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. *Anesth Analg* 2005; **101**: 1546–1553.
 - 29 MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* 2006; **93**: 1469–1474.
 - 30 Holte K, Foss NB, Andersen J, Valentiner L, Lund C, Bie P *et al.* Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth* 2007; **99**: 500–508.
 - 31 Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; **57**: 845–849.
 - 32 Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR *et al.* Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95**: 634–642.
 - 33 Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; **93**: 1069–1076.
 - 34 Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; **154**: 803–810.
 - 35 Moore FD, Shires G. Moderation. *Ann Surg* 1967; **166**: 300–301.
 - 36 Brandstrup B, Svendsen C, Engquist A. Hemorrhage and operation cause a contraction of the extracellular space needing replacement – evidence and implications? A systematic review. *Surgery* 2006; **139**: 419–432.
 - 37 Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 1997; **23**: 276–281.
 - 38 Rehm M, Orth V, Kreimeier U, Thiel M, Haller M, Brechtelsbauer H *et al.* Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. *Anesthesiology* 2000; **92**: 657–664.
 - 39 Rehm M, Haller M, Orth V, Kreimeier U, Jacob M, Dressel H *et al.* Changes in blood volume and hematocrit during acute preoperative volume loading with 5 per cent albumin or 6 per cent hetastarch solutions in patients before radical hysterectomy. *Anesthesiology* 2001; **95**: 849–856.
 - 40 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–429.
 - 41 Jacob M, Chappell D, Rehm M. Clinical update: perioperative fluid management. *Lancet* 2007; **369**: 1984–1986.
 - 42 Mayor S. New approach to surgical care aims to improve recovery and reduce length of hospital stay. *BMJ* 2007; **334**: 816–817.