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Intraoperative Goal-directed Fluid Therapy in Elective Major Abdominal Surgery

A Meta-analysis of Randomized Controlled Trials

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Objectives: To compare the effects of intraoperative goal-directed fluid therapy (GDFT) with conventional fluid therapy, and determine whether there was a difference in outcome between studies that did and did not use Enhanced Recovery After Surgery (ERAS) protocols.

Methods: Meta-analysis of randomized controlled trials of adult patients undergoing elective major abdominal surgery comparing intraoperative GDFT versus conventional fluid therapy. The outcome measures were postoperative morbidity, length of stay, gastrointestinal function and 30-day mortality.

Results: A total of 23 studies were included with 2099 patients: 1040 who underwent GDFT and 1059 who received conventional fluid therapy. GDFT was associated with a significant reduction in morbidity (risk ratio [RR] 0.76, 95% confidence interval [CI] 0.66–0.89, $P = 0.0007$), hospital length of stay (LOS; mean difference −1.55 days, 95% CI −2.73 to −0.36, $P = 0.01$), intensive care LOS (mean difference −0.63 days, 95% CI −1.18 to −0.09, $P = 0.02$), and time to passage of feces (mean difference −0.90 days, 95% CI −1.48 to −0.32 days, $P = 0.002$). However, no difference was seen in mortality, return of flatus, or risk of paralytic ileus. If patients were managed in an ERAS pathway, the only significant reductions were in intensive care LOS (mean difference −0.63 days, 95% CI −0.94 to −0.32, $P < 0.0001$) and time to passage of feces (mean difference −1.09 days, 95% CI −2.03 to −0.15, $P = 0.02$). If managed in a traditional care setting, a significant reduction was seen in both overall morbidity (RR 0.69, 95% CI 0.57 to −0.84, $P = 0.0002$) and total hospital LOS (mean difference −2.14, 95% CI −4.15 to −0.13, $P = 0.04$).

Conclusions: GDFT may not be of benefit to all elective patients undergoing major abdominal surgery, particularly those managed in an ERAS setting.

Keywords: complications, goal-directed fluid therapy, intraoperative, meta-analysis, outcome

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Intraoperative hypovolemia caused by loss of as little as 10% to 15% of blood volume can result in an appreciable fall in splanchnic perfusion, which often outlasts the period of hypovolemia.[1] This results in an intramucosal acidosis of the gut,[2] leading to a cascade of events that impair postoperative gastrointestinal function and cause complications.[3] Postoperative gastrointestinal morbidity in the form of an inability to tolerate oral or enteral tube feeding, nausea, vomiting, and abdominal distension can be responsible for over half of delayed discharges.[4] This concept led to the use of intraoperative goal-directed fluid therapy (GDFT) in which relatively small-volume (200–250 mL) boluses of fluid (usually a colloid) over background crystalloid infusions have been used to increase stroke volume and cardiac output, improve gut perfusion,[1] and decrease gut mucosal acidosis.

A number of methods, including transesophageal Doppler (TED), lithium dilution, arterial pulse contour analysis, thoracic electrical bioimpedance, partial non-rebreathing systems, and transpulmonary thermodilution techniques have been used to measure intraoperative stroke volume and cardiac output and, thereby, help direct fluid therapy.[5] The methods used most frequently in clinical practice are the TED and lithium dilution techniques. The commonest algorithm assesses the change in stroke volume in response to a fluid bolus of 200 to 250 mL infused over 5 to 10 minutes. An increase in stroke volume of more than 10% in response to this bolus signifies hypovolemia and indicates the need for a further bolus. An increase in stroke volume of 10% or less suggests adequate filling and continuation of the background crystalloid infusion without the need for another fluid bolus. A reduction in stroke volume by more than 10% during continued monitoring necessitates a further bolus and repetition of the cycle. Variations in this methodology include monitoring of stroke volume variation and corrected flow time (FTc).[6,7]

Randomized controlled trials and meta-analyses[8–11] published in the first decade of the twenty-first century suggested that intraoperative GDFT resulted in a statistically significant reduction in postoperative complication rates and length of stay (LOS) when compared with patients receiving conventional intraoperative fluid therapy. This led to intraoperative GDFT being recommended as a standard of care by the UK National Institute for Health and Clinical Excellence (NICE).[12] However, postoperative fluid therapy regimens were not clear in most of the early studies, and perioperative care was not standardized. Avoidance of postoperative salt and water overload and maintaining patients in as near a state to zero fluid balance as possible has been shown to reduce both complication rates and length of hospital stay even in patients not receiving GDFT.[13–16] In addition, the use of fast-track or Enhanced Recovery After Surgery (ERAS) protocols,[17,18] which are multimodal perioperative care pathways designed to reduce the metabolic stress of surgery and accelerate postoperative recovery, have resulted in fewer complications [risk ratio 0.5, 95% confidence interval (CI) 0.4–0.7] and

reduction in LOS by 2.5 (95% CI −3.5 to −1.5) days after colorectal surgery when compared with patients managed with traditional care.[19] More recent trials[14,17,18] in which patients have been managed within ERAS protocols with avoidance of postoperative fluid overload have suggested that, although intraoperative GDFT resulted in improvement of cardiovascular variables when compared with conventional fluid therapy, there was no significant difference in clinical outcomes.[14,20,21]

The aims of this meta-analysis of randomized clinical trials of intraoperative GDFT versus conventional fluid therapy in patients undergoing elective major abdominal surgery were to

- compare the effects of intraoperative GDFT with conventional fluid therapy on postoperative complications, length of hospital stay, gastrointestinal function, and mortality.
- determine whether there was a difference in outcome between studies that used ERAS protocols for perioperative care and those that did not.

METHODS

Search Strategy

A search of the PubMed, MEDLINE, Web of Science, Google™ Scholar, and Cochrane Library databases was conducted to identify studies evaluating the impact of intraoperative goal-directed fluid therapy on postoperative elective surgical outcomes in all branches of surgery published in all languages between January 1995 and December 2014. Electronic search terms used were [''goal-directed fluid therapy'' OR ''flow-directed fluid therapy''] AND [''surgery'' OR ''intraoperative''] and the search was limited to adult patients undergoing elective surgery. The bibliography of studies that met the inclusion criteria were also searched for other relevant articles and conference abstracts to ensure study inclusion was as comprehensive as possible. The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22]

Selection of Articles

Full-text articles were screened after exclusion of citations on the basis of article title and abstract. We selected studies if they included adult patients undergoing elective major abdominal surgery who were randomized to receive either GDFT or conventional intraoperative fluid therapy and if the study reported at least 1 relevant postoperative outcome. ''Major abdominal surgery'' included general, vascular, gynecologic, and urologic procedures where the bowel was handled. We excluded studies if they involved patients undergoing non-abdominal surgery such as cardiac, orthopedic, or peripheral vascular surgery, included emergency surgical procedures, did not report any relevant clinical outcome measures, or if both groups received GDFT. One study[23] was excluded due to retraction of a large number of articles by 1 of the authors. We discussed studies where the inclusion criteria were not clear and made a final decision.

Data Extraction

Data were extracted by 1 author (KER) and checked by another (DNL). The primary outcome measure was postoperative morbidity with secondary outcome measures being 30-day mortality, hospital and intensive care LOS, time to return of gastrointestinal function (flatus and feces), and incidence of paralytic ileus. Data were also collated on patient demographics (age, sex, American Society of Anesthesiology [ASA] grade), surgical variables (surgical procedure, number of laparoscopic cases, and estimated blood loss), and intraoperative fluid administration (overall, colloid and crystalloid, and inotrope administration). We noted the method of administration of GDFT and whether patients were managed using ERAS principles (eg, if stated by the authors or having a combination of 4 or more elements such as avoidance of prolonged preoperative starvation, provision of preoperative carbohydrate loading, use of thoracic epidural analgesia, avoidance of premedication, opioids and postoperative fluid overload, and early postoperative feeding and mobilization)[17,18] or traditional care. We contacted the corresponding author on 3 occasions over a 6-week period if the data required were not available in the article. If the authors did not provide the data, the medians and interquartile ranges (IQR) were converted to means and standard deviations (SDs) using the technique described by Hozo et al.[24] This technique uses the median as the best estimate of the mean, and the SD is calculated by the following formula:

$$\mathrm{SD} = \frac{\text{Upper limit of IQR} - \text{Lower limit of IQR}}{1.35}$$

The risk of bias was assessed using the Cochrane Collaboration tool in RevMan 5.3,[25] which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

Statistical Analysis

RevMan 5.3 software[25] was used for data analysis. Dichotomous variables were quoted as a risk ratio (RR) with 95% CI and analyzed using the Mantel–Haenszel random effects model. Continuous variables were quoted as a mean difference using a random effects model with 95% CI and analyzed using the inverse-variance random effects model. Forest plots were constructed and a P value less than 0.05 on 2-tailed testing signified a statistically significant difference. Study heterogeneity and inconsistency was assessed using the I^2 statistic[26]: less than 25%—low heterogeneity, 25% to 50%—moderate heterogeneity, and more than 50%—high heterogeneity. A predetermined secondary analysis was conducted on results obtained when the intervention was delivered within or without ERAS protocols. The quality of the evidence for each outcome was comprehensively assessed and graded using GRADEpro software.[27]

Protocol Registration

We registered the protocol for this meta-analysis with the PROSPERO database (www.crd.york.ac.uk/prospero)—registration no. CRD42014015595.

RESULTS

From 294 studies identified, 23 studies were eligible for inclusion (Fig. 1).[6,7,21,28–47] There were 8 studies based in colorectal surgery,[6,21,36–39,45,46] 1 in upper gastrointestinal surgery,[29] 2 in urology,[34,40] 1 in abdominal vascular surgery,[47] 1 in gynecology,[35] and 10 in a range of abdominal procedures.[7,28,30–33,41–44] The risk of bias in the studies included was low and, in general, study quality was high (see Supplemental Digital Content Table 1, available at http://links.lww.com/SLA/A853). The quality of the evidence for each outcome in the meta-analysis is summarized in Supplemental Digital Content Table 2, available at http://links.lww.com/SLA/A854. Although there was no risk of bias or indirectness for all end-points, there was inconsistency and imprecision for hospital and intensive therapy unit (ITU) LOS.

Demographics

The 23 randomized controlled trials included a total of 2099 patients, of whom 1040 had been randomized to intraoperative

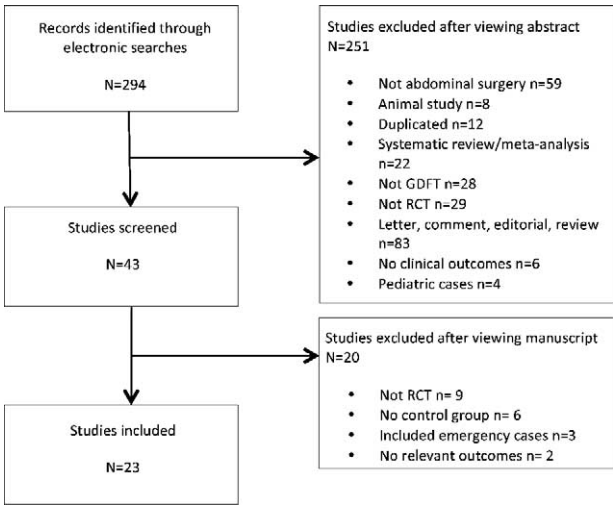

FIGURE 1. PRISMA diagram showing identification of relevant studies from initial search.

GDFT and 1059 to traditional intraoperative fluid management strategies. GDFT was administered as part of an ERAS program in 10 studies[6,21,30,34,36–40,45] and as part of a traditional recovery pathway in 13.[7,28,29,31–33,35,41–44,46,47] The method for administering GDFT in the studies was: TED in 12,[6,7,21,34–40,45,46] hemodynamic parameters from radial arterial line (including lithium dilution) in 9,[29–33,42–44,47] pleth variability index from the pulse oximeter in 1,[41] and a noninvasive cardiac output monitoring device in 1.[28] Patient demographics are detailed in Table 1.

Fluid Therapy

There was some variation in fluid therapy over time (Table 2). One of the earliest studies[7] infused 4405 ± 2650 mL lactated Ringer solution and 847 ± 373 mL 6% hydroxyethyl starch (HES) intraoperatively in the GDFT group versus 4375 ± 2452 mL Ringer and 282 ± 470 mL HES in the control group. In contrast, the most recently published study[21] administered 1500 mL (1000–2000 mL) intraoperative crystalloid and 500 mL (250–750 mL) colloid in the GDFT group versus 1400 mL (1000–1900 mL) and 0 mL (0–300 mL) in the control group.

Morbidity

Eighteen studies[6,7,21,28,31,32,35–39,41,42,44–47] on 899 patients managed with GDFT versus 914 patients with traditional fluid management reported morbidity rates (Fig. 2). These were further divided by whether the patients had been managed as part of an ERAS pathway (866 patients) or as part of a traditional care pathway (947 patients). One study[30] focused on cardiac morbidity alone, but these data are included in the overall analysis. Overall morbidity was significantly lower in patients managed with GDFT versus those in the control group (RR 0.76, 95% CI 0.66–0.89, $P = 0.0007$). When just those managed with GDFT in a traditional care pathway setting were considered, morbidity rates were also significantly lower in the GDFT group when compared with controls (RR 0.69, 95% CI 0.57–0.84, $P = 0.0002$). However, when the GDFT was administered in conjunction with an ERAS pathway, it did not result in a reduction in morbidity risk (RR 0.86, 95% CI 0.70–1.05, $P = 0.14$). The funnel plot for the primary outcome measure of morbidity showed no major asymmetry to indicate a significant bias in either group.

Mortality

Mortality rates were detailed in 18 studies[6,7,21,28,29,32,35,37–47] that included 855 patients in the GDFT group and 870 in the traditional group (Fig. 3). Overall, there was no statistically significant difference in the incidence of mortality between GDFT and control patients, nor was there any difference in those managed with an ERAS pathway or traditional care.

Hospital Length of Stay

Overall hospital LOS was reported in all studies except one[32] included in the meta-analysis (Fig. 4). However, 2 studies[30,34] reported only median (IQR) data, and we were unable to obtain the mean ± SD from the authors. These data were estimated using the technique described by Hozo et al.[24] and all data were included in the analysis of hospital LOS. There were 1043 patients managed in an ERAS setting and 1014 in a traditional setting (Fig. 4). GDFT resulted in a significant decrease in hospital length of stay in the overall group (mean difference −1.55 days, 95% CI −2.73 to −0.36, $P = 0.01$). If patients managed in a traditional care setting were specifically examined, GDFT again resulted in a significant reduction in overall hospital LOS (mean difference −2.14 days, 95% CI −4.15 to −0.13, $P = 0.04$). However, there was no significant difference in hospital LOS in those managed with an ERAS pathway (mean difference −0.71 days, 95% CI −1.91 to 0.49, $P = 0.25$).

Intensive Care Length of Stay

Postoperative LOS in the ITU was reported in 8 studies[28,30,32,41–44,46] (Fig. 4). Again, 3 studies[30,44,46] provided only median (IQR) data; therefore, estimated mean ± SD data were included for these studies. Only 1 study in an ERAS setting reported intensive care LOS,[30] whereas 7 studies in a traditional setting reported this. GDFT resulted in a significant reduction in intensive care LOS (Fig. 4) in all patients (mean difference −0.63 days, 95% CI −1.18 to −0.09, $P = 0.02$) and in the 1 study in which patients were managed with an ERAS pathway (mean difference −0.63 days, 95% CI −0.94 to −0.32, $P < 0.0001$). GDFT, however, made no significant difference to intensive care LOS in those patients managed within a traditional care setting.

Return of Gastrointestinal Function

Eleven studies examined time to return of gastrointestinal function postoperatively, in the form of passage of flatus,[28,31,38] feces,[6,29,33,35,45] or both.[30,39,40] First, considering time to passage flatus in all studies including those with calculated data (Fig. 5), there were 334 patients who were managed with GDFT and 345 in the control group. There was no significant difference in the time to passage of flatus in either the overall group or in those managed in combination with traditional care or an ERAS pathway.

When time to passage of feces was considered, 365 patients were managed with GDFT and 370 with control intraoperative fluid (Fig. 5). GDFT resulted in a significant reduction in time to passage of feces in the overall group (mean difference −0.90 days, 95% CI −1.48 to −0.32 days, $P = 0.002$) as well as those managed with GDFT in combination with an ERAS pathway (mean difference −1.09 days, 95% CI −2.03 to −0.15, $P = 0.02$). However, this difference was not significant in patients managed in a traditional care setting.

Incidence of Postoperative Ileus

Seven studies (707 patients) included data on the incidence of postoperative ileus in 345 patients managed with intraoperative

TABLE 1. Baseline Patient Demographics for All Included Studies

Reference	ERAS or Traditional	Number of Patients		Type of Surgery		Laparoscopic Approach		ASA 1:2:3:4	
		GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control
Pestana 2014[28]	Traditional	72	70	54 colonic, 2 abdominoperineal resection, 11 gastric surgery, 5 other	50 colonic, 3 abdominoperineal, 11 gastric, 6 other	0	0	2:31:37:2	2:34:34:0
Phan 2014[21]	ERAS	50	50	12 right hemicolectomy, 17 anterior resection, 21 other (29 cancer surgery)	14 right hemicolectomy, 22 anterior resection, 1 abdominoperineal, 13 other (34 cancer surgery)	31 (additional 8 converted to open)	28 (additional 8 converted to open)	Median ASA class 2 (1–3)	Median ASA class 2 (1–3)
Zeng 2014[29]	Traditional	30	30	All radical gastric cancer surgery	All radical gastric cancer surgery	Not stated	Not stated	0:31:9:0	0:32:8:0
Zheng 2013[30]	ERAS	30	30	6 gastrectomy, 4 radical gastrectomy for cancer, 7 proctectomy, 9 partial small bowel resection, 4 radical colectomy for cancer	5 gastrectomy, 6 radical gastrectomy for cancer, 6 proctectomy, 7 partial small bowel resection, 6 radical colectomy for cancer	0	0	0:11:19:0	0:13:17:0
Salzwedel 2013[31]	Traditional	79	81	47 bowel, 32 non-bowel	41 bowel, 40 non-bowel	0	0	33 ASA III	33 ASA III
Scheeren 2013[32]	Traditional	26	26	11 major abdominal surgery, 15 radical cystectomy	12 major abdominal surgery, 14 radical cystectomy	Not stated	Not stated	0:0:24:2	0:0:26:0
Ramsingh 2013[33]	Traditional	18	20	8 gyneoncology including TAH/BSO, 5 GI surgery inc. small and large bowel, 3 urologic oncology inc. cystectomy with ileal conduit, 2 Whipple's procedures	9 gyneoncology, 8 GI surgery, 0 urologic, 3 Whipple's procedures	0	0	Not stated	Not stated
Bundgaard-Nielsen 2013[34]	ERAS	21	21	All open radical prostatectomy	All open radical prostatectomy	0	0	14:7:0:0	12:9:0:0
McKenny 2013[35]	Traditional	51	50	51 major gynecologic (36 malignant; 19 ovarian cancer)	50 major gynecologic (36 malignant; 17 ovarian cancer)	0	0	Mean ASA 2.0 (0.6)	Mean ASA 2.0 (0.7)
Srinivasa 2013[36]	ERAS	37	37	14 right hemicolectomy, 4 extended right hemicolectomy, 14 high anterior resection, 5 total/subtotal colectomy	17 right hemicolectomy, 5 extended right hemicolectomy, 14 high anterior resection, 1 total/subtotal colectomy	5	6	5:20:12:0	5:15:17:0
Zakhaleva 2013[38]	ERAS	32	40	24 colectomy, 7 proctectomy, 1 small bowel resection - 16 malignant, 11 benign, 5 inflammatory bowel disease	30 colectomy, 6 proctectomy, 4 small bowel resection - 17 malignant, 19 benign, 4 inflammatory bowel disease	16 + 2 converted to open	19 + 5 converted to open	0:7:26:0	0:7:32:0
Brandstrup 2012[37]	ERAS	71	79	All elective colorectal	All elective colorectal	32, additional 11 converted from laparoscopic to open	38, additional 12 converted from laparoscopic to open	26:37:8:0	20:43:16:0
Challand 2012[39]	ERAS	89	90	32 colonic, 57 rectal (65 carcinoma)	37 colonic, 53 rectal (68 carcinoma)	28	37	11:51:27 (3 + 4)	11:52:27 (3 + 4)
Pillai 2011[40]	ERAS	32	34	All radical cystectomy for bladder cancer	All radical cystectomy for bladder cancer	0	0	Mean ASA class 1.87 (95% CI 1.77–2.04)	Mean ASA class 1.92 (1.08–2.04)

TABLE 1. (*Continued*)

Reference	ERAS or Traditional	Number of Patients		Type of Surgery		Laparoscopic Approach		ASA 1:2:3:4	
		GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control
Forget 2010[41]	Traditional	41	41	7 upper gastrointestinal, 11 hepatobiliary, 24 lower gastrointestinal	5 upper gastrointestinal, 15 hepatobiliary, 22 lower gastrointestinal	5	5	0:22:19:0	0:22:19:0
Benes 2010[42]	Traditional	60	60	17 colorectal, 5 pancreatic, 38 intraabdominal vascular	16 colorectal, 3 pancreatic, 41 intraabdominal vascular	Not stated	Not stated	0:14:37:9	0:11:40:9
Buettner 2008[43]	Traditional	40	40	Elective major abdominal surgery	Elective major abdominal surgery	Not stated	Not stated	Median ASA class 2 (1–3)	Median ASA class 2 (1–3)
Lopes 2007[44]	Traditional	17	16	4 upper gastrointestinal, 3 hepatobiliary, 10 colorectal	4 upper gastrointestinal, 2 hepatobiliary, 8 colorectal, 1 urology, 1 other	Not stated	Not stated	0:3:8:6	0:3:9:4
Noblett 2006[6]	ERAS	51	52	30 colonic, 24 rectal	25 colonic, 29 rectal	13	13	Mean ASA class 2.1 (0.6)	Mean ASA class 2.2 (0.6)
Wakeling 2005[45]	ERAS	64	64	31 anterior and abdomino-perineal resection, 15 left hemi and sigmoid colectomy, 15 right hemicolectomy, 3 reversal of Hartmann's	33 anterior and abdomino-perineal resection, 15 left hemi and sigmoid colectomy, 9 right hemicolectomy, 4 subtotal colectomy, 2 reversal of Hartmann's, 1 Crohn's resection	Not stated	Not stated	Median ASA class 2 (1)	Median ASA class 2 (1)
Conway 2002[46]	Traditional	29	28	All major bowel surgery	All major bowel surgery	Not stated	Not stated	Median ASA class 1 (1–3)	Median ASA class 2 (1–3)
Gan 2002[7]	Traditional	50	50	16 general, 13 gynecology, 21 urology	15 general, 19 gynecology, 16 urology			3:36:11:0	8:32:10:0
Bonazzi 2002[47]	Traditional	50	50	All infrarenal abdominal aortic aneurysm repair	All infrarenal abdominal aortic aneurysm repair	0	0	Not stated	Not stated

A total of 569 males and 400 females in the GDFT arm versus 570 males and 418 females in the control group. Patient sex was not stated in 2 studies.[6,36]

TABLE 2. Intraoperative Fluid Infused in the Goal-directed and Control Groups

	Average Total Fluid Infused (mL)		Average Crystalloid (mL)		Average Colloid Bolus (mL)		Average Blood Loss (mL)		Requirement for Perioperative Inotropes	
Reference	**GDFT**	**Control**	**GDFT**	**Control**	**GDFT**	**Control**	**GDFT**	**Control**	**GDFT**	**Control**
Pestana 2014[28]	2500 (1625–3000)	2325 (1600–3000)	Not stated	Not stated	2.4 boluses ± 1.8*	1.3 boluses ± 1.4*	300 (200–500)	250 (200–400)	18 dobutamine, 5 noradrenaline, 25 ephedrine	1 dobutamine, 4 noradrenaline, 22 ephedrine
Phan 2014[21]	2190 (1350–2560)*	1500 (1200–2000)*	1500 (1000–2000)	1400 (1000–1900)	500 (250–750)*	0 (0–300)*	Not stated	Not stated	Not stated	Not stated
Zeng 2014[29]	2732 ± 488*	3135 ± 346*	Not stated	Not stated	1225 ± 360*	760 ± 280*	482 ± 168	473 ± 156	Not stated	Not stated
Zheng 2013[30]	2650 (2400–3200)*	3950 (2875–4200)*	1550 (1400–1925)*	2350 (2000–2925)*	1000 (900–1100)*	800 (600–1000)*	200 (100–362.5)	200 (100–800)	4 (13.3)	6 (20)
Salzwedel 2013[31]	3854.2 ± 1954.2	3770.8 ± 2827.5	2862 ± 1216	2680.2 ± 1153.8	773.7 ± 664.6	724.7 ± 720.2	668.2 ± 676.6	704.4 ± 889.6	33 dobutamine*, 26 norepinephrine, 0 phenylephrine, 11 ephedrine	0 dobutamine*, 32 norepinephrine, 4 phenylephrine, 8 ephedrine
Scheeren 2013[32]	4477 (2107)	4528 (2387)	Not stated	Not stated	1589 (1283)*	927 (845)*	984 (647)	1118 (1057)	Norepinephrine dosage 0.04 μg/kg/min (0.06)	0.05 μg/kg/min (0.05)
Ramsingh 2013[33]	4082.2 ± 2044*	6845.6 ± 3893.4*	3343.3 ± 1563.7*	5851.5 ± 3197.9*	544.4 ± 493.5	422.5 ± 590.8	Not stated	Not stated	Not stated	Not stated
Bundgaard-Nielsen 2013[34]	Not stated	Not stated	1879 (1205–2052)	1636 (1428–1843)	1758 (1441–2076)*	1057 (778–1336)*	1285 (875–1696)	1152 (774–1530)	Average 9 mg ephedrine (4–13)	Average 15 mg ephedrine (8–22)
McKenny 2013[35]	2620	2881	1000 (787–1750)*	2000 (1725–2500)*	1000 (1000–1500)*	500 (0–1000)*	500 (311–745)	600 (326–1000)	Not stated	Not stated
Srinivasa 2013[36]	1994 (590)*	1614 (420)*	Not stated	Not stated	591 (471)*	297 (275)*	Not stated	Not stated	31 (83.7)	34 (91.9)
Zakhaleva 2013[38]	3100 (700–77000)	4000 (900–6200)	2700 (500–6500)	3200 (500–5600)	500 (0–2800)*	300 (0–4500)*	100 (10–650)	100 (10–500)	Not stated	Not stated
Brandstrup 2012[37]	1876*	1491*	Saline and LR: 483 (419)	443 (480)	810 (543)*	475 (598)*	Not stated	Not stated	Not stated	Not stated
Challand 2012[39]	Not stated	Not stated	3479 (1181)	3593 (1398)	1718 (446)*	336 (623)*	500 (200–1000)*	250 (100–500)*	Not stated	Not stated
Pillai 2011[40]	0.23 mL/kg/min (0.21–0.25)*	0.19 mL/kg/min (0.15–0.2)*	Not stated	Not stated	Not stated	Not stated	9.82 mL/kg (95% CI 7.53–12.12)	10.7 mL/kg (8.42–12.9)	Not stated	Not stated
Forget 2010[41]	2394 (2097–2692)*	2918 (2478–3358)*	1363 (1185–1540)*	1815 (1568–2064)*	890 (709–1072)	1003 (779–1227)	349 (230–468)	440 (242–637)	9 continuous norepinephrine infusion	9 continuous norepinephrine infusion
Benes 2010[42]	Not stated	Not stated	2321 ± 681	2459 ± 930	1425 (1000–1500)*	1000 (540–1250)*	700 (500–1200)	800 (400–1325)	3 (5.88%) norepinephrine, 2 (3.92%) dobutamine	11 (20.37%) norepinephrine, 0 dobutamine
Buettner 2008[43]	6000	5250	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	30	29
Lopes 2007[44]	4618 ± 1557*	1694 ± 705*	2176 ± 1060	1563 ± 02	2247 ± 697*	0*	Not stated	Not stated	Not stated	Not stated

TABLE 2. (*Continued*)

Reference	Average Total Fluid Infused (mL)		Average Crystalloid (mL)		Average Colloid Bolus (mL)		Average Blood Loss (mL)		Requirement for Perioperative Inotropes	
	GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control
Noblett 2006[6]	Not stated	Not stated	2298 (863)	2625 (1004)	1340 (838)	1209 (824)	250 (40–2455)	475 (100–2900)	16 (31)*	26 (50)*
Wakeling 2005[45]	Not stated	Not stated	3000	3000	2000*	1500*	500 (700)	500 (975)	Not stated	Not stated
Conway 2002[46]	64.6 mL/kg (36.4)	55.2 mL/kg (24)	Not stated	Not stated	28 mL/kg (16)	19.4 mL/kg (14.7)	Not stated	Not stated	Not stated	Not stated
Gan 2002[7]	Not stated	Not stated	4405 ± 2650	4375 ± 2452	847 ± 373*	282 ± 470*	703 ± 649	624 ± 632	8 (16)	13 (26)
Bonazzi 2002[47]	4500 (3250–6500)*	3250 (2500–4750)*	Not stated	Not stated	Not stated	Not stated	1000 (450–2750)	1100 (500–2500)	Not stated	Not stated

*Indicates statistically significant difference between GDFT and control groups.

GDFT versus 362 patients in the control group[6,21,28,36–38,40] (Fig. 5). The use of GDFT did not affect the incidence of postoperative ileus significantly in either the overall group or in those managed in combination with either traditional care or an ERAS pathway.

DISCUSSION

This meta-analysis of 23 randomized controlled trials including 2099 patients has demonstrated that, in patients undergoing elective major abdominal surgery, GDFT was associated with a significant reduction in overall morbidity, LOS (both hospital and intensive care), and time to passage of feces when compared with conventional intraoperative fluid therapy when all studies were considered. However, there were no significant differences in short-term mortality, time to passage of flatus, or risk of paralytic ileus.

When the effect of GDFT was considered in the setting of ERAS pathways, which are being implemented increasingly internationally, there was no statistically significant impact on morbidity and mortality, hospital LOS, time to passage of flatus, or incidence of paralytic ileus. A significant reduction in intensive care LOS with GDFT was seen, but this was based on a single study.[30] When the impact of GDFT was considered in the setting of a traditional care pathway, a significant reduction in morbidity and overall hospital LOS was seen when compared with controls, but there was no significant difference in any other outcome considered.

The studies included in this meta-analysis were conducted over a 12-year period during which significant advances have been made in the concept and implementation of ERAS principles and there is evidence that ERAS programs are associated with reduced hospital LOS,[19,48,49] decreased morbidity, and improved cost-effectiveness.[50] The studies were conducted in a variety of surgical specialties which have differing expected LOS; however, if the studies examining colorectal surgery alone are analyzed,[6,21,36–39,45] LOS has declined progressively over a temporal scale from 12.0 ± 7.5 days in 2005[45] to 7.48 ± 3.8 days in 2014.[21] With the ongoing push for decreasing LOS, reinforced by recent reports of 2-day[51] and 23-hour[52] hospital stays for laparoscopic colorectal resection, the margin for overall improvement in LOS provided by GDFT may decrease. Overall heterogeneity was high for LOS (90%) and, although it reduced to 61% for the ERAS group, it was still high. Therefore, it is not certain whether the lack of difference in the LOS in the ERAS subgroup was a time-dependent effect or a reflection of the effect of ERAS pathways.

The other issue raised by the temporal spread of the results is that of the volume of fluid infused intraoperatively. This volume has changed drastically from the earliest to more recent papers, with a progressively greater difference in volume infused between GDFT and conventional fluid management groups, suggesting that the concept and impact of GDFT may have changed during this period. It is possible that, in the early phase of introduction of GDFT, patients were being frequently fluid overloaded intraoperatively. Given that postoperative morbidity is associated in a U-shaped manner with the volume of intraoperative fluid infused,[51] excessive fluid administration in some of these studies may have attenuated some of the potential benefits of GDFT. Further to this, the majority of early studies did not consider the importance of postoperative salt and water overload, which may also have impacted negatively on outcome. In contrast, near-zero fluid balance is considered more carefully in recent studies due to advancing knowledge of the importance of these factors[52] in the perioperative setting. The provision of high–chloride-containing fluids, with the resultant undesirable hyperchloremic acidosis,[53–55] may also have masked some benefits provided by GDFT. Worldwide, there is now a move away from 0.9% saline-based fluids to balanced crystalloids and colloids, and this

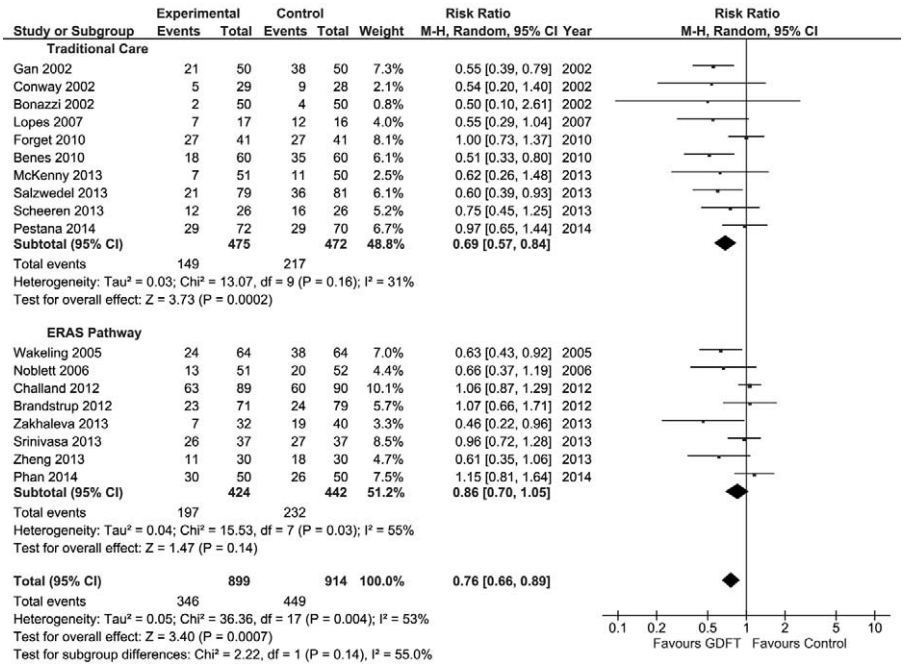

FIGURE 2. Forest plot comparing overall morbidity rate for patients receiving GDFT versus control, divided by those managed using ERAS or traditional principles. A Mantel–Haenszel random effects model was used to conduct the meta-analysis, and risk ratios are quoted including 95% confidence intervals. (Zheng et al., 2013[30] considered cardiac morbidity alone).

may lead to a further improvement in outcomes.[56] One further factor to consider is that different studies have employed different goals for GDFT, and the emphasis of this has evolved over time. In the earlier studies included in this meta-analysis, patients were given fluid boluses if they were fluid responsive, regardless of their hemodynamic status, to maximize stroke volume by pushing patients to the top of their Frank–Starling curve. This approach is likely to result in fluid overload by ''optimizing'' patients to a point where they are no longer fluid responsive rather than assessing ''good enough'' resuscitation. In contrast, more contemporary studies administer bolus fluid only if patients were fluid responsive and had evidence of hemodynamic compromise, which may be reflected in the overall smaller volumes administered in more recent studies where a target of near-zero fluid balance was employed.

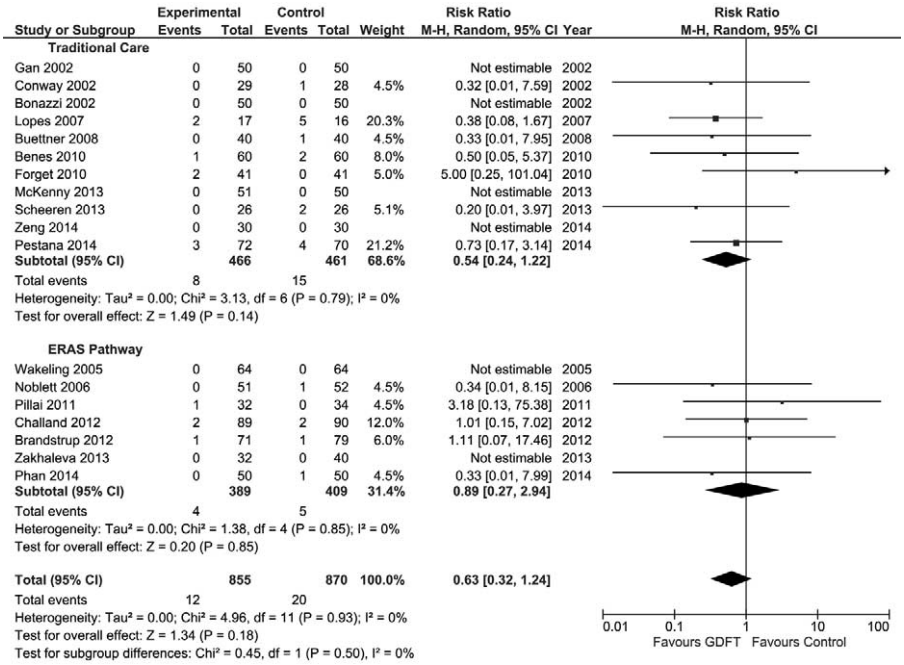

FIGURE 3. Forest plot comparing in-hospital or 30-day mortality rate for patients receiving GDFT versus control, divided by those managed using ERAS or traditional principles. A Mantel–Haenszel random effects model was used to conduct the meta-analysis, and risk ratios are quoted including 95% confidence intervals.

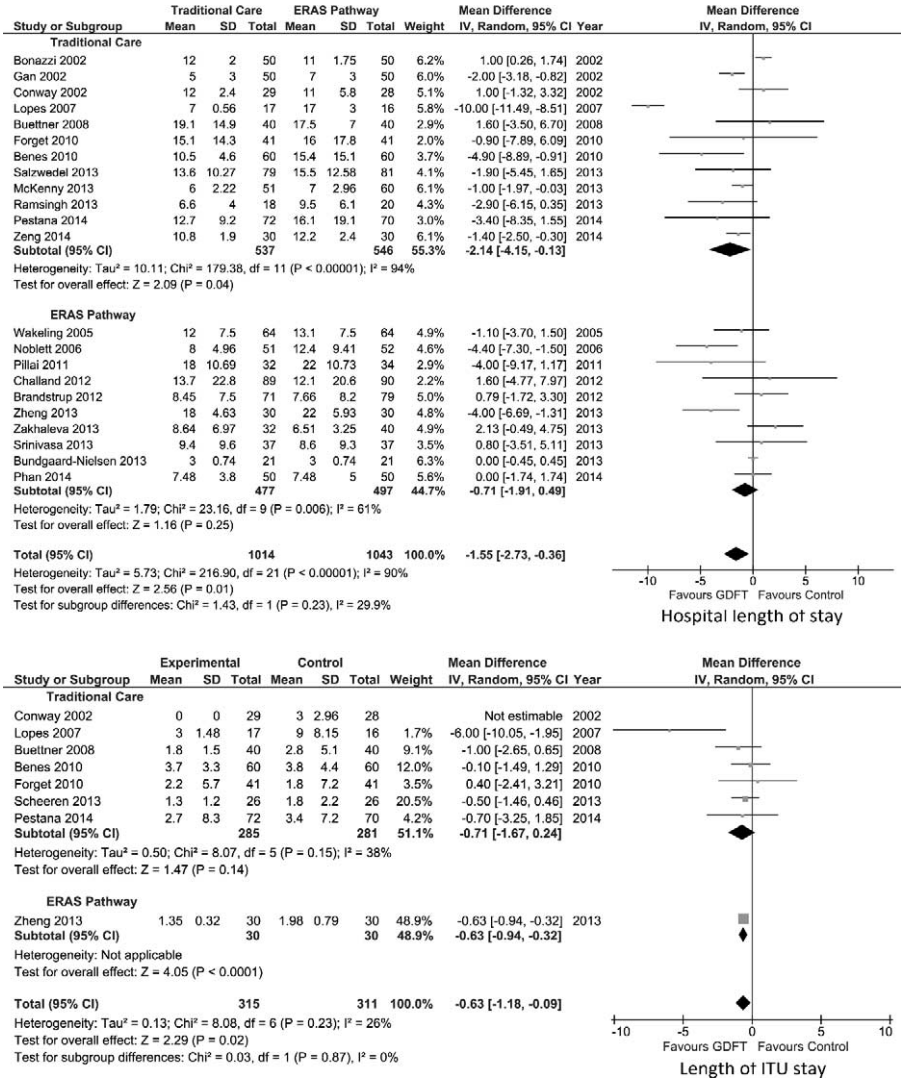

FIGURE 4. Forest plot comparing overall hospital LOS (top) and intensive treatment unit (ITU) LOS (bottom) for patients receiving GDFT versus control including studies with estimated data, divided by those managed using ERAS or traditional principles. An inverse-variance random effects model was used to conduct the meta-analysis, and mean differences are quoted including 95% confidence intervals.

The present study was conducted using rigorous methodology and represents the largest meta-analysis examining the role of GDFT versus conventional intraoperative fluid management in patients undergoing elective major abdominal surgery. Not only did we set out to establish the difference in clinical outcome measures but also at the outset a secondary outcome of comparing those managed within ERAS pathways with those who were managed in traditional care setting was specified. This secondary analysis has resulted in some interesting observations in outcomes between the 2 settings, which appear to differ considerably. A further strength was that to ensure the data were as complete as possible for all studies included, most importantly the mean ± SD data for continuous variables, all authors were contacted on 3 separate occasions requesting the necessary raw data rather than the median (IQR). Unfortunately, not all authors responded to the request for information, and data for several studies [30,34,40,44] were estimated for inclusion in the meta-analysis. This estimation was done using an established method[24] that has been employed in other meta-analyses.

This meta-analysis had several weaknesses inherent in its design and conduct. The methodology for conducting GDFT differed greatly between studies, including TED,[6,7,21,34–40,45,46] hemodynamic parameters from an arterial line,[29–33,42–44,47] pleth variability index from the pulse oximeter,[41] and a noninvasive cardiac output monitoring device.[28] Inclusion of all techniques for conducting GDFT was chosen purposefully to ensure that the conclusions of this meta-analysis were generalizable to different GDFT methods. However, subgroup analyses comparing the various methods was not feasible because of the small numbers of patients who were managed with techniques other than TED or monitoring of hemodynamic parameters from arterial lines. One factor that was not measured consistently between the studies was that of postoperative fluid administration and overall balance, which may significantly impact upon some of the postoperative outcomes. The use of rescue therapy such as diuretics and inotropes is also difficult to discern from the studies. None of the ERAS pathway studies included an assessment of compliance with the ERAS standards, which is particularly important because of the correlation between compliance with the standards and clinical outcomes.[57–59]

There was a large degree of heterogeneity in the studies included in this review. Using the I^2 statistic[26] for the 7 clinical outcomes, 1 outcome had low ($I^2 < 25\%$), 3 had moderate (I^2 25%–50%), and 3 had high heterogeneity ($I^2 > 50\%$). This great variation may have impacted upon the significance of the results. In addition,

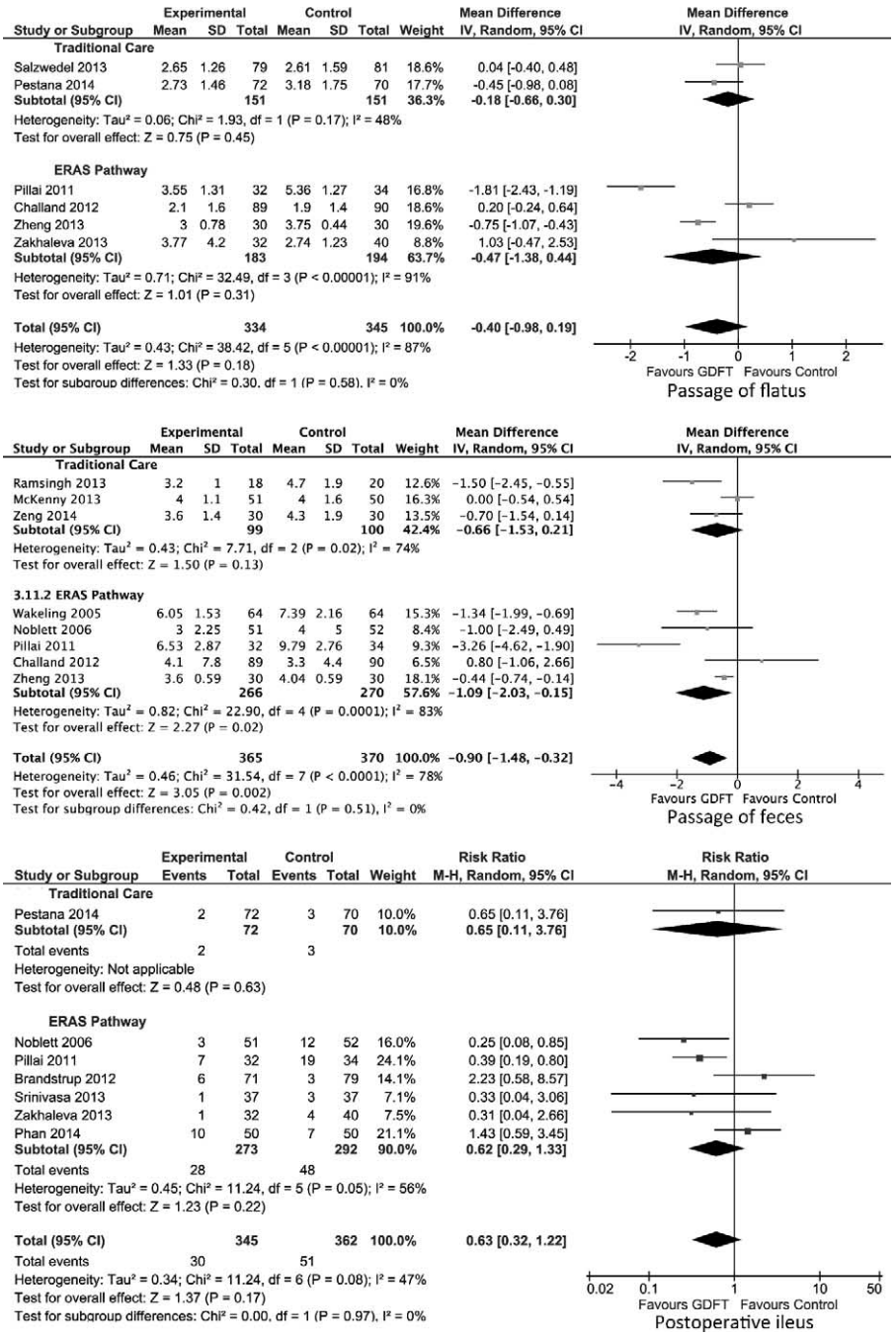

FIGURE 5. Forest plot comparing time to return of flatus and feces and incidence of paralytic ileus for patients receiving GDFT versus control including studies with estimated data, divided by those managed using ERAS or traditional principles. An inverse-variance random effects model was used to conduct the meta-analysis, and mean differences are quoted including 95% confidence intervals. The Mantel-Haenszel random effects model with risk ratios was used for postoperative ileus.

to improve generalizability, we included all studies that included patients who had major abdominal surgery where the bowel was handled. It was also not possible to differentiate the effects of temporal changes in perioperative management algorithms and other treatment interventions such as the use of vasopressors from the effect of GDFT.

NICE guidance[12] released in 2011 on the use of TED-guided fluid therapy has recommended its use ''in patients undergoing major or high-risk surgery or other surgical patients in whom a clinician would consider using invasive cardiovascular monitoring.'' However, this guidance was made mainly on the findings of older studies, some of which were on patients undergoing cardiac and hip fracture surgery and most of which were conducted within a traditional setting of perioperative care. All studies included in the present meta-analysis focused on patients who would meet the criteria for major or high-risk surgery, making this meta-analysis an excellent setting in which to examine the potential benefits of this technique. By comparing the older studies with newer studies that have been conducted using multimodal enhanced recovery perioperative care pathways, we have shown in our meta-analysis that modern perioperative care reduces the impact of GDFT on outcome. This could help inform healthcare providers better and facilitate a more rational

decision-making process before recommending GDFT as ''standard of care.'' Given the unclear benefits of GDFT found in this study, particularly in those managed within an ERAS pathway, it is uncertain whether this recommendation ought to be adopted for all patients undergoing elective major abdominal surgery.

The bolus fluid administered as part of the GDFT protocol in the included studies was variable, with HES being the documented fluid administered in 14 studies.[7,21,28,29,32,34,35,37,39,41–44,46] However, there has recently been a moratorium in Europe on the use of HES due to concerns of increased risk of acute kidney injury requiring renal replacement therapy,[60–62] as well as mortality[60,62] based on recent randomized controlled trials in critically ill patients. Given that much of the evidence in this study, as well as other meta-analyses, are based upon the use of HES as the bolus fluid administered for GDFT, the impact of GDFT using gelatin (or other colloid)-based fluid may differ from current evidence. Further literature[63] has examined the role of balanced crystalloid (Hartmann solution) versus colloid (6% HES) as the bolus agent for GDFT, demonstrating no clinical benefit from colloid in terms of morbidity or coagulopathy. Only 2 of the studies included in this meta-analysis[30,47] administered crystalloid as the bolus agent. Crystalloids may be increasingly utilized in future studies regarding GDFT due to suggested therapeutic equivalence of colloid and crystalloid in combination with concerns with regard to some forms of colloid.

An updated meta-analysis on perioperative administration of fluids, with or without inotropes/vasoactive drugs, targeted to increase blood flow (relative to control) against measured goals in patients undergoing abdominal and extra-abdominal surgery, including emergency procedures showed that patients randomized to a hemodynamic therapy algorithm, had fewer complications and shorter LOS than controls.[64] Nevertheless, the findings of the present meta-analysis for patients managed within ERAS pathways are in agreement with a previous meta-analysis of 6 trials of 691 patients undergoing elective colorectal surgery in which it was shown that TED-guided GDFT did not influence LOS or complications.[65]

However, although the benefits of GDFT on clinical outcomes may be marginal, the presence of an important benefit such as cost savings cannot be ruled out on the basis of this meta-analysis. Further large-scale randomized trials addressing all the issues that we have highlighted, including a cost-effectiveness analysis, are necessary before the real impact of GDFT in elective abdominal surgery is known.

CONCLUSIONS

This meta-analysis has shown that the benefits of GDFT may not be as clear as has been suggested historically. The overall perioperative management of patients has changed during the period of inclusion of studies in this meta-analysis, including decreasing expected hospital LOS, overall decreasing volumes of intraoperative fluid infusion, avoidance of postoperative salt and water overload, and introduction and compliance with ERAS programs. Despite the NICE Guidance[12] which recommends that GDFT technology should be used ''in patients undergoing major or high-risk surgery,'' this study suggests that GDFT may not be of use to all elective patients undergoing major abdominal surgery. The benefit conveyed by GDFT is particularly attenuated by its combination with ERAS pathways that are being increasingly implemented internationally. GDFT may be more of use in the intraoperative care of high-risk patients; however, as yet, there are no definitive data to support this belief.

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