Systematic Review and Meta-Analysis

Medicine®

OPEN

Goal-directed fluid therapy does not reduce postoperative ileus in gastrointestinal surgery

A meta-analysis of randomized controlled trials

Xiongxin Zhang, MD, Wei Zheng, MD, Chaoqin Chen, MD, Xianhui Kang, PhD, Yueying Zheng, PhD, Fangping Bao, MD, Shuyuan Gan, MD, Shengmei Zhu, PhD*

Abstract

Background: Perioperative goal-directed fluid therapy (GDFT) aiming to maintain individual fluid balance based on sensitive parameters was prevalent in major surgery, especially in enhanced recovery after surgery (ERAS) pathway. This meta-analysis was conducted for the purpose of evaluating whether GDFT impacts on occurrence of postoperative ileus and whether its application is worthwhile in gastrointestinal surgery.

Methods: A systematic search of RCTs compared GDFT with other fluid management in patients undergoing gastrointestinal surgery from the PubMed, Web of Science, Embase, Cochrane Library databases was implemented. The primary outcome is incidence of postoperative ileus. Other outcome measures were length of hospital stay (LOS), postoperative morbidity and mortality. Subgroup analysis was planed a prior to verify the definite role of GDFT.

Results: 12 trials consisted of 1836 patients were included in the final analysis. GDFT did not influence the occurrence of postoperative ileus (relative risk, RR 0.71, 95% confidence interval, CI 0.47–1.07, $P = .10$), with moderate heterogeneity ($I^2 = 29\%$, $P = .16$). No difference was found between GDFT and control groups in LOS (mean difference –0.17 days, 95% CI –0.73 to 0.39, $P = .55$), total complication rate (RR 0.92, 95% CI 0.81–1.05, $P = .23$), and 30-day mortality (RR 0.91, 95% CI 0.47–1.75, $P = .77$). In other secondary outcomes, only wound infection rate was lower in the GDFT group (RR 0.68, 95% CI 0.50–0.93, $P = .02$). When performed subgroup analysis, GDFT was superior in reduction ileus only when compared with standard therapy or in those outside ERAS.

Conclusions: It is possible that GDFT dose not affect the occurrence of postoperative ileus in gastrointestinal surgery. It scarcely influences postoperative morbidity and mortality as well. However, lower incidence of ileus is observed in GDFT group either outside ERAS or compared with standard fluid therapy. Probably, GDFT may not be necessary in the ERAS pathway or if a hybrid approach is adopted.

Abbreviations: CIs = confidence intervals, ERAS = enhanced recovery after surgery, FTc = corrected flow time, GDFT = goal-directed fluid therapy, LOS = length of hospital stay, PPV = pulse pressure variation, RCTs = randomized clinical trials, RR = Risk ratio, SDs = standard deviations, SVV = stroke volume variation, TED = transesophageal Doppler, TSA = trial sequential analysis, WMD = weighted mean difference.

Keywords: anesthesia, fluid therapy, gastrointestinal surgery, goal-directed, meta-analysis, postoperative ileus

1. Introduction

Prolonged postoperative ileus is a common complication manifested by nausea and vomiting, intolerance of oral intake, abdominal distention and delayed passage of flatus and feces, especially following abdominal surgery. The incidence of postoperative ileus in colorectal resection is approximate 10%,[1] leading to increased length of hospital stay (LOS), total complication rate and impart clinical and economic burden on healthcare institutions.[2,3] Apart from complicated interaction among neurogenic, humoral and pharmacologic components, fluid and electrolyte management in perioperative period also play a crucial role in pathophysiological mechanisms of ileus. Intestinal edema and stretch resulting from fluid overload can influence smooth muscle relaxation via activating intracellular mediators.[4,5] Therefore, a restricted or "zero-balance" fluid therapy was proposed to replace liberal regimen with the aim of maintaining preoperative body weight while avoiding excess salt and water, which is usually performed by background infusion of balanced solution at 1 to 3 $mL\,kg^{-1}\,h^{-1}$ and additional boluses of fluid are given if necessary.[6] In this circumstance, the demand for fluid probably underestimated as the consumption of fluid boluses or inotrope is still under anesthesiologists discretion based on standard hemodynamic parameters such as blood pressure, heart rate and central venous pressure, which also result in fluid insufficiency and bring about complications. Thus, goal-directed fluid therapy (GDFT) was applied with the purpose of chasing optimized cardiac output according to Frank–Starling

Editor: Chien-Kun Ting.

XZ and WZ contributed equally.

The study is supported by the Projects of Medical and Health Technology Program in Zhejiang Province, China (2018KY069).

The authors declare no conflicts of interest interests.

Supplemental Digital Content is available for this article.

Department of Anesthesiology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Zhejiang, China.

* Correspondence: Shengmei Zhu, Department of Anesthesiology, the First Affiliated Hospital, College of Medicine, Zhejiang University, No. 79 Qingchun Rd., Hangzhou, Zhejiang, China (e-mail: smzhu20088@zju.edu.cn).

Medicine (2018) 97:45(e13097)

Received: 16 January 2018 / Accepted: 4 October 2018

http://dx.doi.org/10.1097/MD.0000000000013097

law or reaching other sensitive goals except for standard parameters.[7] The specific methods used in clinical practice include transesophageal Doppler (TED), lithium dilution, arterial pulse contour analysis, transpulmonary thermodilution techniques, etc. Currently, most frequently used parameters involve stroke volume variation (SVV), corrected flow time (FTc) and pulse pressure variation (PPV).[8]

Though previous studies including meta-analysis revealed the superiority of GDFT,[9–13] while focused on enhanced recovery after surgery (ERAS) pathway, GDFT may not decrease mortality, morbidity and LOS in elective major abdominal surgery.[8] Previous meta-analysis also showed GDFT was facilitated to bowel function recovery and alleviated gastrointestinal dysfunction after operation.[14,15] Nevertheless, the view has been challenged since more recent evidence has not affirmed these results, especially in field of colorectal surgery.[16–22]

On account of these controversial evidence, we conducted this meta-analysis concentrating on the impact of GDFT on specific complication—postoperative ileus in patients undergoing gastrointestinal surgery with the aim to evaluate clinical benefit of this hemodynamic therapy, particularly compared with restrict fluid therapy or in ERAS pathway.

2. Methods

2.1. Search strategy

A systematic search of the PubMed, Web of Science, Embase, and Cochrane Library databases was implemented independently by 2 authors following the PICOS (patient, intervention, comparison, outcomes, study design) strategy according to PRISMA statement. The study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. Last update was in May, 2017. The search terms included medical subject headings and their synonyms associated with GDFT and gastrointestinal surgery, such as "fluid therapy" " fluid management" "stroke volume" "goal directed" "colorectal surgery" " colorectomy" "gastrectomy" "gastroenterostomy" (supplement 1, http://links.lww.com/MD/C619). The references listed in papers which fulfilled inclusion criteria or in related review articles, as well as conference abstracts were also searched to verify the further studies.

2.2. Selection of articles

We selected the studies if they were: randomized clinical trials (RCTs); patients undergoing gastrointestinal surgery were randomized to receive either GDFT or other intraoperative fluid therapy; the incidence of postoperative ileus was reported. Exclusion criteria were: trials were not RCTs; Non-gastrointestinal surgery; trials in which all patients used GDFT or abandoned it; the outcome missed ileus incidence; trials in children who under 18 years old. Non-English papers were also excluded.

2.3. Data extraction

Data were extracted by two researchers independently and were checked by each other. The primary outcome was the occurrence of postoperative ileus. Other major outcomes of interest were LOS, 30-day mortality and total complication rate defined as the percentage of patients who suffered any postoperative complications in 30 days. Fluid administration, wound infection, anastomotic leak, time to first flatus, rate of respiratory, cardiovascular, and neurologic complications were concerned as well. The following data were also collected: first author's name, publication year, type of surgery, primary outcome, American Society of Anesthesiology (ASA) grade and intraoperative fluid administration. Corresponding authors were contacted to obtain missing information. The medians and interquartile ranges were transformed to means and standard deviations (SDs) applying the formula presented by Hozo et al[23] if authors did not provide the data after contacting. The quality of including studies were assessed using the Cochrane Collaboration tool in RevMan 5.3.[24] If disagreement existed, an open discussion would be held to achieve a consensus.

2.4. Statistical analysis

The meta-analysis was accomplished using RevMan Version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). Risk ratio (RR) with 95% confidence intervals (CIs) was calculated for the dichotomous data and weighted mean difference (WMD) of the groups with 95% CIs was calculated for the continuous outcomes, which analyzed with the Mantel–Haenszel random effects model and the inverse-variance random effects model, respectively. The results of RCTs that compared multigroup using GDFT were pooled, using the formula described in the Cochrane Handbook.[24] The inconsistency index (I^2) was calculated using a χ^2-based test of homogeneity: less than 25%–low heterogeneity, 25% to 50%–moderate heterogeneity, more than 50%–high heterogeneity.[25] The cut-off for statistical significance was set at $P < .05$ on 2-tailed testing. A predetermined subgroup analysis was conducted to identify the clinical benefit of GDFT according to whether performed restrict fluid therapy or ERAS program. A sensitivity analysis was held to determine the effect of the single study using leave-one-out approach. Moreover, Publication bias was judged by visual assessment of funnel plots and quantified Egger test using Stata software program 12.0. To further verify whether the evidence of this meta-analysis is reliable, the sample size (required information size) was calculated by applying trial sequential analysis (TSA) with TSA viewer Version 0.9.5.5.[26]

3. Results

A total of 2234 papers were identified after duplicates removal in the original search, among which 2191 papers were excluded via reading titles and abstracts, and then 43 articles were considered for eligibility. After attempting to obtain and read these full-texts, 12 RCTs studies meeting inclusive criteria were selected in this analysis. The PRISMA diagram is shown in Figure 1. The trials included spanned the time from 2006 to 2017. There were 6 studies based on colorectal surgery,[11,16,18,20,22,27] 2 on bowel [12,19] and 4 on a range of gastrointestinal surgery.[13,21,28,29] The risk of bias in studies was low, as presented in Table 1. The overall studies totally enrolled 1836 patients, of whom 926 had been randomly received intraoperative GDFT (GDFT group) and 910 to standard or restrict fluid regimen (control group). The standard therapy emphasized more fluid infusion for the supplement of fluid losses which contained the loss-to-third-space and restricted therapy replaced fluid losses with a goal of zero fluid balance. The specific fluid administration and other characteristics in the studies are summarized in Table 2. The parameters applied in GDFT were: SV, SVV, FTc, PPV measured by TED, or other cardiac output monitoring in 9

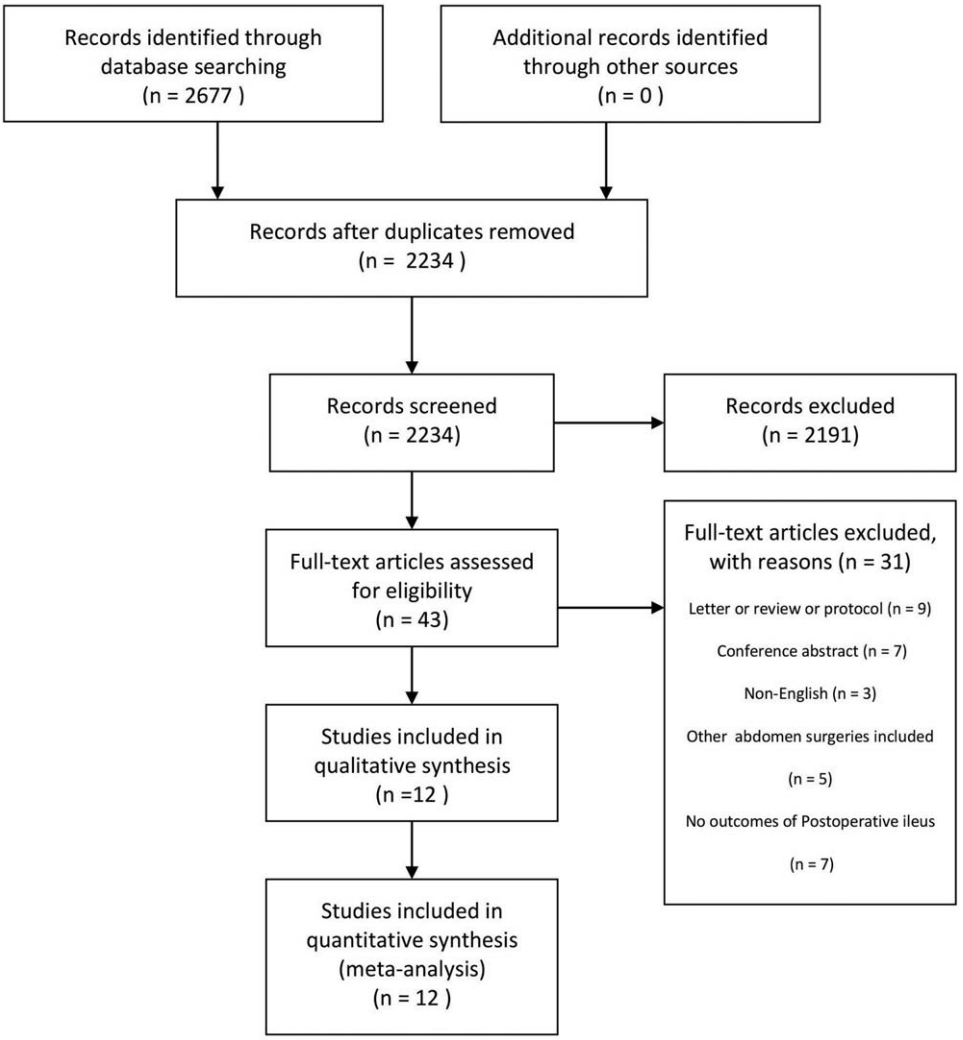

Figure 1. PRISMA diagram describing the identification of studies for the review.

studies,[11–13,16,20–22,28,29] pleth variability index using the pulse oximeter in 1,[27] central venous oxygen saturation in 1,[19] tissue oxygen saturation measured by near-infrared spectroscopy in 1.[18] GDFT was compared with standard [11–14,18,19,21,27,29] or restrict therapy [20,22,28] in 9 and 3 trials respectively. In addition, GDFT was administrated in ERAS pathway in 6 RCTs.[12–14,20,22,27] Only 4 studies applied GDFT after surgery, among which 2 studies[13,21] continued GDFT for 24 hours, 1 study[29] for 6 hours, and 1 study[19] received GDFT until 8: 00 AM on postoperative day 1.

3.1. Postoperative ileus

Intraoperative GDFT did not impact occurrence of postoperative ileus (RR 0.71, 95% CI 0.47–1.07, $P=.10$). The heterogeneity in the results was moderate ($I^2=29\%$, $P=.16$). When sensitive analysis was performed by omitting studies one by one, the result did not significantly change. The funnel plot in Figure 2 showed it roughly symmetric indicating no publication bias existed, which was confirmed by Egger test ($P=.571$). However, when just considered those received standard therapy in control group, GDFT indeed decrease incidence of postoperative ileus (RR 0.59, 95% CI 0.38–0.92, $P=.02$). The similar result was acquired when GDFT was managed out of ERAS pathway (RR 0.47, 95% CI 0.29–0.76, $P=.002$). There was no difference between the GDFT group and control group when GDFT was compared with restrict fluid therapy (Fig. 3) or when it was administered in ERAS pathway (Fig. 4).

3.2. Length of hospital stay

All the included studies reported LOS except one.[18] There were 910 patients underwent GDFT and 902 patients were allotted in the control group. Intraoperative GDFT did not influence LOS in gastrointestinal surgery (mean difference –0.17 days, 95% CI –0.73 to 0.39, $P=.55$). There was moderate heterogeneity ($I^2=37\%$, $P=.10$) and no publication bias was found (Egger test, $P=.641$). Sensitive analysis showed the result was stable. No significant difference was found in LOS between GDFT group and control group when subgroup analysis was conducted (supplement 2, Fig. 1 and Fig. 2, http://links.lww.com/MD/C619).

3.3. Total complication rate

Ten studies except 2[13,27] including 886 patients in the GDFT group and 869 patient in the control group evaluated the effect of

Table 1

Risk of bias of the included studies.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Brandstrup et al[20] (2012)	+	+	+	?	+	?	+
Cohn et al[18] (2010)	+	+	+	+	+	?	?
Forget et al[27] (2013)	+	?	?	+	+	–	?
Gomez-Izquierdo et al[16] (2017)	+	+	+	+	+	?	+
Jammer et al[19] (2010)	+	+	+	+	+	?	+
Noblett et al[11] (2006)	?	?	+	?	+	?	+
Pearse et al[29] (2014)	+	+	?	+	+	+	–
Pestana et al[21] (2014)	+	+	?	+	+	?	–
Phan et al[22] (2014)	+	?	+	+	+	?	?
Zakhaleva et al[12] (2013)	+	?	?	?	–	+	+
Zhang et al[28] (2012)	+	?	?	+	+	+	?
Zheng et al[13] (2013)	+	?	+	+	–	?	–

+ = low risk of bias, ? = unclear risk of bias, – = high risk of bias.

GDFT on 30-day total complication rate. There was no difference between two groups: 326 (36.8%) in the GDFT group and 353 (40.6%) in the control group (RR 0.92, 95% CI 0.81–1.05, $P=.23$), with low heterogeneity between studies ($I^2=11\%$, $P=.34$). No publication bias was found (Egger test, $P=.996$). Sensitive analysis did not change the result. Meanwhile, no significant distinction was detected in total complication rate between 2 groups though subgroup analysis was performed (supplement 2, Fig. 3 and Fig. 4, http://links.lww.com/MD/C619).

3.4. 30-day mortality

A total of 10 studies except 2 [13,18] examined the 30-day mortality, involving 880 and 872 patients in the GDFT group and control group, respectively. GDFT did not decrease 30-day mortality in gastrointestinal surgery between 2 groups (RR 0.91, 95% CI 0.47–1.75, $P=.77$), with no heterogeneity between studies ($I^2=0$, $P=.90$). Publication bias had not been found by Egger test ($P=.109$). Sensitive analysis did not change the result. Subgroup analysis did not found significant difference between 2 groups in 30-day mortality as well (supplement 2, Fig. 5 and Fig. 6, http://links.lww.com/MD/C619).

3.5. Fluid administration

7 studies reported intraoperative total fluid volume administrated.[12,13,16,18,21,22,27] There was no significant difference between two groups (mean difference -442.73 mL, 95% CI –1095.34 to 209.88 mL, $P=.18$) (supplement 2, Fig. 7, http://links.lww.com/MD/C619). However, when omitted the study conducted by Phan et al[22] which considered restricted fluid therapy as control group, the result showed GDFT group received less fluid. Subgroup analysis did not perform because of scarce studies. Two of the above 7 studies still applied GDFT during 24 hours postoperatively. One study[13] administrated 2150 mL (1875–2300 mL) fluid in the GDFT group versus 2100 mL (1900–2225 mL) in the control group and the other one[21] infused 3200 mL (2650–3875 mL) fluid in the GDFT group versus 3100 mL (2750–3800 mL) fluid in the control group postoperatively.

3.6. Other outcomes

Seven of the included studies concerned time to first flatus,[11–13,16,18,21,28] 11 including studies except 1[11] reported anastomotic leak and 10 studies except 2 [11,13] examined wound infection. No significant difference was found between 2 groups in time to first flatus (standard mean difference –0.26, 95% CI –0.54 to 0.02, $P=.07$, $I^2=62\%$) or in anastomotic leak occurrence (RR 0.62, 95% CI 0.39–0.99, $P=.05$, $I^2=0$) (supplement 2, Fig. 8 and Fig. 9, http://links.lww.com/MD/C619). However, the incidence of wound infection in GDFT group was lower in control group (RR 0.68, 95% CI 0.50 to .93, $P=.02$, $I^2=0$) (supplement 2, Fig. 10, http://links.lww.com/MD/C619). Nine,[12,16,18–22,28,29] 11,[12,13,16,18–22,27–29] and 8[12,16,19–22,28,29] studies separately reported the rate of respiratory, cardiovascular, and neurologic complications. There was no significant difference between 2 groups in the rate of respiratory (RR 1.01, 95% CI 0.75–1.36, $P=.95$), cardiovascular (RR 0.90, 95% CI 0.69–1.16, $P=.41$) and neurologic complications (RR 0.89, 95% CI 0.38–2.07, $P=.78$) (supplement 2, Fig. 11, 12, 13, http://links.lww.com/MD/C619). There was no heterogeneity between studies when analyzed three outcomes mentioned above ($I^2=0$).

3.7. Reliability of the compound outcomes

To determine required information size of this meta-analysis in postoperative ileus we hypothesized a 10% control event rate [1] and 32% relative risk reduction (the RRR in our meta-analysis) with 80% power and a 0.05 2- sided α. The calculation result inferred the required information size acquired to find out a convincible GDFT effect on postoperative ileus is 4334, far more than the patients included in actual. Meanwhile, the sequential monitoring boundary has not been crossed as well, suggesting this cumulative evidence is less trustworthy and inconclusive (supplement 3, Fig. 1, http://links.lww.com/MD/C619). Similarly, except for the incidence of wound infection in overall group and ileus in standard fluid therapy or outside ERAS group (supplement 3, Fig. 2, 3, 4, http://links.lww.com/MD/C619), other outcomes were less reliable because of small sample size.

4. Discussion

This meta-analysis of 12 RCTs including 1836 patients showed the result that GDFT did not influence the occurrence of postoperative ileus in patients undergoing gastrointestinal surgery, which in accordance with the conclusion from Gomez-Izquierdo et al[16] who considered postoperative ileus as the primary outcome in their RCT. This review also

Table 2

Summary characteristics of the included studies.

Reference	Types of surgery	Sample size	GDFT group (monitor, fluid management, hemodynamic parameters followed to guide)	Control group (fluid management, hemodynamic parameters followed to guide)	Median ASA grade	Original outcome	ERAS	Fluid restriction in control group
Brandstrup et al[20] (2012)	Colorectal	150	Esophageal Doppler; basic fluid therapy as control group, 200 ml HES bolus if needed; SV	Normal saline at no specific rate if preoperative oral intake < 500 mL, slow infusion of 6% HES (130/400) for blood loss, extra 500 mL if needed, 200 ml colloid bolus if needed; MAP, HR, CVP	II	30-Day complication, mortality	Yes	Yes
Cohn et al[18] (2010)	Colorectal	24	Near-infrared spectroscopy; 2 mL/kg/h LR, 250 mL LR if needed; tissue oxygen saturation, standard hemodynamic parameters	500 mL LR induction bolus, 7 mL/kg in first hour, then 5 mL/kg/h, 250 ml LR if needed; BP, HR, urine output, blood loss	III	30-Day major complication	No	No
Forget et al[27] (2013)	Colorectal	21	Masimo Set; 10 mL/kg crystalloid in first hour, then 2 mL/kg/h, 250 mL6% HES if needed; Pleth Variability Index	10 mL/kg crystalloid in first hour, then 5 mL/kg/h, 250 mL 6% HES if needed; MAP	II	The amount of perioperative fluid	Yes	No
Gomez-Izquierdo et al[16] (2017)	Colorectal	128	Esophageal Doppler; 1.5 mL/kg/h LR, 200 ml HES (130/0.4) if needed; SV	LR; 4/2/1 rule for maintenance, colloid if needed; standard hemodynamic variables	II	Primary postoperative ileus during hospital stay	Yes	No
Jammer et al[19] (2010)	Colorectal	241	central venous blood-gas analyzer; 100 mL/h crystalloid, a bolus of 3 mL/kg HES if needed; central venous oxygen saturation	10–12 mL/kg/h LR, LR or HES (130/0.4) if needed; BP, urine output, blood loss	II	30-Day complication	No	No
Noblett et al[11] (2006)	Colorectal	108	esophageal Doppler; a bolus of 7 mL/kg then 3 mL/kg colloid if needed; FTc, SV	crystalloid or colloid; intraoperative losses and standard hemodynamic parameters	II	LOS	No	No
Pearse et al[29] (2014)	Major gastrointestinal	734	LiDCOrapid; 250-mL colloid boluse if needed; cardiac output, SV	usual perioperative care; CVP, HR, urine output	II	30-Day complication and mortality	No	No
Pestana et al[21] (2014)	Colorectal, gastrectomy, small bowel resection	142	NICOM (a noninvasive cardiac output monitoring); crystalloid following standard procedures, 250 mL colloid if needed; MAP, cardiac index, SV	standard procedures, at the anesthesiologist's discretion	III	LOS and complication	No	No
Phan et al[22] (2014)	Colorectal	100	esophageal Doppler; 5 mL/kg/hr Hartmann's solution, 250 mL colloid if needed; FTc, SVI	5 mL/kg/hr Hartmann's solution, 250 mL colloid if needed; blood loss, BP	II	LOS	Yes	Yes
Zakhaleva et al[12] (2013)	Colorectal	72	esophageal Doppler; 7 mL/kg bolus first then 3 mL/kg colloid if needed; FTc, stroke volume variation	4–8 mL/kg/h crystalloids; blood loss and insensible loss	III	LOS and complication rate	Yes	No
Zhang et al[28] (2012)	Gastrointestinal	60	Datex Ohmeda S/5; 4 mL/kg/h LR, 250 mL boluse of LR or HES (130/0.4) if needed; pulse pressure variation	4 ml/kg/h LR, 250 mL boluse of LR if needed; urine output, CVP, MAP, blood loss	II	LOS	No	Yes
Zheng et al[13] (2013)	Gastrointestinal	60	Vigileo/FloTrac; a bolus of BSS 500 mL or added colloid 250 mL if needed; MAP, SVI, cardiac index, SV	a basal amount of BSS using the 4/2/1 rule, colloid if needed; MAP, blood loss	III	Cardiac complication, LOS	Yes	No

ASA = American Society of Anesthesiology, BBS = balanced salt solution, BP = blood pressure, CVP = central venous pressure, ERAS = enhanced recovery after surgery, FTc = flow time corrected, GDFT = goal-directed fluid therapy, HES = hydroxyethyl starch, HR = heart rate, LOS = Length of hospital stay, LR = lactated ringer's, MAP = mean arterial pressure, SV = stroke volume, SVI = stroke volume index.

demonstrated that GDFT were not associated with the reduction of LOS, 30-day complication rate and mortality. But as mentioned above, the number of patients randomized is much smaller than our calculation. However, GDFT displayed the advantage when subgroup analysis was performed. It indeed decreased the incidence of ileus when compared with liberal fluid therapy or outside ERAS program.

Though it is lacking of exact definition of postoperative ileus in most studies included in this review, the total incidence of 8.7% was close to 10% summarized in previous meta-analysis.[1] It is well known that fluid overload is related to intestinal edema, which can lead to postoperative ileus.[4] GDFT based on individual objective measures is commonly regard as an effective methods to not only avoid excess salt and water but also prevent fluid insufficiency. However, we did not found GDFT group had less intraoperative total fluid administration in this study. It is probably that we did not recognize the lower ileus incidence in GDFT group because of the clinical heterogeneity and small required information size. In fact, when we divided the control group by whether experienced restrict fluid therapy, the heterogeneity between studies became low because the value of I^2 dropped from 29% to 20% in the standard group and zero in the restrict group. Then this subgroup analysis revealed superiority of GDFT in standard therapy. Similar results were found when subgroup analysis were conducted by whether implemented ERAS program, that is, heterogeneity decreased and

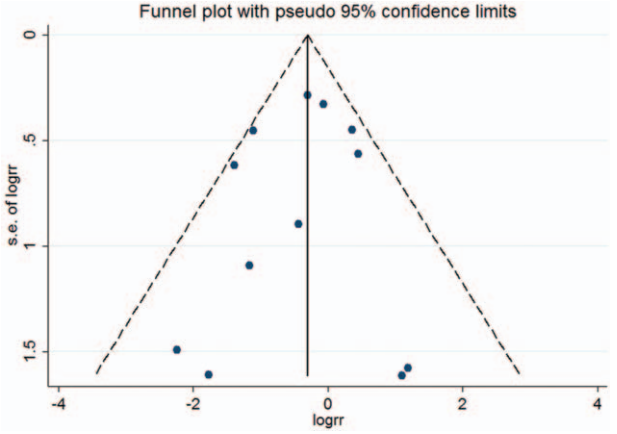

Figure 2. Funnel plot for postoperative ileus. The scatter represents single studies. Log risk ratio (RR), natural logarithm of the RR; SE (log RR), standard error of the log RR.

incidence of ileus was lower outside ERAS. ERAS consisted of multiple interventions for the purpose of accelerating patient's recovery represents a fundamental reform in perioperative management. It emphasizes preoperative optimization such as education, abandon of mechanical bowl preparation, minimized fasting and carbohydrate treatment,[30] which indicates patients arrive at operative room without fluid insufficient thus they may not benefit from GDFT.

Since the exclusive criteria, 7 studies concerned about GDFT in gastrointestinal surgery were discarded owing to absence of reporting ileus occurrence, as shown in Figure 1. Undoubtedly, this incomprehensive meta-analysis for other outcomes were compromised. Nevertheless, the result that there was no difference between GDFT and control groups in LOS, 30-day complication rate and mortality were still relatively reliable as no publication bias were found. In addition, the result is in consistency with the previous meta conducted by Srinivasa et al. which evaluated Doppler-guided fluid management in colorectal surgery.[17] Meanwhile, much earlier meta-analysis of the resemble subject had shown the opposite result yet.[10] The explanation may be we and Srinivasa et al. incorporated more recent trials carried out under more optimized perioperative care and researchers paid more attention on avoiding fluid overload in control group.[17] As listed in Table 1, among including trials, only 1 conducted by Noblett et al[8] were published before 2010. We also noticed that the latest meta-analysis covered a range of major abdominal surgery indicated GDFT facilitated the decrease of LOS and overall morbidity, but their heterogeneity was high (LOS, $I^2 = 90\%$; morbidity, $I^2 = 53\%$). Whereas they found it had no effect on outcomes in those managed combining ERAS program, which in agreement with our results. Unfortunately, we failed to identify the distinguish in LOS and overall morbidity if control group either received liberal fluid therapy or outside ERAS as well, which partly due to incomplete inclusive trials or data (most studies report LOS using medias and interquartile ranges).

As no difference was found in total complication rate, we further examined systematic complications such as respiratory, cardiovascular, neurologic and specific complications such as anastomotic leak and wound infection. Only the occurrence of wound infection was lower in GDFT group. However, this

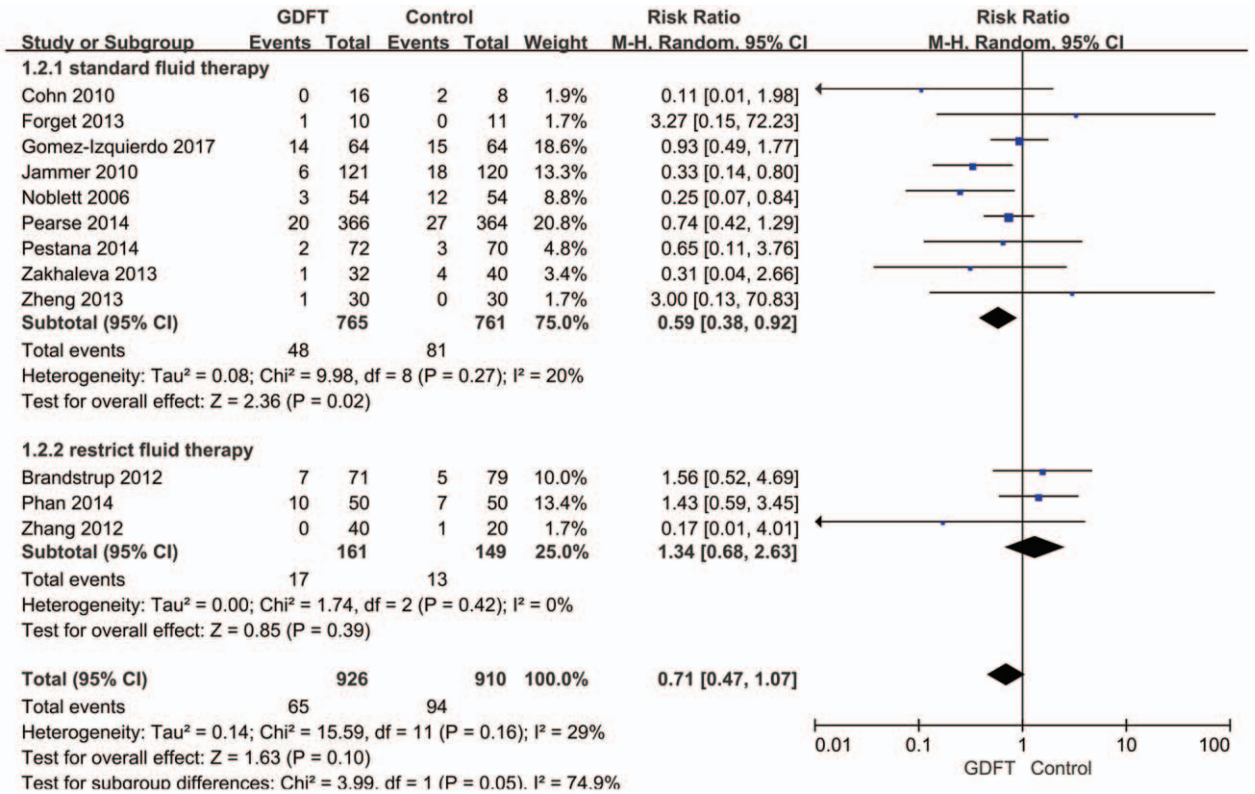

Figure 3. Forest plots of subgroup analysis of comparing postoperative ileus between the GDFT group and the control group in gastrointestinal surgery (GDFT vs standard therapy or restrict therapy).

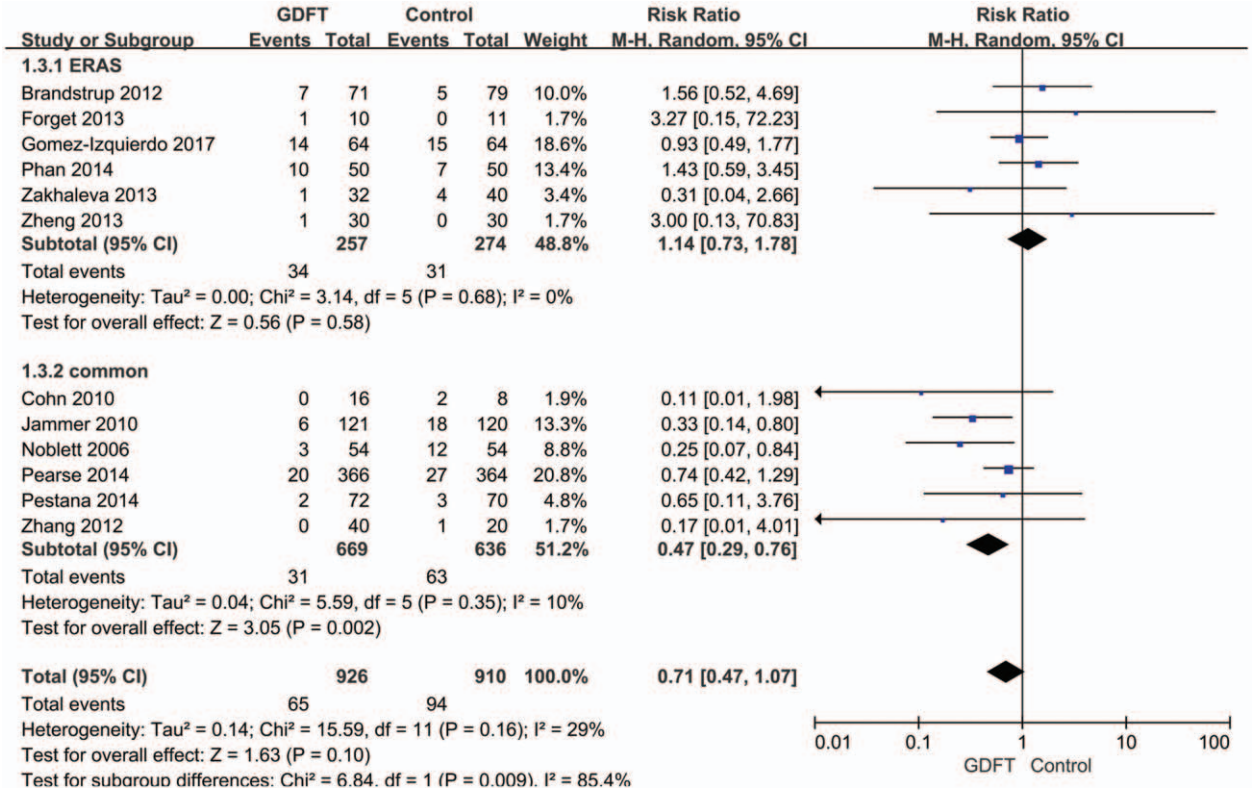

Figure 4. Forest plots of subgroup analysis of comparing postoperative ileus between the GDFT group and the control group in gastrointestinal surgery (GDFT was applied in ERAS pathway or non-ERAS pathway).

superiority disappeared when the study owning the largest sample size was removed.[29] Meanwhile, previous studies had already demonstrated fluid imbalance may impair tissue oxygenation thus delayed wound healing and facilitated infection.[31] Therefore, GDFT may be beneficial to reduce surgical site infections and it was confirmed by recent study.[32] The result of anastomotic leak was also unstable because it had statistical significance when omitted the latest study [16] or the study conducted by Jammer et al. 2010.[19] Allowing for correlation between anastomotic leak and wound infection, this result should be considered with caution. The impact from GDFT on bowel function recovery also had been evaluated by analyzing time to first flatus and negative result was acquired in this review. Despite Gomez-Izquierdo et al[14] had already proved GDFT shortened the time to the first bowel motion, time to tolerate oral intake and reduced postoperative nausea and vomiting after abdominal sugary, they found no difference in time to first flatus as well.

This meta-analysis had several limitations in the design and conduct. First, the specific methods and parameters applied in GDFT are diversified and only 4 studies continued GDFT strategy in the postoperatively period, which increases clinical heterogeneity. Second, 7 trials involving GDFT were excluded for lack of ileus occurrence and 3 trials were excluded because of non-English, which make outcomes analysis incomprehensive and added bias. Third, the number of patients included for most outcomes analysis did not satisfy the required information size we calculated indicating the results were inconclusive.

Although with these weaknesses, this meta-analysis revealed that GDFT probably had no impact on postoperative ileus and other major outcomes in overall groups in gastrointestinal surgery, it was still helpful when compared to liberal fluid therapy or outside ERAS program. Thus, maybe there is no essential applying GDFT in ERAS program or already accepting restrict fluid therapy. Whether GDFT should be recommended as an standard measure in major or high risk surgery requires more cautious consideration because most evidences are based on much earlier trials when the impairment from fluid overload were underestimated. Even the latest evidence from meta-analysis showing GDFT deceased LOS and morbidity should be conservatively treated as their high heterogeneity.[8] In general, to determine whether GDFT affects postoperative ileus, more RCTs focusing on it will be needed. Further work will be expected to found out which goals should be chased and which patient groups would mostly get benefit from GDFT.

Acknowledgments

We would like to acknowledge all the authors of the original articles included in this meta-analysis.

Author contributions

XZ and WZ equally contributed to this article and joined first authorship is proposed. XZ, WZ, and CC helped undertake the search, selection, extraction, data analysis, and wrote the initial article. XK and YZ undertake extraction and participate in interpretation of the analysis. FB and SG undertake data analysis and made the assessment of risk of bias. SZ designed the study protocol and helped with the article preparation. All authors have read and revised the article.

Conceptualization: Wei Zheng.

Data curation: Chaoqin Chen.
Investigation: Fangping Bao, Shuyuan Gan.
Methodology: Xianhui Kang.
Resources: Yueying Zheng.
Validation: Shengmei Zhu.
Writing – original draft: Xiongxin Zhang, Wei Zheng.
Writing – review & editing: Wei Zheng.

References

[1] Wolthuis AM, Bislenghi G, Fieuws S, et al. Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. Colorectal Dis 2016;18:1–9.
[2] Barletta JF, Senagore AJ. Reducing the burden of postoperative ileus: evaluating and implementing an evidence-based strategy. World J Surg 2014;38:1966–77.
[3] Vather R, O'Grady G, Bissett IP, et al. Postoperative ileus: mechanisms and future directions for research. Clin Exp Pharmacol Physiol 2014;41:358–70.
[4] Bragg D, El-Sharkawy AM, Psaltis E, et al. Postoperative ileus: recent developments in pathophysiology and management. Clin Nutr (Edinburgh, Scotland) 2015;34:367–76.
[5] Marjanovic G, Villain C, Juettner E, et al. Impact of different crystalloid volume regimes on intestinal anastomotic stability. Ann Surg 2009;249:181–5.
[6] Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to enhanced recovery after surgery (ERAS). Can J Anesth 2015;62:158–68.
[7] Gupta R, Gan TJ. Peri-operative fluid management to enhance recovery. Anesthesia 2016;71(Suppl 1):40–5.
[8] Rollins KE, Lobo DN. Intraoperative goal-directed fluid therapy in elective major abdominal surgery: a meta-analysis of randomized controlled trials. Ann Surg 2016;263:465–76.
[9] Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 2005;9: R687–693.
[10] Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anesthesia 2008;63:44–51.
[11] Noblett SE, Snowden CP, Shenton BK, et al. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Brit J Surg 2006;1069–76.
[12] Zakhaleva J, Tam J, Denoya PI, et al. The impact of intravenous fluid administration on complication rates in bowel surgery within an enhanced recovery protocol: a randomized controlled trial. Colorectal Dis 2013;15:892–9.
[13] Zheng H, Guo H, Ye J-R, et al. Goal-directed fluid therapy in gastrointestinal surgery in older coronary heart disease patients: randomized trial. World J Surg 2013;37:2820–9.
[14] Gomez-Izquierdo JC, Feldman LS, Carli F, et al. Meta-analysis of the effect of goal-directed therapy on bowel function after abdominal surgery. Brit J Surg 2015;102:577–89.
[15] Giglio MT, Marucci M, Testini M, et al. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Brit J Anesth 2009;103:637–46.
[16] Gomez-Izquierdo JC, Trainito A, Mirzakandov D, et al. Goal-directed fluid therapy does not reduce primary postoperative ileus after elective laparoscopic colorectal surgery: a randomized controlled trial. Anesthesiology 2017;127:136–49.
[17] Srinivasa S, Lemanu DP, Singh PP, et al. Systematic review and meta-analysis of oesophageal Doppler-guided fluid management in colorectal surgery. Brit J Surg 2013;100:1701–8.
[18] Cohn SM, Pearl RG, Acosta SM, et al. A prospective randomized pilot study of near-infrared spectroscopy-directed restricted fluid therapy versus standard fluid therapy in patients undergoing elective colorectal surgery. Am Surg 2010;76:1384–92.
[19] Jammer I, Ulvik A, Erichsen C, et al. Does central venous oxygen saturation-directed fluid therapy affect postoperative morbidity after colorectal surgery? A randomized assessor-blinded controlled trial. Anesthesiology 2010;113:1072–80.
[20] Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: Near-maximal stroke volume or zero fluid balance? Brit J Anaesth 2012;109:191–9.
[21] Pestaña D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). Anesth Analg 2014;119:579–87.
[22] Phan TD, D'Souza B, Rattray MJ, et al. A randomised controlled trial of fluid restriction compared to oesophageal Doppler-guided goal-directed fluid therapy in elective major colorectal surgery within an enhanced recovery after surgery program. Anesth Intensive Care 2014;42:752–60.
[23] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
[24] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane–handbook.org.
[25] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[26] Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Contr Clin Trials 1997;18:580–93. discussion 661–586.
[27] Forget P, Lois F, Kartheuser A, et al. The concept of titration can be transposed to fluid management. But does is change the volumes? Randomised trial on pleth variability index during fast-track colonic surgery. Curr Clin Pharmacol 2013;8:110–4.
[28] Zhang J, Qiao H, He Z, et al. Intraoperative fluid management in open gastrointestinal surgery: goal-directed versus restrictive. Clinics 2012;67: 1149–55.
[29] Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA 2014;311:2181–90.
[30] Gustafsson UO, Scott MJ, Schwenk W, et al. Enhanced Recovery After Surgery Society fPC, European Society for Clinical N, Metabolism, International Association for Surgical M, NutritionGuidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg 2013;37: 259–84.
[31] Mauermann WJ, Nemergut EC. The anesthesiologist's role in the prevention of surgical site infections. Anesthesiology 2006;105:413–21.
[32] Yuan J, Sun Y, Pan C, et al. Goal-directed fluid therapy for reducing risk of surgical site infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials. Int J Surg (London, England) 2017;39:74–87.