Goal-directed fluid therapy does not reduce postoperative ileus in gastrointestinal surgery
A meta-analysis of randomized controlled trials

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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 planned 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 (I² = 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 does 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: CI = 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 approximately 10%, leading to increased length of hospital stay (LOS), total complication rate and impart clinical and economic burden on healthcare institutions. 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. 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. 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
law or reaching other sensitive goals except for standard parameters. 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).

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

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 PICO5 (patient, intervention, comparison, outcome, 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 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. 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. 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. 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 multidose using GDFT were pooled, using the formula described in the Cochrane Handbook. The inconsistency index ($I^2$) was calculated using a $x^2$-based test of homogeneity: less than 25%–low heterogeneity, 25% to 50%–moderate heterogeneity, more than 50%–high heterogeneity. 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.

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, 2 on bowel and 4 on a range of gastrointestinal surgery. 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
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 11–14,18–21,27,29 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 (I² = 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 (I² = 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 213,27 including 886 patients in the GDFT group and 869 patient in the control group evaluated the effect of
GDF on 30-day total complication rate. There was no difference between two groups: 326 (36.8%) in the GDF group and 333 (40.6%) in the control group (RR 0.92, 95% CI 0.81–1.03, \( P = .23 \)), with low heterogeneity between studies (\( I^2 = 11\% \), \( P = .34 \)). No publication bias was found (Egger test, \( P = .96 \)). Sensitive analysis did not change the result. Meanwhile, no significant distinction was detected in total complication rate between two 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 GDF group and control group, respectively. GDF 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 find 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 [12,13,16,18,22,27]. 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 GDF group received less fluid. Subgroup analysis did not perform because of scarce studies. Two of the above 7 studies still applied GDF during 24 hours postoperatively. One study [13] administrated 2150 mL (1875–2300 mL) fluid in the GDF 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 GDF 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 GDF group was lower in control group (RR 0.68, 95% CI 0.50 to 0.93, \( P = .02 \), \( I^2 = 0 \)) (supplement 2, Fig. 10, http://links.lww.com/MD/C619). Nine [11,12,16,18,22,28,29] 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 a. The calculation result inferred the required information size acquired to find out a convincible GDF 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). Similar-ly, 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 GDF 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
Brandstrup et al[12] (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 (130/0.4) for blood loss, extra 500 mL if needed, 200 mL colloid bolus if needed; MAP, HR, CVP | I | 30-Day complication, mortality | Yes | Yes |

Cohn et al[13] (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, then 5 mL/kg/h for 1 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[14] (2013) | Colorectal | 21 | Maximo Set; 10 mL/kg crystalloid in first hour, then 2 mL/kg/h, 250 mL 6% HES if needed; PHiTH Variability Index | 10 mL/kg crystalloid in first hour, then 5 mL/kg/h, 250 mL 6% HES if needed, MAP | I | The amount of perioperative fluid | Yes | No |

Gomes-Beziqueiro et al[15] (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 | I | Primary postoperative ileus during hospital stay | Yes | No |

Jammer et al[16] (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 | esophageal Doppler; a bolus of 7 mL/kg then 3 mL/kg colloid if needed; Ftc, SV | I | 30-Day complication | No | No |

Noblett et al[17] (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 | I | LOS | No | No |

Pearse et al[18] (2014) | Major gastrointestinal | 734 | LDCOrapid; 250 mL colloid bolus if needed; cardiac output, SV | usual perioperative care; CVP, HR, urine output | I | 30-Day complication and mortality | No | No |

Pestana et al[19] (2014) | Colorectal, gastrectomy, small bowel resection | 142 | NICOM (n invas 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[20] (2014) | Colorectal | 100 | esophageal Doppler; 5 mL/kg Hr Hartmann’s solution, 250 mL colloid if needed, Ftc, SV | 5 mL/kg/hr Hartmann’s solution, 250 mL colloid if needed; blood loss, BP | II | LOS | Yes | Yes |

Zakhvaleva et al[21] (2013) | Colorectal | 72 | esophageal Doppler; 7 mL/kg bolus first then 3 mL/kg colloid if needed; Ftc, SV; stroke volume variation | 4–8 mL/kg crystalloids; blood loss and insensible loss | II | LOS and complication rate | No | Yes |

Zhang et al[22] (2012) | Gastrointestinal | 60 | DextOmeda S/S; 4 mL/kg/h LR, 250 mL bolus of LR or HES (130/0.4) if needed; pulse pressure variation | 4 mL/kg/h LR, 250 mL bolus of LR if needed, urine output, CVP, MAP, blood loss | I | LOS | No | Yes |

Zhang et al[23] (2013) | Gastrointestinal | 60 | VigileoFlotrac; a bolus of BSS 500 mL or added colloid 250 mL if needed; MAP, cardiac index, SV | a basal amount of BSS using the 4:3:1 rule; colloid if needed; MAP, blood loss | I | 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, SW = stroke volume index.

demonstrated that GDFT were not associated with the reduction of LOSs, 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. It is well known that fluid overload is related to intestinal edema, which can lead to postoperative ileus. 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 I² 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
The 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 bowel preparation, minimized fasting and carbohydrate treatment, 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. Meanwhile, much earlier meta-analysis of the resemble subject had shown the opposite result yet. 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. As listed in Table 1, among including trials, only 1 conducted by Noblett et al 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, I² = 90%; morbidity, I² = 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
superiority disappeared when the study owning the largest sample size was removed.\(^\text{[29]}\) Meanwhile, previous studies had already demonstrated fluid imbalance may impair tissue oxygenation thus delayed wound healing and facilitated infection.\(^\text{[31]}\) Therefore, GDFT may be beneficial to reduce surgical site infections and it was confirmed by recent study.\(^\text{[32]}\) The result of anastomotic leak was also unstable because it had statistical significance when omitted the latest study\(^\text{[16]}\) or the study conducted by Jammer et al. 2010.\(^\text{[19]}\) 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.\(^\text{[14]}\) 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 incomplete 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.\(^\text{[14]}\) 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.

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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.

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