“Goal directed fluid therapy and gastrointestinal function after abdominal surgery”

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This thesis is dedicated to my beloved wife, Maria del Pilar Fajardo, and my mother, Maria Constanza Izquierdo. Without their support and inspiration this Odyssey would not have been possible.

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Abstract

Title: "Goal directed fluid therapy and gastrointestinal function after abdominal surgery"

Introduction: Goal directed fluid therapy (GDFT) aims at optimizing oxygen delivery by administering intravenous fluids, with or without inotropes, based on the assessment of stroke volume or cardiac output. It has demonstrated to decrease perioperative morbidity mostly in high-risk patients. However, very few studies have primarily investigated the impact of GDFT on the occurrence of primary postoperative ileus (PPOI). PPOI in the absence of surgical complications constitutes an important economic burden for healthcare systems, since it increases postoperative morbidity and delays hospital discharge. GDFT can prevent the occurrence of both hypovolemia and fluid overload by administrating intravenous fluids based on more objective measures of the intravascular volume.

The objectives of this thesis are 1) to review the evidence supporting the use of GDFT to facilitate the recovery of bowel function after abdominal surgery, 2) investigate whether GDFT compared to traditional fluid administration can reduce the incidence of PPOI after laparoscopic colorectal surgery in the context of an Enhanced Recovery After Surgery Program, 3) and determine the effect of GDFT on sub-lingual microcirculation, as a surrogate measure of splanchnic tissue perfusion.

Methods: First, a systematic review of the literature and meta-analysis was performed to evaluate the effects of GDFT on the recovery of bowel function after abdominal surgery. Second, a randomized controlled trial comparing intraoperative GDFT with a traditional fluid administration technique was conducted in patients undergoing laparoscopic colorectal surgery in the context of an ERAS program; PPOI was the primary outcome. Finally, perioperative sub-

lingual microcirculatory measurements were acquired in a subgroup of patients to analyze the microcirculatory effects of the 2 different fluid strategies.

Results: the results of the systematic review and meta-analysis indicated that GDFT facilitated the recovery of bowel function, particularly in patients not treated within an ERAS program and in those undergoing colorectal surgery. Sub-group analysis including only high-quality studies showed limited gastrointestinal benefits with GDFT. Only a few trials primarily investigated the effect of GDFT on the recovery of bowel function. However, the validity of these results was influenced by a high degree of statistical and clinical heterogeneity.

In the randomized controlled trial, GDFT did not reduce the incidence of PPOI when compared to fluid therapy based on traditional principles (21.9% in both groups, p=1.000), even though patients treated with GDFT had a more pronounced and sustained increase of stroke volume and cardiac output during surgery, and received less intravenous fluids. Sub-lingual microcirculation analysis demonstrated that GDFT improved the proportion of perfused vessels (PPV) ($p = 0.023$), but this effect did not translate into less PPOI and better bowel function. Patients who presented with PPOI exhibited a lower sub-lingual PPV than patients without PPOI, probably indicating suboptimal splanchnic perfusion in the former (82.76 ± 3.19 vs 87.29 ± 4.20, $p = 0.026$).

Conclusions: GDFT might be beneficial to improve bowel function after abdominal surgery, mainly in patients not treated with an ERAS program. Despite increasing systemic perfusion and PPV, possibly indicating better splanchnic tissue perfusion and oxygenation, GDFT did not translate into better recovery of bowel function in patients undergoing colorectal surgery within an ERAS program.

Résumé

Titre: « Thérapie des fluides ciblée par objectifs hémodynamiques et la fonction gastro-intestinale après une chirurgie abdominale »

Introduction : La thérapie des fluides ciblée par objectifs hémodynamiques (TFCOH) a pour but l'optimisation de l'apport d'oxygène par l'administration de liquides intraveineux, avec ou sans inotropes, sur la base d'une évaluation du volume d'éjection systolique et du débit cardiaque. Cette technique a démontré la diminution de la morbidité peropératoire, surtout chez les patients qui ont un risque peropératoire élevé. Pourtant, seulement quelques études ont investigué comme objectif principal l'effet de la TFCOH sur l'incidence d'iléus postopératoire primaire (IPP). L'IPP, en l'absence de complications chirurgicales, constitue un problème économique qui affecte de façon très importante les systèmes de santé parce qu'il augmente la morbidité peropératoire et retarde le congé hospitalier des patients. La TFCOH peut prévenir l'occurrence d'hypovolémie et la surcharge de liquides intraveineux par l'administration de liquides intraveineux sur la base de paramètres physiologiques plus objectifs du volume intravasculaire.

Les objectifs de cette thèse sont les suivants : 1) réviser l'évidence qui appuie l'utilisation de la TFCOH pour faciliter la récupération de la fonction intestinale après la chirurgie abdominale ; 2) investiguer si la TFCOH, comparativement à la façon traditionnelle d'administration de liquides intraveineux pendant les chirurgies, pourrait réduire l'incidence d'IPP après les chirurgies colorectales par laparoscopie dans le contexte d'un programme de « récupération rapide des patients après la chirurgie » (RRAC) ; 3) déterminer l'effet de la TFCOH sur la microcirculation sous-linguale comme mesure indirecte de la circulation splanchnique.

Méthodes : D'abord, une revue systématique de la littérature et une méta-analyse ont été effectuées pour évaluer les effets de la TFCOH sur la récupération de la fonction intestinale après

la chirurgie abdominale. De même, une étude randomisée contrôlée, laquelle compare la TFCOH intra-opératoire avec une technique traditionnelle d'administration de liquides intraveineux pendant les chirurgies, a été effectuée chez des patients subissant des chirurgies colorectales par laparoscopie dans le contexte d'un programme de RRAC. Le principal objectif de cette étude était d'évaluer l'incidence d'IPP. Finalement, un sous-groupe de patients a été analysé pour évaluer l'effet des deux techniques d'administration intra-opératoires de liquides intraveineux sur la microcirculation sous-linguale.

Résultats : Les résultats de la revue systématique de la littérature et la méta-analyse ont indiqué que la TFCOH facilitait la récupération de la fonction intestinale, en particulier chez les patients qui ne sont pas traités avec un programme de RRAC et chez les patients subissant une chirurgie colorectale. L'analyse des études par sous-groupe, incluant seulement ces études considérées comme étant de haute qualité, a démontré des avantages limités avec la TFCOH. Aussi, on a observé que seulement quelques études avaient comme objectif principal d'investiguer l'effet de la TFCOH sur la récupération de la fonction intestinale après la chirurgie. Cependant, la validité des résultats de l'étude a été influencée par le haut niveau d'hétérogénéité statistique et clinique.

La comparaison de la TFCOH avec l'administration intra-opératoire de liquides intraveineux de façon traditionnelle, n'a pas réduit l'incidence IPP après la chirurgie colorectale par laparoscopie (21,9 % dans les deux groupes d'intervention, avec une valeur $p = 1,000$), même si les patients traités avec la TFCOH avaient une augmentation plus remarquable et soutenue du volume d'éjection systolique et du débit cardiaque pendant la chirurgie et ont reçu moins de liquides intraveineux.

L'analyse de la microcirculation sous-linguale a démontré que la TFCOH améliorait la proportion de vaisseaux perfusés (PVP) (avec une valeur $p = 0,023$), mais cet effet n'entraînait pas moins d'incidence d'IPP ni une meilleure fonction intestinale. Les patients subissant IPP ont

démontré une PVP inférieur que le patients sans cette complication, ce qui indique une perfusion splanchnique plus déficient dans ces patients (82.76 ± 3.19 vs 87.29 ± 4.20, p = 0.026).

Conclusion : La TFCOH pourrait être utile pour améliorer la fonction intestinale après la chirurgie abdominale, principalement chez les patients qui ne sont pas traités avec un programme de RRAC. Malgré l'augmentation de la perfusion systémique a été plus remarquable et soutenue avec la TFCOH pendant la chirurgie et une PVP plus haute avec la TFCOH, ce qui indique probablement une meilleure perfusion du tissu splanchnique et une meilleure oxygénation, ces avantages n'ont pas entraîné une meilleure récupération de la fonction intestinale.

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- Mr. Mirzakandov David: intraoperative database management, patient recruitment, intraoperative data acquisition for the randomized controlled trial
- Dr. Mwale Fackson: Thesis chairman
- Dr. Pecorelli Nicolò: data acquisition about postoperative complications for the randomized controlled trial
- Dr. Qian Jin: microcirculation study database management, data acquisition of microcirculatory measurements in the cohort study, video analysis of microcirculation measurements
- Dr. Rodelo Karoll: development of the algorithm to diagnose and treat patients with postoperative ileus. Data acquisition in a cohort study from which the sample size for the randomized controlled study (Chapter 2) was calculated
- Dr. Stein Barry L: development of the algorithm to diagnose and treat patients with postoperative ileus; surgeon performing colorectal laparoscopic surgery; facilitated data acquisition during surgery; member of the thesis committee
- Dr. Trainito Alessandro: intraoperative database management, preoperative and intraoperative data acquisition for the randomized controlled trial, patient recruitment
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Author contributions

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- **Juan C. Gómez-Izquierdo,** MD; Jin Qian, MD; Mohamed Badawy, MD; Dr. Liane Feldman, MD; Gabriel Baldini, MD, M. Sc. Sub-lingual microcirculatory effects of Goal-Directed Fluid Therapy as a surrogate measure of splanchnic perfusion: a mechanistic cohort study. Conference paper. Presented at the 5th International Conference and Exhibition on Surgery. November 7 and 8, 2016. Alicante, Spain. Design of the study, patient recruitment, data acquisition, statistical analysis, database management, data interpretation, manuscript preparation and revision, submission to conference, paper presentation

Preface

Goal directed fluid therapy (GDFT) aims at optimizing oxygen delivery by administering intravenous fluids, with or without inotropes, based on the assessment of stroke volume or cardiac output. It has demonstrated to decrease overall perioperative morbidity and facilitate surgical recovery, especially in high-risk patients[1, 2]. However, very few studies have primarily investigated the impact of GDFT on specific complications, such as the occurrence of primary postoperative ileus (PPOI). PPOI is a physiologic disruption of the normal propulsive motor activity of the gastrointestinal tract that occurs in the absence of surgical complications. It constitutes an important economic burden for healthcare systems as it increases postoperative morbidity and delays hospital discharge[3, 4]. GDFT allows the administration of intravenous fluids based on a more objective assessment of the intravascular volumes[5]. This intervention may reduce the incidence of PPOI by preventing the occurrence of hypovolemia or fluid overload, both important determinants of postoperative gastrointestinal dysfunction.

The content of the present dissertation includes 1) a review of the evidence regarding the use of GDFT to facilitate the recovery of bowel function after abdominal surgery through a systematic review of the literature and meta-analysis 2) a randomized controlled trial investigating the effect of intraoperative GDFT compared to a traditional fluid administration on the incidence of PPOI after laparoscopic colorectal surgery in the context of an ERP 3) a cohort study investigating the effect of intraoperative GDFT on sub-lingual microcirculation, as a surrogate measure of splanchnic tissue perfusion. This dissertation constitutes original research and a distinct contribution to the knowledge in perioperative fluid administration and Goal directed fluid therapy.

Introduction

Enhanced Recovery Programs (ERPs) are multidisciplinary care pathways that include standardized perioperative evidence-based interventions aiming at attenuating organ dysfunction induced by surgical stress, reducing morbidity and supporting rapid functional recovery[6-9]. Evidence-based guidelines for best practices in perioperative care are available for different types of abdominal procedures, including colon surgery, rectal and pelvic surgery, gastrectomy, radical cystectomy and pancreaticoduodenectomy[10-14]. These guidelines and international consensus statements on perioperative fluid management emphasize the importance of adequate perioperative fluid management[15-17]. Adequate perioperative fluid management is essential to ensure optimal organ perfusion. This should be achieved by avoiding fluid overload or excessive fluid restriction that can both significantly impair organ function[18, 19]. Clinical and experimental evidence shows that excessive perioperative fluid administration leading to hypervolemia delays the recovery of bowel function increases overall morbidity and prolongs hospital stay[19-23]. On the other hand, hypoperfusion secondary to hypovolemia also increases postoperative complications[18], and it should be avoided particularly in patients undergoing gastrointestinal surgery, in whom occult splanchnic hypoperfusion frequently occurs[24].

Despite its clinical relevance, fluid therapy remains a controversial topic. Over the years there has been a significant reduction of the amount of fluids commonly infused during abdominal surgery, as common principles supporting the need of administering large volume of fluids to maintain normovolemia have been challenged[25]. In fact, emerging evidence from clinical and experimental studies has shown that the volume of fluids needed to maintain adequate organ perfusion is significantly lower than what expected and commonly administered. However, large variability in

fluids administration still exists within and between centers[26, 27], possibly explaining variability in clinical outcomes.

PPOI occurs in 20-40 % of patients after abdominal surgery and it represents one of the major determinants of postoperative convalescence[4]. Although its pathogenesis is multifactorial, inadequate fluid therapy can significantly affect its occurrence. Surgical trauma leads to impairment of gastrointestinal motility, which can be aggravated by both hypovolemia and excessive fluid administration[18]. The former causes splanchnic hypoperfusion[24, 28, 29] and as a consequence postoperative gastrointestinal dysfunction[30], while the latter causes edema of the intestinal wall and surrounding structures, resulting in a reduction of bowel peristalsis and tissue hypoxia[19, 31]. Fluid excess also affects tissue perfusion by increasing intra-abdominal pressure[32], directly reduces the absorption of nutrients and prolongs postoperative ileus[33, 34]. Furthermore, excessive fluid administration or splanchnic ischemia secondary to hypovolemia can both significantly impair intestinal anastomotic healing and increase the risk of anastomotic dehiscence[35, 36].

Intraoperatively, the clinical need of infusing intravenous fluids to maintain normovolemia is justified by the reduction of the intravascular volume due to blood loss and to the shifting of intravascular fluids into the interstitial space due to an increased endovascular permeability induced by surgery (type II shifting). However, maintaining normovolemia is challenging since common clinical measures of hypovolemia such as heart rate, blood pressure, urine output, central venous pressure and pulmonary wedge pressure are inaccurate measures of cardiac preload[37, 38] and fluid responsiveness[39]. During laparoscopy surgery it is even more complicated, as pneumoperitoneum and frequent changes in position can significantly affect hemodynamic

variables, independently from the intravascular volume status. These considerations are particularly important for patients undergoing gastrointestinal surgery as minimal blood loss (10-15% of the circulating volume) can cause splanchnic hypoperfusion before clinical signs of hypovolemia are manifested[24, 30]. It has been found that gastric perfusion measured by tonometry is reduced in healthy subjects exposed to an acute reduction of 25 to 30% of their circulating volume, without manifesting any change in heart rate or blood pressure[24]. This indicates that the standard hemodynamic variables used to guide fluid administration during surgery such as heart rate, blood pressure, urinary output and central venous pressure are not accurate enough to early detect splanchnic hypoperfusion[40, 41]. Moreover, the lack of gastrointestinal-specific biomarkers of splanchnic hypoperfusion, increases the challenge to early detect bowel ischemia.

GDFT aims at optimizing intravascular volume based on more objective measures of hypovolemia to ensure optimal cardiac output and organ perfusion. Based on the Frank-Starling curve, the only reason to administer intravenous fluids is to increase cardiac preload to an extent to produce a significant increase in cardiac output (≥ 10-15%). This requires cardiac output measurements before and after volume expansion and, when indicated, the use of inotrope agents to increase myocardial contractility in patients with poor ventricular systolic function. Dynamic indices of preload such as pulse pressure variation (PPV), stroke volume variation (SVV), and systolic pressure variation (SPV) are useful hemodynamic indices that can highly predict fluid responsiveness before intravenous fluids are administered. However it must be acknowledged that the accuracy of these indices to predict fluid responsiveness has been validated in paralyzed mechanically ventilated patients with a tidal volume > of 8 milliliters^{-1} Kilogram^{-1}, in sinus rhythm and without an open thorax or increased abdominal pressure. Unfortunately these conditions are present in only 53% of the patients undergoing general anesthesia for abdominal

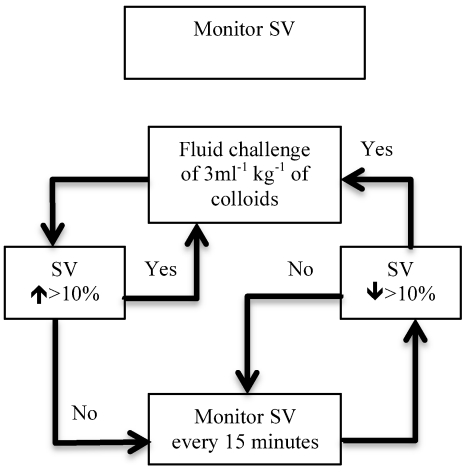
surgery[42], and probably even less during laparoscopic surgery, limiting the clinical applicability of these indices[43-46]. In these settings a fluid challenge may be a more valuable alternative to predict fluid responsiveness[39, 47]. Several GDFT algorithms have been used. They can be summarized in two categories: GDFT algorithms aiming at pre-emptively maximize stroke volume (stroke volume maximization), and GDFT algorithms aiming at optimizing stroke volume when clinically indicated (stroke volume optimization) (**Figure 1**). Studies comparing these 2 different approaches are lacking. Similarly, several non-invasive cardiac output monitors have been used to guide GDFT[48], but most of the evidence available is based on the use of the esophageal Doppler and on pulse contour analysis[49, 50]. Notably, it has been shown that in high-risk patients the benefit of using GDFT is independent from the type of hemodynamic monitor used[2]. Colloids have been mainly used to optimize intravascular volume during GDFT. Although experimental studies have shown that colloids are superior to crystalloid at improving macro and microcirculatory splanchnic perfusion[51], clinical studies comparing GDFT with colloid versus GDFT with crystalloids have failed to reproduce these findings[52]. Patients treated with GDFT with crystalloids receive more vasopressors[53] and intravenous fluids resulting in a greater postoperative weight gain[52-54]. Nevertheless, large volumes of colloids (2605 ml ± 612) can impair coagulation and increase blood loss[54].

The beneficial impact of GDFT on postoperative outcomes remains controversial, especially within the context of an ERP[55]. A recent meta-analysis[50], including 31 randomized controlled trials of patients undergoing major surgery mainly without an ERP, found that GDFT, with or without inotropes, reduced the number of patients with complications, specifically, renal impairment (Relative Risk, RR = 0.71, 95% Confidence Interval, CI = 0.57 to 0.90), wound infection (RR=0.65, 95%CI = 0.50 to 0.84), respiratory failure (RR=0.51, 95%CI = 0.28 to 0.93),

and shortened the length of hospital stay by approximately 1 day (Weighted Mean Difference, WMD = -1.16, 95%CI= -1.89 to -1.43). Similarly, the results of another meta-analysis showed reduction of cardiovascular complications (Odds Ratio, OR=0.54, 95%CI = 0.38 to 0.76, p=0.0005) and arrhythmias (OR=0.54, 95%CI=0.35 to 0.85, p=0.007)[56]. However, four consecutive studies[57-60], mainly conducted in the context of an ERP, and including 2 large multicenter RCTs[58 59], did not confirm these findings. It might be possible that the benefits observed in patients treated with GDFT and reported in the early studies might be offset by advancement of perioperative and surgical care and a more judicious use intravenous fluids, as represented by the ERP approach. Nevertheless, GDFT might still be beneficial in patients undergoing high-risk surgery (associated with large fluid shifts and with extensive blood loss (ex. > 7milliliters^{-1} Kilogram^{-1}), or in high-risk patients[1, 2, 10-14].

Even though experimental trials[51] and inconclusive clinical evidence[20, 61-63] have suggested that GDFT might accelerate the recovery of bowel function after abdominal surgery and reduce the incidence of PPOI, the role that GDFT can have in attenuating postoperative gastrointestinal dysfunction remains uncertain, especially in the context of advanced perioperative care. Based on this considerations, the objectives of this doctoral thesis are 1) reviewing the evidence supporting the use of GDFT to facilitate the recovery of bowel function after abdominal surgery through a systematic review of the literature and meta-analysis, 2) investigating whether intraoperative GDFT compared to traditional fluid administration can reduce the incidence of PPOI after laparoscopic colorectal surgery in the context of an ERP, 3) determining the effects of GDFT on sub-lingual microcirculation, as a surrogate measure of splanchnic tissue perfusion.

Pre-emptive SV maximization (A)



SV optimization (B)

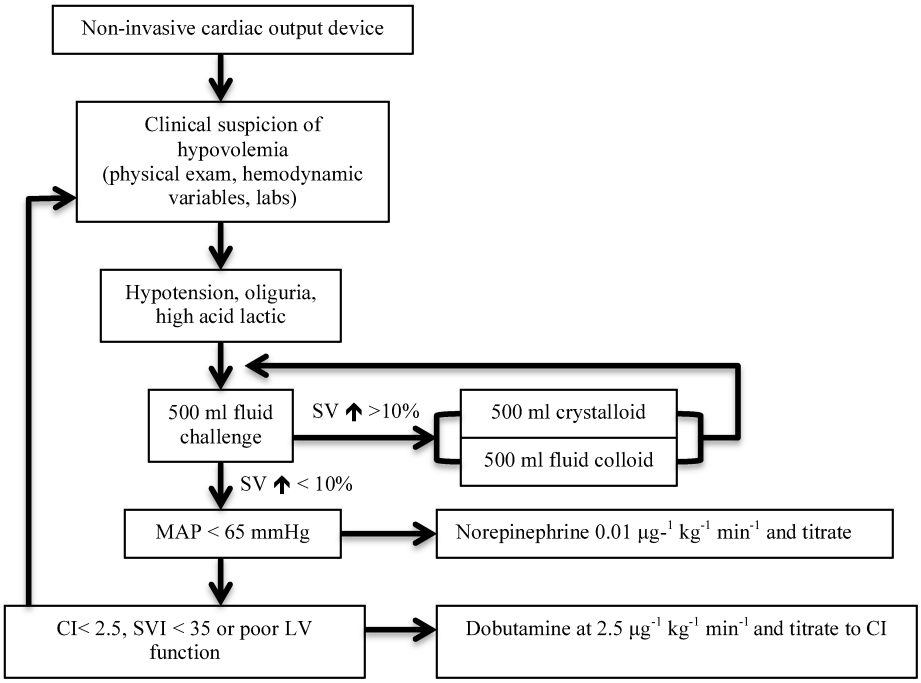


Figure 1. Goal Directed Fluid Therapy (GDFT): examples of pre-emptive Stroke Volume (SV) maximization (A)[64] and SV optimization (B)[65]. CI = Cardiac Index; SVI = Stroke Volume Index; LV = Left Ventricular, MAP = Mean arterial pressure, labs = laboratory results, ↑ = increase, ↓ = decrease.

Chapter 1

"Meta-analysis of the effect of goal-directed therapy on bowel function after abdominal surgery"

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Ph. D Experimental Surgery

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Meta-analysis of clinical trials studying the effect of intraoperative Goal directed Fluid Therapy (GDFT) on the recovery of bowel function after abdominal surgery

Preamble

While it is well established that avoiding intravenous fluid excess[31] and splanchnic hypoperfusion[30] attenuate bowel dysfunction, the beneficial impact of GDFT on postoperative gastrointestinal function remains to be proven, specifically in the context of an ERP.

Animal studies[51] and small RCTs[61-63] have suggested that guiding fluid therapy with objective measures of hypovolemia can accelerate recovery of bowel function and reduce gastrointestinal complications[5, 20], perhaps by limiting the risk of bowel edema or splanchnic hypoperfusion. However, the results of these studies are inconclusive, and several methodological limitations need to be considered. First, most of the RCTs were underpowered, as the recovery of bowel function was mostly reported as a secondary outcome[53, 61-63, 66, 67]. Second, gastrointestinal endpoints used to assess gastrointestinal function were different between the studies, as well as the definition of PPOI, resulting difficult to determine the clinical impact of GDFT. Third, clinical studies reporting positive results compared GDFT with fluid regimens that included the administration of large volumes of crystalloids, and this could have negatively affected the recovery of bowel function in patients of the control group[61-63, 66, 67]. In fact, recent RCTs comparing GDFT with more rational and evidence-based fluid regimens, failed to demonstrate the former benefits. Of note, those initial benefits of GDFT were mostly seen in patients undergoing moderate-major surgery[61, 63]. Finally, most of the studies were conducted in an unstandardized clinical setting, and several perioperative confounding factors might have affected

bowel function, independently from the type of fluid regimen received. When the effect of GDFT on the recovery of bowel function was evaluated in the context of an ERP, which includes several standardized perioperative interventions that have shown to accelerate the recovery of bowel function, these findings were partially confirmed[68].

In light of these several methodological limitations and controversial evidence, establishing the exact role of GDFT in attenuating postoperative gastrointestinal dysfunction after abdominal surgery is warranted. As first step, a systematic review and meta-analysis of clinical trials reporting the effect of intraoperative GDFT on the recovery of bowel function was performed. Clinical trials were also grouped based on the type of surgery, preoperative risk stratification, and on the presence of a perioperative ERPs.

Meta-analysis of the effect of goal-directed therapy on bowel function after abdominal surgery

Introduction

Gastrointestinal dysfunction is commonly observed after abdominal surgery in the absence of postoperative complications[69]. Normal gastrointestinal function is an essential prerequisite to ensure early postoperative feeding, which has been proven to be safe and beneficial[70] and is currently recommended after abdominal surgery[10, 12-14, 70-73]. Inability to tolerate oral intake prolongs hospital stay[74], as tolerance of oral diet is a well-recognized hospital discharge criterion after abdominal surgery[75].

Despite the improvements yielded by enhanced recovery programs, postoperative gastrointestinal dysfunction still remains a clinically relevant problem following abdominal surgery[14, 76, 77]. Postoperative gastrointestinal dysfunction is identified by symptoms such as nausea, vomiting, abdominal distension, intolerance of oral diet, and absence of flatus or bowel motion, and is commonly reported as primary postoperative ileus[78]. Primary postoperative ileus has been estimated to burden the healthcare system in the USA by approximately $750 million to $1 billion annually[79] (approximately €600 – 800 million), and prolongs hospital stay[80].

The pathogenesis of postoperative gastrointestinal dysfunction is multifactorial, and many perioperative factors can influence its severity and duration[69]. Adequate perioperative fluid management plays a critical role, as fluid overload and mesenteric hypoperfusion caused by hypovolemia have a negative impact on the recovery of bowel function[5, 31]. Goal-directed therapy

(GDT) aims to optimize organ perfusion to achieve predetermined hemodynamic goals, and has been shown to decrease the length of hospital stay and postoperative complications, especially in high-risk patients undergoing major abdominal surgery[5, 81, 82]. Evidence from experimental studies[51, 83] and small clinical trials[62, 63, 67] suggests that GDT might facilitate the recovery of bowel function after major abdominal surgery. A further consideration is the impact of GDT in the context of enhanced recovery programs.

The aim of this meta-analysis was to determine the effect of intraoperative GDT on recovery of bowel function in patients undergoing elective abdominal surgery.

Methods

Systematic literature search

The characteristics of this systematic review and meta-analysis were defined following the PICO (patient/problem, intervention, comparison, outcomes) strategy[84, 85]. The objective was to evaluate the effect of GDT (I) on bowel function (O) compared with other fluid administration strategies (C), during elective abdominal surgeries (P), by means of a systematic review of the literature and meta-analysis.

A systematic search of MEDLINE, Embase, the Cochrane Library and PubMed was performed including medical subject headings (MeSH) terms associated with GDT, such as monitoring devices, physiological methods, parameters employed to guide fluid administration and the types of fluid used. The results were combined with MeSH terms related to surgical procedures in abdominal and digestive surgery (*AppendixS1*, supporting information). No language restrictions were used.

Inclusion and exclusion criteria

Studies were included if they were: randomized clinical trials or cohort studies, performed between January 1989 and June 2013 (the lower limit of this time frame was chosen because the concept of GDT started to appear in the medical literature around that year[86-88]), in patients undergoing elective abdominal and digestive surgery; studies that used an objective physiological parameter other than urinary output, BP and heart rate as a goal to guide intraoperative fluid administration with or without inotropes. Patients undergoing emergency surgery were excluded.

Study selection and validity assessment

Two assessors independently evaluated the quality of the retrieved studies, as indicated by the Cochrane Handbook[89] (Cochrane Collaboration's tool for assessing risk of bias in randomized clinical trials and the tool to assess risk of bias in cohort studies). High- and low-quality trials were not defined *a priori*. Detailed criteria for judgments about the risk of bias (high, uncertain or low) for each of the items listed in the Cochrane Collaboration's tool[89] were followed to determine which studies to include in the analysis. Based on these criteria, only trials that were considered independently by the assessors to be of high quality were included. Any disagreement was resolved by open discussion[89]. The inter-rater reliability to determine the quality of the eligible studies was calculated using the $\varkappa$ (kappa) statistic[90].

Data extraction

Data extraction was achieved by means of a pro forma. The following data were extracted: first author, year of publication, total number of patients, number of patients per treatment group, type of surgery, type of GDT, type of intervention received in the control group, primary outcome,

and measures to estimate bowel function. Bowel function measures included were: time to first flatus, time to first bowel motion, time to tolerate oral diet, postoperative nausea and vomiting, and the incidence of primary postoperative ileus. The main authors of the selected articles were contacted and asked for additional data on bowel function or information about fluid management when not reported.

Statistical analysis

Statistical analysis was performed only when it was possible to cluster at least two studies that reported the same bowel function measure, using Review Manager version 5.2 software (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). When not reported, mean (standard deviation, s.d.) values were calculated from the median (interquartile range, i.q.r.), using the method described by Hozo *et al*.[91] The results of studies that compared multiple groups using GDT were pooled, employing the formula described in the Cochrane Handbook[89]. Data were reported as risk difference (RD) with 95 per cent confidence interval (c.i.) if the incidence of the reported outcome was zero, as the odds ratio (OR) with 95 per cent c.i. for dichotomous outcomes, and as the weighted mean difference (WMD) with 95 per cent c.i. for continuous outcomes[89]. ORs and RDs were calculated using Mantel–Haenszel models, and WMD using the generic inverse of variance method. Heterogeneity was measured using the I^2 statistic[89] (less than 25 per cent, low heterogeneity; 25–50 per cent, moderate heterogeneity; more than 50 per cent, high heterogeneity). In addition, a χ^2 analysis for heterogeneity was performed and $P<$ 0.100 was set to determine significance[89]. Outcomes with moderate and high heterogeneity were analyzed using a random-effects model, whereas a fixed-effect model was used for outcomes with low heterogeneity[89].

A subgroup analysis was planned *a priori* and performed, when possible, by clustering the studies according to whether or not they were performed in the context of an enhanced recovery program or in high-risk patients. High-risk patients were defined as reported previously[2, 92] or, if aerobically unfit, by an anaerobic threshold of between 8.0 and 10.9 ml oxygen per kg per min[64], or, in patients undergoing surgery, those with anticipated blood loss greater than 500 ml[63]. For the purpose of this investigation, an enhanced recovery program was confirmed when the authors reported at least seven perioperative elements of an enhanced recovery program in the study[93, 94]. Other subgroup analyses were also planned *a priori* to establish the effect of thoracic epidural analgesia, type of surgery and laparoscopic surgery on recovery of bowel function. The volume and the type of intraoperative intravenous fluids used in each study were analyzed in patients treated and not treated with GDT. Data were reported as weighted mean (s.d.), and compared using two independent-samples unpaired *t* test with a two-tailed statistical significance level set at $P<0.050$. A sensitivity analysis was performed to determine the effect of studies with an unclear risk of bias or the presence of other sources of bias. Publication bias was determined by visual assessment of funnel plots.

Results

The search identified 27842 records; 139 articles were screened after removal of duplicates and 34 papers were considered for eligibility (***Figure. 1***). Fifteen studies were excluded because all patients were treated with GDT, and six were excluded because of low quality (*Supplementary material B and C*). Overall, 13 randomized clinical trials[53, 57, 61-64, 66, 67, 95-99] were selected for analysis (***Table 1***). The $\varkappa$ statistic showed substantial agreement between the assessors ($\varkappa = 0.6$, $P < 0.001$), and disagreement was found for only six of the 34 studies considered for eligibility.

Study characteristics

A total of 1399 patients were included in the analysis; 704 patients received GDT and 695 did not. Bowel function was the primary outcome in only one study[61], and bowel function measures were reported inconsistently (***Table 2***). Perioperative care in the included studies is reported in ***Table 3***.

Outcomes

Intraoperative GDT shortened the time to the first bowel motion (WMD –0.67, 95 per cent c.i. –1.23 to –0.11; $P = 0.020$) and the time to tolerate oral intake (WMD –0.95, –1.81 to –0.10; $P = 0.030$), and decreased the incidence of postoperative nausea and vomiting (RD –0.15, –0.26 to –0.03; $P = 0.010$). GDT did not affect the incidence of primary postoperative ileus (RD –0.02, –0.10 to 0.06; $P = 0.560$) or time to the first flatus (WMD –0.41, –0.85 to 0.04; $P = 0.070$) (***Figure. 2***). Funnel plot asymmetry could not be tested as the number of studies for each gastrointestinal outcome was less than ten[89]. Visual inspection of funnel plots did not show major asymmetries in the distribution of trials.

Sensitivity analysis

When the analysis was repeated excluding studies where the intervention was extended in the postoperative period for a maximum of 24 h after surgery[96, 99, 100], and those with unclear risk of bias (the primary outcome reported on ClinicalTrials.gov did not correspond to the primary outcome reported in the study; NCT00816153[97]), intraoperative GDT shortened the time to tolerate oral intake (WMD –1.18, –2.03 to –0.33; $P = 0.006$) (***Figure. 3***), but did not shorten the time to the first bowel motion (WMD –0.82, –1.76 to 0.11; $P = 0.080$) or the time to the first flatus (WMD –0.29, –0.78 to 0.20; $P = 0.240$). Similarly, GDT did not reduce the incidence of primary

postoperative ileus (RD –0.02, –0.10 to 0.06; *P* = 0.560) or post- operative nausea and vomiting (OR 0.49, 0.15 to 1.64; *P* = 0.250).

Subgroup analysis

Perioperative care and recovery of bowel function

Ten studies[53, 61-63, 66, 67, 95-97, 99] were conducted without an enhanced recovery program. In the absence of an enhanced recovery program, GDT shortened the time to tolerate oral intake (WMD –1.16, –2.11 to –0.22; *P* = 0.020), time to the first bowel motion (WMD –0.92, –1.54 to –0.29; *P* = 0.004), and the incidence of post-operative nausea and vomiting (RD –0.15, –0.26 to –0.03; *P* = 0.010) (***Figure. 4***), but did not shorten the time to the first flatus (WMD –0.53, –1.09 to 0.03; *P* = 0.060) or the incidence of primary postoperative ileus (RD –0.03, –0.10 to 0.04; *P* = 0.410). Three studies[57, 64, 98] were conducted in a context of an enhanced recovery program. Subgroup analysis to establish the influence of these programs on recovery of bowel function was possible for only two studies[57, 98] reporting the incidence of primary postoperative ileus. When GDT was used in the context of an enhanced recovery program it did not reduce the incidence of primary postoperative ileus (OR 1.40, 0.50 to 3.88; *P* = 0.520).

High-risk patients and recovery of bowel function

Five studies[61, 63, 64, 95, 99] evaluated the effect of intraoperative GDT on postoperative outcomes in high-risk patients. GDT did not affect the time to first flatus (WMD –0.39, –1.12 to 0.34; *P* = 0.300), time to the first bowel motion (WMD –0.58, –1.33 to 0.17; *P* = 0.130) or time to tolerate oral intake (WMD –0.59, –1.92 to 0.75; *P* = 0.390), but it did reduce the incidence of post-operative nausea and vomiting (OR 0.27, 0.13 to 0.57; *P*<0.001).

Colorectal surgery and recovery of bowel function

Five studies[57, 62, 64, 67, 98] were performed in patients undergoing colorectal surgery. Intraoperative GDT shortened time to tolerate oral intake (WMD −1.02, −1.52 to −0.51; $P<0.001$) and time to the first bowel motion (WMD −1.00, −1.65 to −0.35; $P = 0.002$) (***Forest plot,* supplementary material D**), but did not reduce the incidence of primary postoperative ileus (OR 1.40, 0.50 to 3.88; $P = 0.520$).

A subgroup analysis to establish the effect of thoracic epidural analgesia and laparoscopic surgery on recovery of bowel function was not feasible. Patients received a greater volume of colloids ($P<0.001$), but a smaller volume of crystalloids ($P<0.001$) when a GDT strategy was adopted (***Table 4***).

Discussion

The results of this meta-analysis show that intraoperative GDT shortens the time to the first bowel motion, the time to resume oral intake, and the incidence of post-operative nausea and vomiting after abdominal surgery. The time to first flatus and the incidence of primary post-operative ileus were not affected by GDT. When the analysis was repeated by excluding studies with risk of bias and studies with unclear risk of bias, GDT shortened the time to resume oral intake but did not impact on other gastrointestinal outcome measures. Although GDT was compared with different fluid regimens, patients treated with GDT received a greater volume of intravenous colloid and smaller volume of crystalloids compared with patients not treated with GDT.

Adequate gastrointestinal function is an essential pre- requisite to ensure early postoperative oral

feeding. It is well known that fluid overload impairs bowel function by causing bowel edema and impairing bowel motility[31]. Similarly, splanchnic hypoperfusion secondary to hypovolemia can also decrease bowel function[83, 101, 102]. The use of GDT has been shown to reduce postoperative morbidity, and it is currently recommended in the context of enhanced recovery programs, especially in moderate- to high-risk patients[2] and for prolonged surgical procedures[103, 104]. Evidence from experimental studies[51, 83] and small single-centre clinical trials[62, 63, 67] has shown that GDT is beneficial in accelerating recovery of bowel function, mainly improving bowel perfusion and avoiding fluid overload. However, none of these studies was done in a context of an enhanced recovery program.

The findings of this meta-analysis suggest that GDT impacts on relevant endpoints that indicate recovery of bowel function, such as time to first bowel motion and time to resume oral intake. These gastrointestinal measures seem important, as shown by the study[105] that assessed gastrointestinal transit radiologically after colorectal surgery. The combination of tolerance of solid food and passage of stool correlated best with the recovery of gastrointestinal function after colorectal surgery, with a positive predictive value of 93 per cent.

The results of the subgroup analysis indicate that GDT is beneficial mainly when used outside enhanced recovery programs and in patients undergoing colorectal surgery. These findings are in agreement with other investigations[98, 106] that did not show a faster recovery of gastrointestinal function in patients undergoing colorectal surgery and treated with an enhanced recovery program, thereby questioning the need for GDT in this setting[98, 106]. Enhanced recovery programs include multimodal interventions such as opioid-sparing strategies, use of thoracic epidural analgesia; avoidance of fluid overload, minimally invasive surgery, routine use of prokinetics, and early feeding. It may be hypothesized that these regimens attenuate postoperative

gastrointestinal dysfunction and therefore decrease the benefits reported with GDT in previous studies. In contrast, the greater volume of colloid administered to patients treated with GDT may have a negative effect on recovery of bowel function[106]. Patients treated with an enhanced recovery program are less likely to be volume-depleted, because preoperative carbohydrate drinks are administered, mechanical bowel preparation avoided and fasting times minimized[103]. It has been shown that a restrictive fluid regimen is as effective as GDT for an adequate cardiac index throughout surgery, without negatively affecting the recovery of bowel function[98]. Limiting the amount of fluids to maintain adequate bowel perfusion might suffice in patients enrolled in enhanced recovery programs.

Subgroup analysis in high-risk patients showed that intraoperative GDT reduced only postoperative nausea and vomiting without impacting on other gastrointestinal outcomes.

Although this meta-analysis has shown that intraoperative GDT might facilitate recovery of bowel function, the validity of these results is influenced by the quality of the included randomized clinical trials, as indicated by the sensitive analysis, and also by the high degree of statistical and clinical heterogeneity. Definitions of primary postoperative ileus differed among studies, and gastrointestinal outcome measures were reported inconsistently. As a result, data that could be clustered to perform meta-analysis were limited. The included studies used different GDT strategies and different fluid regimens. Although the purpose of this meta-analysis was to determine the effect of intraoperative GDT on recovery of bowel function, three studies[66, 96, 99] continued GDT in the early postoperative period. The analysis of high-quality studies that did not include these three articles showed limited gastrointestinal benefits with GDT. It cannot be excluded that GDT might be more effective if continued in the postoperative period.

With these limitations, intraoperative GDT seems to facilitate the recovery of bowel function, particularly in patients undergoing surgery outside an enhanced recovery program and in patients having colorectal surgery.

Figures

Figure. 1 PRISMA diagram of included and excluded studies. GDT, goal-directed therapy

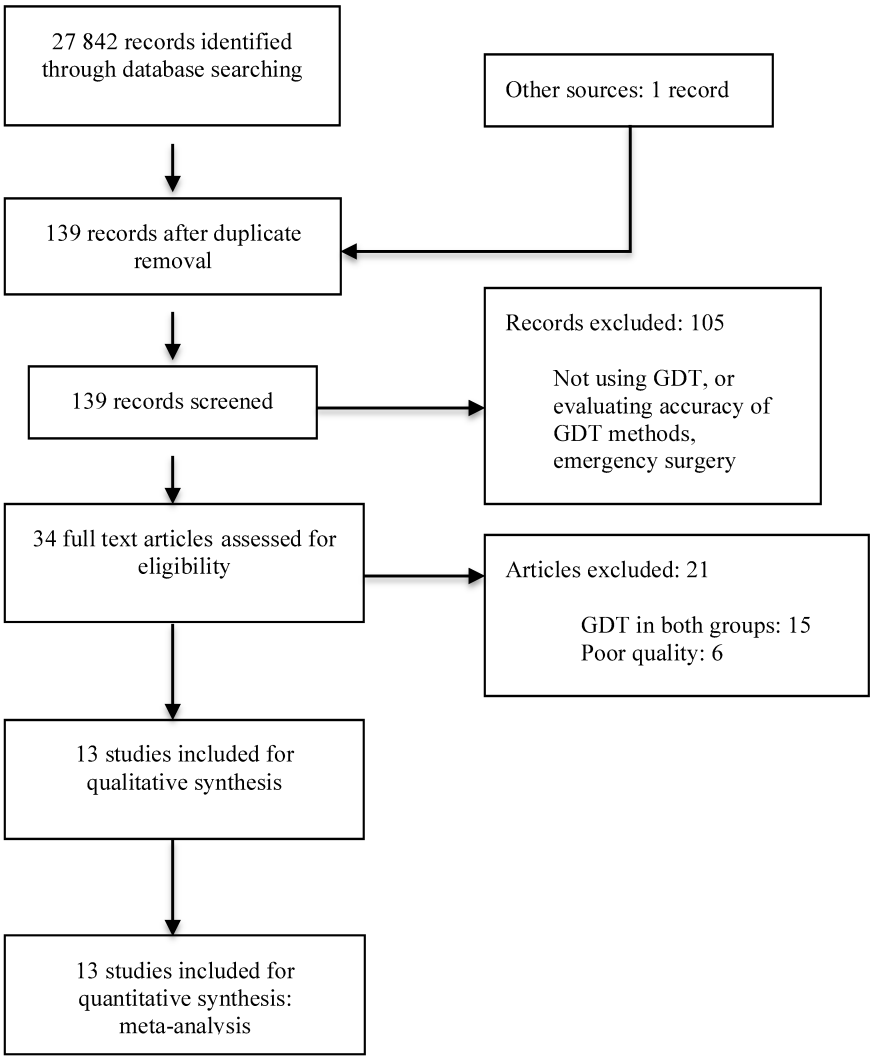
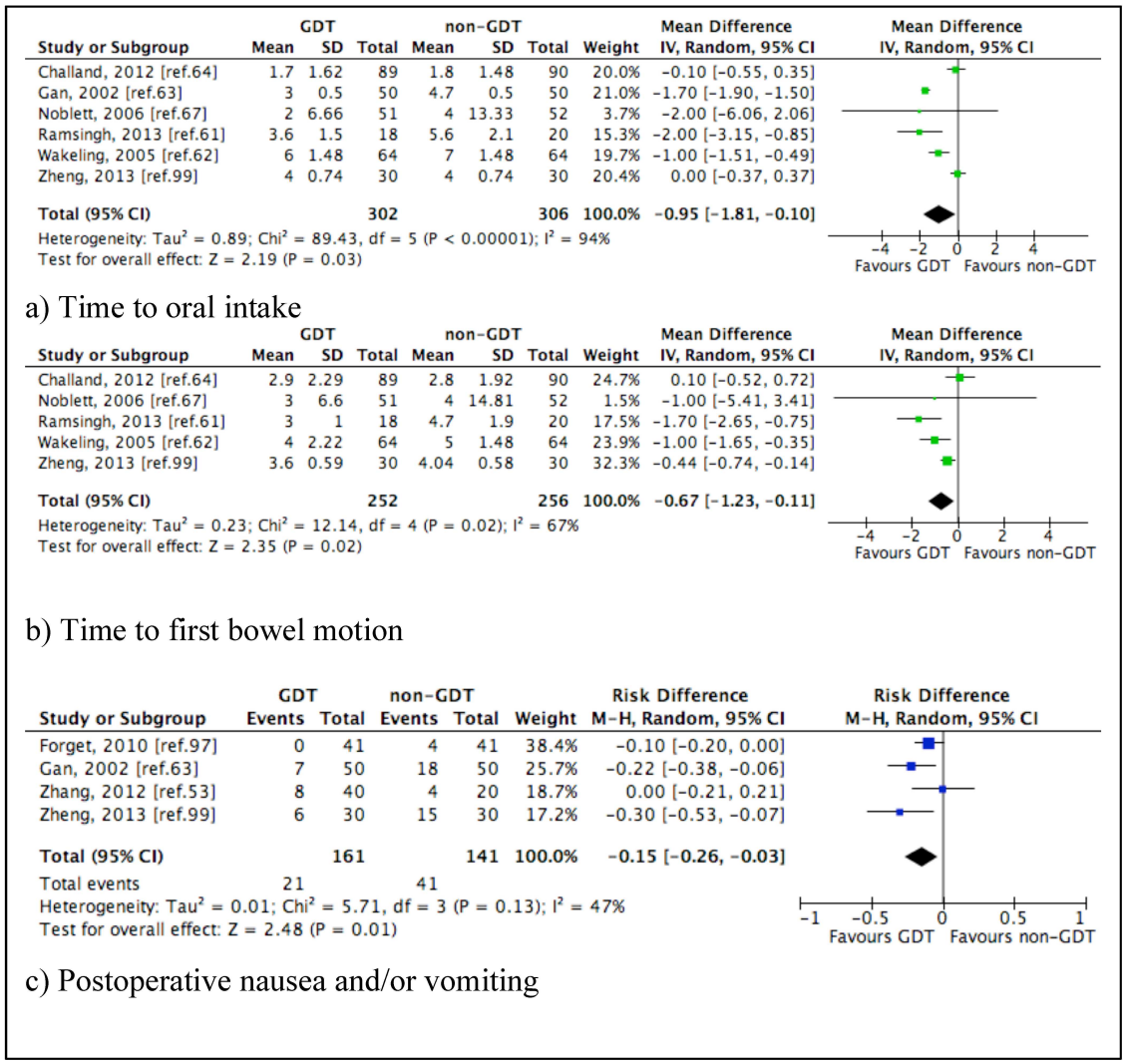
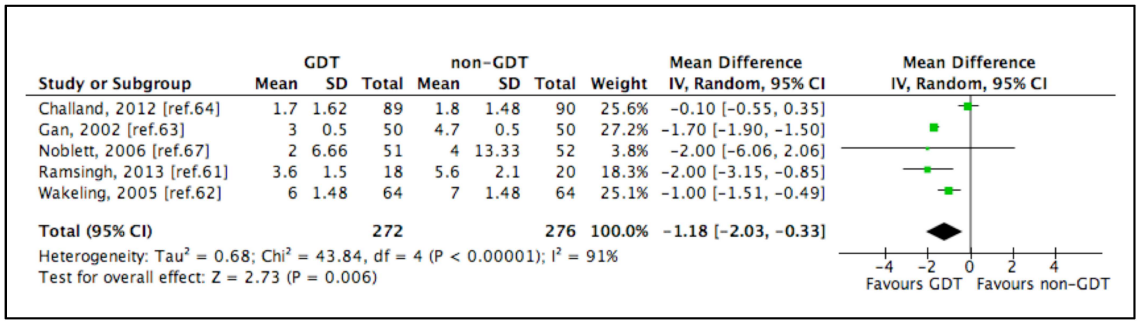


Figure. 2 Forest plots illustrating the effect of goal-directed therapy (GDT) on bowel function after abdominal surgery:



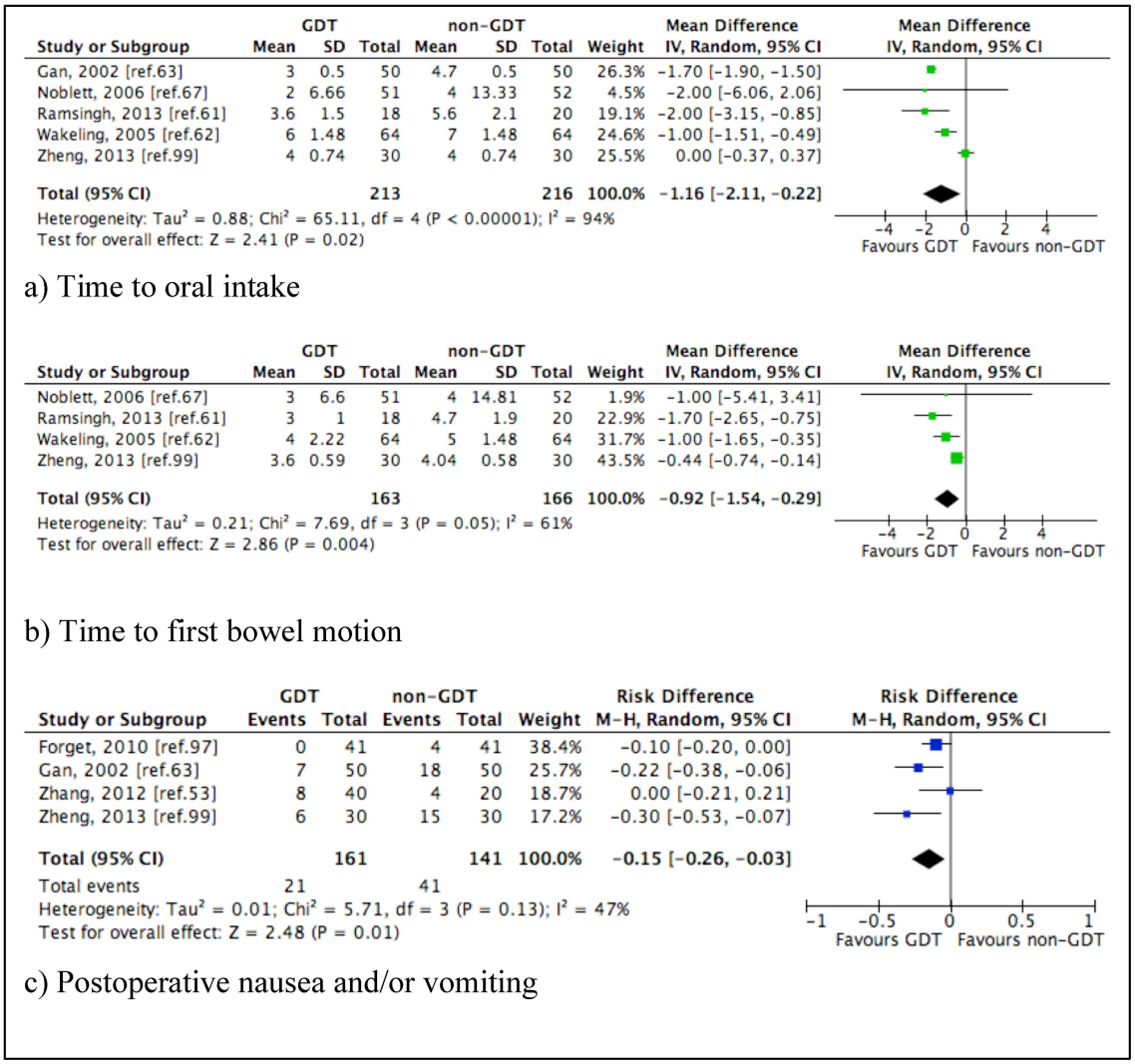
a) Time to tolerate oral intake; **b)** time to first bowel motion; **c)** postoperative nausea and/or vomiting. **a, b** An inverse-variance random-effects model was used for meta-analysis. Weighted mean differences (WMDs) are shown with 95 per cent c.i. **c)** A Mantel–Haenszel random-effects model was used for meta-analysis. Risk differences are shown with 95 per cent c.i.

Figure. 3 Forest plot illustrating the effect of goal-directed therapy (GDT) on time to tolerate oral intake, excluding studies with other sources of bias[66, 96, 99] or uncertain risk of bias[97].



An inverse-variance random-effects model was used for meta-analysis. Weighted mean differences (WMDs) are shown with 95 per cent c.i.

Figure. 4 Forest plots illustrating effect of goal-directed therapy (GDT) on bowel function without an enhanced recovery program.



a) Time to tolerate oral intake; **b)** time to first bowel motion; **c)** postoperative nausea and/or vomiting. **a,b** An inverse-variance random-effects model was used for meta-analysis. Weighted mean differences (WMDs) are shown with 95 per cent c.i. **c** A Mantel–Haenszel random-effects model was used for meta-analysis. Risk differences are shown with 95 per cent c.i.

Tables

Table 1. Quality assessment and risk of bias of the included studies

	Random sequence generation	Allocation concealment	Blinding of patients and surgeons	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources*
Benes, 2010[95]	?	+	+	+	+	?	+
Bisgaard, 2013[96]	+	?	+	+	+	+	-★
Brandstrup, 2012[57]	+	+	+	?	+	?	+
Challand, 2012[64]	?	+	+	+	+	?	+
Forget, 2010[97]	?	?	+	+	+	?	+
Gan, 2002[63]	+	?	+	+	+	?	+
Jammer, 2010[66]	+	+	+	+	+	+	-★
Noblett, 2006[67]	?	?	+	?	+	?	+
Ramisingh, 2013[61]	+	?	+	?	+	+	+
Srinivasa, 2013[98]	+	+	+	?	+	+	+
Wakeling, 2005[62]	?	+	+	?	+	?	+
Zhang, 2012[53]	+	?	?	+	+	+	+
Zheng, 2013[99]	+	?	+	+	+	+	-★

+; low risk of bias, ? ; unclear risk of bias, - ; high risk of bias. * For example, the study design was inappropriate, the study was stopped earlier, extreme baseline imbalance between groups★ Intraoperative goal directed therapy was extended to the postoperative period.

Table 2. Summary of the included articles

Study/population	Goal directed therapy (Monitor/type of fluids, inotropes / volume/ hemodynamic parameters followed to guide fluid administration)	Control Group (Type of fluids, inotropes/clinical and hemodynamic parameters followed to guide fluid administration	Assessment of bowel function/outcome measures
Benes, 2010[95] n= 120 high-risk major abdominal surgery (open)	Vigileo/FloTrac ® 6% HES (130/0.4), 3 ml^{-1} kg^{-1} Dobutamine CVP and Cardiac index, stroke volume variation	Basal plasmalyte ® infusion 8 ml^{-1} kg^{-1} h^{-1} Additional intravenous fluids if needed MAP, HR, CVP, urine output	Any paresis of the gastrointestinal tract (no peristalsis distinguishable, intolerance of oral or enteral feeding or liquids) lasting more than 3 days after surgery or its new onset
Bisgaard, 2013[96] n = 70 Open abdominal aortic surgery	LiDCO plus Dobutamine (postoperative) 6% HES (130/0.4) Stroke volume index	6% HES (130/0.4) Fluid losses, hemodynamic parameters, arterial blood gas	Incidence of gastrointestinal paralysis
Brandstrup, 2012[57] n=150 Open and laparoscopic colorectal surgery	Esophageal doppler 6% HES, 200 ml Stroke volume	Normal saline infusion if preoperative oral intake <500 ml 6% HES (130/0.4), 200 ml if needed BP, HR, CVP	Paralytic postoperative primary ileus: minimum 5 days without flatus or feces
Challand, 2012[64] n=179, high-risk (n=56) Major open and laparoscopic colorectal surgery	Esophageal doppler 6% HES, (130/0.4), 200 ml Stroke volume	Crystalloid, colloid, blood products, and/or inotropes Fluid losses, hemodynamic parameters	Time to first flatus Time to first bowel movement Time to toleration of oral diet
Forget, 2010[97] n=86 Major abdominal surgery	Datex Ohmeda® S/5 6% HES (130/0.4), 250 ml Pleth variability index	Baseline infusion of crystalloid 4-8 ml^{-1} kg^{-1} h^{-1} Colloid if needed Acute blood loss, MAP, CVP	Nausea and/or vomiting
Gan, 2002[63] n= 100, high-risk Major open elective general, urologic, gynecologic surgery	Esophageal Doppler 6% HES (130/0.4) Flow time corrected, stroke volume	Baseline infusion of lactated Ringer's solution 5 ml^{-1} kg^{-1} h^{-1} Intravenous fluids, 200 ml if needed Urine output, HR, CVP, Systolic blood pressure	Time to tolerance solid diet, severe postoperative nausea and vomiting requiring rescue antiemetic treatment
Jammer, 2010[66] n=241 Open colorectal surgery	Central venous catheter 6% HES (130/0.4), 3 ml^{-1} kg^{-1} Central venous oxygen saturation	Basal infusion of Lactated Ringer's solution 10-12 ml^{-1} kg^{-1} h^{-1} Lactated Ringer's solution or 6% HES (130/0.4) if needed Blood loss, BP, urine output	Paralytic postoperative primary ileus defined as "unable to tolerate enteral diet > 5 days"
Noblett, 2006[67] n=103 Elective open and laparoscopic colorectal surgery	Esophageal doppler 4% Succinylated gelatin, 3 and 7 ml^{-1} kg^{-1} Flow time corrected, stroke volume	Crystalloids and/or colloids Fluid losses, hemodynamic parameters	Return to bowel activity (flatus, bowel movement and diet tolerance, defined as patient able to consume 50% of each meal in a 24 hour period)
Ramsingh, 2013[61] n=38, high-risk Major open abdominal non-vascular surgery	FloTrac/vigileo ® 5% albumin, 250 ml Stroke volume variation	Intravenous fluids Hemodynamic parameters	Elapsed time between the end of the surgery and the first bowel movement and tolerance of postoperative of soft diet (defined by > 50% consumption of breakfast and lunch or breakfast and dinner)
Srinivasa, 2013[98] n=74 Elective open or laparoscopic colectomy	Esophageal doppler 4% Succinylated gelatin 3 and 7 ml^{-1} kg^{-1} Flow time corrected, stroke volume	Plasmalyte ®, maximum 1500ml Gelofusine ®, maximum 500 ml Blood loss, BP, HR and urine output	Paralytic postoperative primary ileus: prolonged cessation of bowel function requiring nasogastric tube placement, excluding patients with secondary ileus
Wakeling, 2005[62] n=128 Large bowel surgery	Esophageal Doppler 3.5% gelatin polypeptides, 250 ml 4% Succinylated gelatin Stroke volume, CVP	Intravenous fluids CVP	Time to tolerate full diet, passing flatus and bowel opening
Zhang[53], 2012 n=60	Datex Ohmeda® S/5 1st group LR 250 ml based on Pulse	Baseline infusion of LR 5 ml^{-1} kg^{-1} h^{-1} Lactated Ringer's solution, 250 ml	Time to first flatus

Elective open gastrointestinal surgery	pressure variation 2nd group HES 250 ml based on Pulse pressure variation Both groups received 6% HES (130/0.4) 1:1 to replace blood loss	6% HES (130/0.4) Blood loss, CVP, urine output	

HES (130/0.4), hydroxyethyl starch (molecular weight 130, degree of substitution 0.4); CVP, central venous pressure; MAP, mean arterial pressure; HR, heart rate; LiDCO, lithium dilution cardiac output. LiDCO plus® (LiDCO Group, London UK); Vigileo/FloTrac® (Edwards Lifesciences, Irvine, California, USA); Plasmalyte® (Baxter, Deerfield, Illinois, USA); Datex Ohmeda® (General Electric, Fairfield, Connecticut, USA); Gelofusine® (B. Braun, Melsungen, Germany).

Table 3. Perioperative care of patients in the included studies

Study	Analgesia	ERP	Postoperative intravenous fluid management	Postoperative nutrition
Benes, 2010[95]	Thoracic epidural analgesia/ lumbar epidural analgesia (local anaesthetic and opioids): goal directed therapy group (58%), control group (62 %), intraoperatively and postoperatively. Duration not specified. Alternative analgesia was not specified	No	Not standardized	Not standardized
Bisgaard, 2013[96]	Thoracic epidural analgesia/ lumbar epidural analgesia (local anaesthetic and opioids) in all patients	No	Goal directed therapy group: LiDCO until 6 hours postoperatively (bolus of 250 ml of colloid until SVI >10% for 20 ≥min. Dobutamine if oxygen delivery index < 600 ml^{-1} min^{-1} m^2 Control group: 6% HES (130/0.4), blood and vasopressors at the discretion of the anaesthesiologist based on fluid losses, hemodynamic parameters and arterial blood gas	Not reported
Brandstrup, 2012[57]	Epidural analgesia (only for open surgery) Analgesia for laparoscopic surgery was not specified	Yes	Intravenous fluid were administered if oral fluid intake was insufficient, in presence of pathological fluid losses or hypovolemia	Oral fluid intake when patients could swallow safely Oral nutrition was encouraged when the patient could swallow safely Parenteral nutrition was commenced if patients did not eat sufficiently for 2–3 days and the condition seemed to continue
Challand, 2012[64]	Epidural analgesia (medications not specified) for open surgery: goal directed therapy group (n=37), control group (n=31); Spinal analgesia (local anaesthetic and opioid), anaesthetic filed blocks were used for laparoscopic surgery	Yes	Not standardized (based on local guidelines that suggested a daily fluid intake of 2 L)	Free oral fluid, light diet, or both the evening of surgery if tolerated
Forget, 2010[97]	Thoracic epidural analgesia	No	Not reported	Not reported
Gan, 2002[63]	Epidural analgesia (local anaesthetic and opioids): goal directed therapy group (12%) in the control group (16%), only postoperatively. Duration was not specified; Systemic opioids	No	Not standardized	Patients who had flatus were started with oral fluid followed by solid food if tolerated (without emetic symptoms within 4 hours)
Jammer, 2010[66]	Thoracic epidural analgesia (local anaesthetic and opioids) for all patients (except five patients in the goal directed therapy group and one in the control group)	No	Goal directed therapy group: glucose 5% at 80 ml per hour until day 1 and replacement of losses from stomas and drains with lactated ringer's solution 1:1. Extra intravenous fluids in presence of clinical signs of hypovolemia central venous oxygen saturation <75% (maximum 6% HES (130/0.4) 50 ml^{-1} Kg^{-1} $24h^{-1}$). Control group: 5% glucose 1000 ml until the morning after surgery. Extra fluids in presence of clinical signs of hypovolemia. 6% HES (130/0.4) in case of hypotension In both groups, after 8 am on day 1 fluid management was left to surgeons, unaware of patients' allocation.	Not reported
Noblett, 2006[67]	Epidural analgesia (medications not specified): goal directed therapy group (63 %), control group (63%),	No	Not standardized. Postoperative fluid administration based on blood pressure, urine	Oral fluid from the evening of surgery, solid diet from the first day after

	intraoperatively and postoperatively for 48 hours; Systemic opioids		output, fluid losses and oral intake.	surgery
Ramsingh, 2013[61]	Epidural analgesia (medications not specified): goal directed therapy group (17%), control group (10%). Timing of intervention and duration were not specified; Systemic opioids	No	Not standardized	Not standardized
Srinivasa, 2013[98]	Epidural analgesia (local anaesthetic and opioids): used intraoperatively and postoperatively for 48 hours	Yes	Intravenous fluids were discontinued when patients arrived to the ward. Fluids were administered in presence of oliguria, tachycardia, hypotension and in case of complications, poor oral intake or paralytic ileus	Oral intake of food, fluids and supplements was encouraged when patients arrived to the ward
Wakeling, 2005[62]	Epidural analgesia (medications not specified): used in the goal directed therapy group (17%), control group (17%) postoperatively. Duration was not specified; Systemic opioids	No	Intravenous fluids were discontinued when oral intake exceeded 1500 ml per day and in absence of nausea, vomiting. Infusion rates were not specified.	Water was allowed on postoperative day 1and clear fluids on postoperative day 2. Progression to soft diet if tolerated on postoperative day 3 and full-unrestricted diet if tolerated on postoperative day 4.
Zhang, 2012[53]	Systemic opioids and NSAIDs	No	Baseline crystalloid infusion 1.5-2 ml^{-1} Kg^{-1} h^{-1}	Not reported
Zheng, 2013[99]	Not reported	No	Goal directed therapy group: goal directed therapy was used up to 24 hours after surgery. Control group: not reported	Clear liquids were encouraged on postoperative day 1 (beginning 24 h after surgery). On postoperative day 3 and 4 patients could have a semi-fluid diet and intravenous feeding was reduced or discontinued.

ERP, enhanced recovery program; GDT, goal-directed therapy; LiDCO, lithium dilution cardiac output; HES (130/0·4), hydroxyethyl starch (molecular weight 130, degree of substitution 0·4). LiDCO plus® (LiDCO Group, London, UK); n.r., not reported; NSAID, non-steroidal anti-inflammatory drug.

Table 4. Intraoperative volume of colloids) and crystalloids

First author, year	Total volume of colloids (ml)		Total volume of crystalloids (ml)	
	GDT (n= 695)	**Non-GDT (n= 689)**	**GDT (n= 677)**	**Non-GDT (n= 669)**
Benes, 2010[95]§	1425 (1000-1500) *	1000 (540-1250) *	2321 ± 681	2459 ± 930
Bisgaard, 2013[96]¶	1683 ± 681	1611 ± 610	2570 ± 896	2888 ± 996
Brandstrup, 2012[57]	810 ± 543	475 ± 598	483 ± 419	443 ± 480
Challand, 2012[64]	358 ± 676	336 ± 623	3479 ± 1181	3593 ± 1398
Forget, 2010[97]#	890 95% c.i. (709-1072)‡	1003 95% c.i. (779-1227)‡	1363 95% c.i. (1185-1540)‡	1815 95% c.i. (1568-2064)‡
Gan, 2002[63]	847 ± 373	282 ± 470	4405 ± 2650	4375 ± 2452
Jammer, 2010[66]	438 ± 419	285 ± 405	Lactated Ringer's solution: 649 ± 333 Other crystalloid: 773 ± 209	Lactated Ringer's solution: 2743 ± 1020 Other crystalloid: 694 ± 247
Noblett, 2006[67]	1340 ± 838	1209 ± 824	2298 ± 863	2625 ± 1004
Ramsingh, 2013[61]	544.4 ± 493.5	422.5 ± 590.8	11.7 ± 6.0**	14.7 ± 5.5**
Srinivasa, 2013[98]	591 ± 471	297 ± 275	1500 [1000-2000]†	1100 [1000-2000]†
Wakeling, 2005[62]	2000 [500-5000]†	1500†	3000†	3000†
Zhang, 2012[53]	GDT-C 865 ± 297.4	252.5 ± 44.4	GDT-C 877.5 ± 130.0	1012.5 ± 238.4
	GDT-LR 256.5 ± 139.9		GDT-LR 1853 ± 381.3	
Zheng, 2013[99]††	1000 (900-1100) *	800 (600-1000) *	1550 (1400-1925) *	2350 (2000-2925) *
Total weighted mean ± SD	903.8 ± 520.5	682.2± 461.5	2154.4± 1096.8	2614.5 ± 1142.9
p-value	p < 0.001‡‡		p < 0.001‡‡	

Values are mean (s.d.) unless indicated otherwise; values are *median (i.q.r.), †median (range, if given), and ‡median (95 per cent c.i.). §Nine patients from the goal-directed therapy (GDT) group and six from the control group were excluded from the analysis; ¶three patients from the GDT group and three from the control group were excluded; #two patients from the GDT group and three from the control group were excluded; **data reported in milliliters per kilogram per hour, and therefore excluded from the final analysis (18 patients in GDT group and 20 in control group); ††two patients from the GDT group and three from the control group were excluded. LR, lactated Ringer's solution; GDT-C, goal-directed therapy with colloids; GDT-LR, goal-directed therapy with lactated Ringer's solution. ‡‡Two independent-samples *t* test.

Chapter 2

"Goal-directed fluid therapy does not reduce the incidence of primary postoperative ileus after elective laparoscopic colorectal surgery in the context of an Enhanced Recovery After Surgery (ERAS) program: a randomized controlled trial"

"This is a non-final version of an article published in final form in Anesthesiology"

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Ph. D Experimental Surgery

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The impact of intraoperative Goal Directed Fluid Therapy (GDFT) on primary postoperative ileus (PPOI) after colorectal surgery in the context of an Enhanced Recovery Program (ERP)

Preamble

Although the results of the previous meta-analysis have shown that intraoperative GDFT might facilitate the recovery of bowel function, the validity of these results is influenced by the quality and by the high-degree of clinical and statistical heterogeneity of the included randomized clinical trials.

It must be also considered that ambiguity about the definition of PPOI still exists, especially in patients treated with an ERP. Traditionally, PPOI is defined based on the presence of time-based endpoints such as the time required to pass gas and/or bowel movements after surgery and the presence of gastrointestinal symptoms. Moreover, in patients treated with traditional surgical care, clear fluid diet is initiated after establishing that postoperative gastrointestinal dysfunction is resolving, and then progressively advanced to regular diet as tolerated. In the context of an ERP, such criteria would poorly identify patients with significant gastrointestinal dysfunction, since regular diet as tolerated is initiated on postoperative day 1, regardless on the presence of gastrointestinal symptoms indicating the recovery of bowel function. As a result, it remains challenging to determine the real effectiveness of perioperative strategies aiming at attenuating postoperative gastrointestinal dysfunction and reducing the incidence of PPOI, especially in the context of an ERP.

Based on these considerations, and after having performed a literature review in 2012, an interdisciplinary consensus was achieved among anesthetists, colorectal surgeons and nurses working at the Montreal General Hospital on how to diagnose and manage postoperative ileus in the context of an ERP. An evidence-based algorithm, mainly focused on the presence of symptoms more than time-based endpoints, was developed and then implemented for 1 year, in patients undergoing elective colorectal surgery within an ERP program at the Montreal General Hospital. Based on this consensus, patients with PPOI were identified by the presence of 2 or more clinical indicators of gastrointestinal dysfunction, at least 1 for each of the 2 following criteria 1) presence of vomiting, OR abdominal distension and 2) absence of passing gas or stool, OR not tolerating oral diet in absence of any precipitating complications. Over this year it was found that PPOI was present in approximately 40% of the patients, and that in the absence of postoperative complications, primary postoperative ileus prolonged hospital stay by a median of 2 days (unpublished data). At that time, several perioperative strategies to reduce the incidence of PPOI had already been implemented as standard of care (laparoscopy, preoperative carbohydrate beverages, opioid-sparing analgesic strategies, early feeding and avoidance of nasogastric tubes), except perioperative fluid management that was left to the discretion of the anesthesiologist in charge and of the surgical team.

In spite of the strong physiologic rational supporting the use of GDFT in major surgical procedures[5, 50], as it can prevent both excessive intravenous fluid administration and restriction and therefore potentially facilitate the recovery of gastrointestinal function, studies primarily investigating the clinical impact of GDFT as intraoperative intervention to decrease the incidence of PPOI after colorectal surgery, and specifically in the context of an ERP program are lacking.

Based on our clinical experience and on the results of the previous systematic review and meta-analysis[107], it was decided to design and perform the following randomized controlled trial, evaluating the effect of intraoperative GDFT on the incidence of PPOI and on the recovery of bowel function, in patients undergoing laparoscopic colorectal surgery in the context of a well established ERP, at the Montreal General Hospital.

Goal-directed fluid therapy does not reduce the incidence of primary postoperative ileus after elective laparoscopic colorectal surgery in the context of an Enhanced Recovery After Surgery (ERAS) program: a randomized controlled trial.

Introduction

Postoperative gastrointestinal dysfunction that occurs in absence of surgical complications, frequently defined as primary postoperative ileus (PPOI), is one of the major determinants of in-hospital recovery after colorectal surgery[108,109]. Despite advancements in surgical and perioperative care, PPOI still remains an unpleasant complication that not only delays early enteral feeding and increases caregivers' workload, but also increases morbidity[3], prolongs hospitalization[110] and increases medical costs[80, 111] .

Experimental and clinical trials have shown that both fluid excess[19, 22, 27, 112-117] or hypovolemia[24] can significantly affect the recovery of bowel function and impair anastomotic healing [22, 118, 119]. Early studies have shown that individualization of fluid therapy based on more objective measures of hypovolemia (goal directed fluid therapy, GDFT) accelerates the recovery of bowel function[63, 120], reduces hospitalization[20, 50] and overall complications[50], especially in high-risk patients[2, 121]. However, the majority of these studies were conducted in an uncontrolled clinical setting, where several perioperative confounding factors might have affected postoperative outcomes. In fact, more recent evidence[55, 57, 58, 122, 123] has not confirmed these results in patients treated with Enhanced Recovery After Surgery (ERAS) programs and thereby receiving a more standardized perioperative care. In these patients, the implementation of several and integrated evidence-based perioperative interventions, that by acting synergistically have shown to improve clinical outcomes after colorectal surgery[124], might have blunted the historical benefits observed

with GDFT[55, 57, 58, 122, 123]. It must be also considered that the number and type of interventions included in the ERAS programs vary between different centers, making difficult to determine and generalize the impact of a single intervention on postoperative outcomes.

In light of this controversial evidence, the impact of GDFT on specific postoperative complications and in a context of an ERAS program remains unknown. Specifically, there is a lack of high-quality studies primarily investigating the effect of GDFT on the recovery of bowel function[55] in a controlled clinical setting where perioperative interventions influencing bowel function are standardized.

The aim of this study is to determine the impact of GDFT on the incidence of PPOI in patients undergoing laparoscopic colorectal surgery and treated with a well-established center-specific ERAS program. It is hypothesized that patients treated with GDFT would experience less PPOI than patients receiving fluid therapy based on traditional principles.

Methods

Trials design and study subjects

This randomized (1:1) parallel-group patient and assessor-blinded trial was approved by the Research Ethics Board of the McGill University Health Centre, Montreal, Quebec, Canada (Study # 12-177-SDR) and the study procedures were carried out in accordance with ethical standards (ClinicalTrials.gov registration: NCT01818375). Patients were recruited between January 2013 and August 2015 at the Montreal General Hospital, a university-affiliated tertiary center. Consecutive patients, scheduled for elective laparoscopic colorectal resection, were approached by a research investigator at the preoperative clinic, and written consent was obtained

in eligible patients. Patients were excluded if they were younger than 18 years old, required emergency surgery, had undergone previous esophageal or gastric surgery, had esophageal varices or cancer; coarctation of the aorta, chronic atrial fibrillation, severe aortic stenosis, preoperative bowel obstruction, coagulopathies, contraindications to epidural analgesia, if they were chronically treated with opioids, and if they did not read or communicate in French or English.

The morning of surgery, eligible patients were randomly assigned by a stratified computer-based block randomization to receive GDFT based on near-maximal stroke volume (SV) optimization (GDFT group)[125] or fluid therapy based on traditional principles[126] (Control group). These include the replacement of preoperative fasting deficit (4/2/1 rule), volume expansion following the induction of anesthesia, and the replacement of insensible blood loss and third space loss (***Supplement 1***). Randomization was stratified by the surgical indication of creating a stoma. Group allocation was concealed using sequentially numbered sealed brown envelopes, opened the morning of surgery by the research investigators.

Perioperative care

Patients were treated according to a well established ERAS program specific for patients undergoing elective colorectal surgery initially implemented at our institution in 2008[127], and subsequently modified (***Supplement 2***).

Anesthesia and analgesia management: on the day of surgery patients were transferred in the preoperative anesthesia area where preoperative weight was measured and an intravenous catheter was inserted. After recording baseline hemodynamic variables, Lactated Ringer's® 27

ml^{-1} Kg^{-1} [128] was infused before induction of anesthesia in patients of the Control group who received mechanical bowel preparation (4 L of polyethylene glycol electrolyte lavage, GoLytely®, Braintree, laboratories, MA, USA). A thoracic epidural catheter was inserted between T8 and T12 and a test dose of 3 ml lidocaine 2% with epinephrine ($5\mu g^{-1}$ ml^{-1}) was used to confirm the correct placement. Presence of sensory block was assessed before surgery with an ice test, and in presence of primary failure epidural catheters were replaced before induction of anesthesia. No subsequent epidural local anesthetics were administered intraoperatively to minimize the hemodynamic effects of epidural blockade. General anesthesia was induced with propofol (2 mg^{-1} kg^{-1}) and remifentanil (1.0 μg^{-1} kg^{-1}) and maintained with desflurane or sevoflurane in a mixture of 40% oxygen and 60% air. Intraoperatively, analgesia was provided with remifentanil infusion (0.05-0.25 μg^{-1} kg^{-1} min^{-1}) titrated to keep heart rate and blood pressure within ± 20% of the baseline values. Rocuronium was used to facilitate orotracheal intubation and maintain adequate neuromuscular blockade during surgery (Train Of Four-TOF count less than 2). Lungs were ventilated with a tidal volume of 8 ml^{-1} Kg^{-1} and with a positive end-expiratory pressure of 5 cmH_2O. End-tidal carbon dioxide was maintained between 35 and 40 mmHg by adjusting the respiratory rate. Postoperative nausea and vomiting (PONV) prophylaxis was achieved with dexamethasone (8 mg), and droperidol (0.625 mg). At the end of surgery, remifentanil was discontinued, 10 ml of lidocaine 2% were bolused in the epidural catheter, and ketorolac (30 mg) was administered if not contraindicated. Then, an epidural mixture of bupivacaine (0.1 mg^{-1} ml^{-1}) and fentanyl (3 μg^{-1} ml^{-1}) was started and infused for 48 h. Celebrex and acetaminophen were also prescribed for the entire hospitalization, unless contraindicated. Systemic opioids were administered after the epidural was discontinued or before if clinically required.

Intraoperative hemodynamic monitoring and management: Electrocardiogram activity, invasive-blood pressure and oxygen saturation were measured in every patient. Following induction of anesthesia, a disposable Esophageal Doppler (ED) probe (DP12 probe) was inserted into the distal third of the esophagus in every patient. Optimal blood flow signal was identified from the descending aorta in the supine position and displayed on the ED monitor (CardioQ-Oesophageal DM; EDT^{TM}; Deltex Medical Inc., Irving, TX, USA) by the treating anesthesiologist in the GDFT group, and by 2 research investigators in the Control group. The machine was calibrated to provide data averaged over 10 cycles[129].

In the GDFT group, the patient was positioned in steep Trendelenburg, and after 30 seconds from the change in position ED-derived hemodynamic variables and standard cardiovascular parameters were recorded. If SV increased by more than 10% the patient was repositioned flat, 200 ml of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride (Voluven®, Fresenius Kabi, Ltd, Cheshire, UK) were administered in 5 minutes, and a new SV measurement obtained. This process was repeated until changing in position did not result in an increase of more than 10% in SV. At this point it was assumed that SV had reached the plateau of the Frank-Starling curve (near-maximal SV), and the patient was considered volume optimized. The final head-down cardiovascular measurement which did not result in an increase in SV by more than 10% was recorded (**T_B),** the patient was repositioned flat, and surgery commenced. This method was previously described to minimize the cardiovascular effects of the pneumoperitoneum and of the changes in position during surgery[130]. After having established the pneumoperitoneum and positioned the patient in Trendelemburg, near-maximal SV was maintained during surgery[125] (***Supplement 3, Figure A***). A background maintenance infusion of Lactated Ringer's® 1.5 ml^{-1} Kg^{-1} h^{-1} was administered until then end of surgery[131].

In the Control group, the ED monitor was turned away from the anesthesia care provider and the screen was covered with a surgical towel after the induction of anesthesia. The cardiovascular response obtained 30 seconds after positioning the patient in steep Trendelenburg and before starting the pneumoperitoneum was measured and recorded ($\mathbf{T_B}$**).** Anesthesiologists were blinded to the measurements obtained with the ED for the entire duration of the study. Additional fluids were administered if clinically deemed based on the judgment of the anesthesiologist in charge.
In both groups blood products were administered when clinically indicated and based on previously reported laboratory cutoffs[63]. Vasopressors and inotropes were also administered based on the clinical judgment of the treating anesthesiologist.

Surgical technique: Surgery was performed by 3 experienced fellowship-trained colorectal surgeons as previously described[132]

Postoperative care: at the end of surgery patients were transferred into the Post anesthesia care unit (PACU) and an intravenous infusion of Lactated Ringer's® 1.5 ml^{-1} Kg^{-1} $hour^{-1}$ was started. After meeting PACU discharge criteria, patients were discharged to the surgical unit and Lactated Ringer's® infusion was reduced to 15 ml^{-1} $hour^{-1}$ (to keep the vein open) until 8.00 AM of the following morning, when intravenous fluids were discontinued. Additional intravenous fluids were administered by the anesthesiologist in charge (in PACU) or by the surgical team (on the surgical unit) as per usual care. The day of surgery patients were encouraged to drink clear fluids (1.5 L^{-1} day^{-1}), and solid diet as tolerated was started the morning after surgery. The acute pain service (APS) visited patients daily to optimize pain control. The surgical team and the APS were blinded to patients' randomization. Patients were discharged if afebrile, tolerated oral diet, pain was well controlled (numeric rating score < 4), and ambulated independently.

Study outcomes, measurements, and data collection

The primary outcome was the incidence of PPOI during the hospital stay. There is a lack of a standard and validated definition of PPOI. Traditional criteria used to define PPOI commonly include time-based endpoints such as the time required to pass gas and/or bowel movements or time to tolerate oral diet. These criteria poorly identify patients with significant postoperative gastrointestinal dysfunction in the context of an ERAS program, as colorectal patients are fed as tolerated in the immediate postoperative period, independently on the presence of such criteria. Based on these considerations and after having performed a literature review, in 2012 an interdisciplinary consensus was achieved among anesthetists and colorectal surgeons working at the Montreal General Hospital on how to diagnose and manage postoperative ileus in the context of an ERAS program. It was found that PPOI in absence of postoperative complications was associated with a median increase of 2 days in length of hospital stay. Patients with PPOI were identified by the presence of 2 or more clinical indicators of gastrointestinal dysfunction, at least 1 for each of the 2 following criteria 1) presence of vomiting, OR abdominal distension and 2) absence of passing gas or stool, OR not tolerating oral diet in absence of any precipitating complications. Secondary outcomes included Quality of Recovery score[133], 30-day complications, readiness to be discharged, length of hospital stay and readmission rates. Postoperative complications were defined *a priori* (***Supplement 4***) and their severity graded by using the Dindo–Clavien classification[134] and the Comprehensive Complication Index[135].

Hemodynamic variables were measured by the treating anesthesiologist in the GDFT group, and by the 2 research investigators in the Control group, all well trained on how to obtain and interpret ED-derived hemodynamic measurements. The ED probe was refocused if necessary, and ED-derived hemodynamic variables were measured 5 minutes after induction of anesthesia

($\mathbf{T_0}$), in steep Trendelemburg ($\mathbf{T_B}$), and every 15 minutes until the end of surgery ($\mathbf{T_{final}}$), before the epidural was bolused. Postoperatively, patients were instructed to drink from a specific 250 ml cup to measure daily oral fluid intake. Patients were also weighed every morning before breakfast. Postoperative gastrointestinal function was assessed by a research investigator after the dinner was served. The amount of systemic opioid consumption was measured daily, and converted to intravenous morphine equivalents[136]

Preoperative and intraoperative data were collected by 2 study investigators, while postoperative data were collected by a third study investigator who was blinded to patients' randomization and to the entire intraoperative management. The study investigators were not involved in clinical decision-making and did not have access to the data collected by the other investigators. Data were initially recorded on specific data collection sheets and then transferred into 2 separate databases, one containing preoperative and intraoperative data, and the other postoperative data. The 2 databases were merged only when the study was terminated.

Sample size calculation and statistical analysis

Based on 40% incidence of primary PPOI observed in 114 patients who underwent elective colorectal surgery in the context of an ERAS program at the Montreal General Hospital, using the same criteria previously described, a power analysis indicated that a sample size of 64 patients in each group was required to show a 50% PPOI reduction in patients treated with GDFT (one-sided-t-test), with a power of 0.8 and a type 1 error (α) = 0.05. The hypothesis that GDFT would reduce to 20% the incidence of PPOI was based on the observation that in 2012, the incidence of PPOI at our institution was exceptionally higher (40%) than what reported in other centers[137],

despite a well established ERAS program that included several perioperative interventions that have shown to accelerate the recovery of bowel function (selective use of MBP, carbohydrate-rich beverages, early feeding, laparoscopic surgery, epidural, chewing gum, opioid sparing strategies etc.). At that time, perioperative fluid management was the only element that was not standardized. We therefore hypothesized that GDFT, by administering intravenous fluids based on more objective measures of hypovolemia, would significantly reduce the incidence of PPOI.

Analysis was performed on an intention-to-treat basis and as per protocol. The primary outcome was evaluated using the Chi-square test (χ^2) or Fisher's exact if appropriate. A pre-planned sub-group analysis of the primary outcome was conducted in patients not receiving a stoma, and in patients undergoing colonic surgery, and in patients undergoing rectal surgery. As the proportion of patients who received MBP was significantly different between the 2 groups ($p = 0.021$), a non-planned adjusted analysis was conducted to calculate the relative risk of PPOI, by adjusting for the use of MBP. Secondary outcomes were evaluated using the Student's t-test for normally distributed data, the Wilcoxon-Mann-Whitney's test for not normally distributed and the Chi-square test (χ^2) or Fisher's exact test when appropriate. Linear mixed model-analysis was used to assess and compare hemodynamic variables over time and between groups. The Tukey's test was used for post-hoc analysis.

Continuous variables are reported as mean ± standard deviation or median (interquartile range), and categorical and ordinal variables as absolute number (percentage). Relative risk with 95% confidence intervals is also reported for categorical variables.

Statistical analysis was performed using IBM SPSS statistic® version 23 (IBM, 2015, NY, USA) or STATA® version 14 (StataCorp, College Station, TX, USA). All statistical tests were 2-sided and a p-value < 0.05 was considered to indicate statistical significance.

Results

Patients' characteristics, operative data and anesthesia care

A total of 196 patients were assessed for eligibility, of which 135 patients were randomized, 68 to the GDFT group and 67 to the Control group. A total of 128 patients were analyzed on an intention-to-treat basis (64 in the GDFT and 64 in the Control group) and 115 patients were analyzed per protocol (56 in the GDFT and 59 in the Control group) (***Figure 1***). Baseline patients' characteristic, operative data, and anesthesia care were similar between the 2 groups (***Table 1*** and ***Supplement 5***).

Intraoperative fluid administration, vasopressors, and hemodynamic data

Patients in the GDFT group received less intravenous fluids (p<0.001) (mainly less crystalloids, p<0.001), but a greater volume of colloids, p<0.001. Estimated blood loss was not different, phenylephrine was used more frequently in the Control group (p = 0.020) and none of the patients required inotropes (***Table 2***). SV and cardiac output (CO) changes over time were significantly different between the 2 groups (slope difference, p<0.001 and p<0.001, respectively). At T_0, SV and Cardiac Output (CO) were higher in the Control Group (p = 0.007 and p = 0.024, respectively). SV remained significantly higher compared to baseline (T_0) in both groups (p<0.0001), but the increase from T_0 to T_B was more pronounced in the GDFT group (estimate GDFT group = 24.02, p<0.001 *vs* estimate Control group = 12.14, p<0.0001). CO remained significantly higher compared to baseline (T_0) only in GDFT group (p<0.0001) and the

increase from T_0 to T_B was more pronounced in the GDFT (estimate GDFT group = 1.15, $p<0.001$ *vs* estimate Control group = 0.39, p = 0.179). Intraoperative SV and CO values were higher in the GDFT group, however the differences between the 2 groups did not reach statistical significance at any of the other time intervals (***Supplement 6, Figures B and C***). Mean arterial pressure changes over time were similar between the 2 groups (slope difference, p = 0.277). ***(Supplement 6, Figure, D)***.

Postoperative data

In PACU, the 2 groups were comparable with regard to the amount of intravenous fluids, systemic opioids and vasopressors received. PONV, the number of hypotension episodes, urine output and length of PACU stay were also similar.

On the surgical unit, patients received a similar amount of intravenous fluids and oral intake was not different. Postoperative weight gain and urine output were higher in the Control group on day 1 (p = 0.002 and p = 0.004, respectively) (***Table 3***). Postoperative pain intensity was similar, but systemic opioid consumption on day 2 and 3 was slightly higher in patients of the Control group (p = 0.024 and p = 0.035, respectively ***Table 4***).

Outcomes

Primary outcome and gastrointestinal function: overall, the incidence of PPOI was similar between the 2 groups, on intention to treat analysis (21.9% in the GDFT group and 21.9% in the Control group, Relative Risk = 1.00, 95% confidence interval = 0.52 to 1.92, p = 1.000), and per protocol (p = 1.000). By adjusting for the use of MBP, the risk of developing PPOI did not change (Relative $Risk_{adjusted}$ = 1.00, 95% confidence interval = 0.53 to 1.86, p = 0.094). Recovery measures of gastrointestinal function and gastrointestinal symptoms were also similar (***Table 5***).

Secondary outcomes: Quality of Recovery score, readiness to be discharged, length of hospital stay, overall 30-day medical and surgical complications, emergency department visits and readmission rates were not different. More patients in the GDFT developed intra-or-retroperitoneal abscesses (p = 0.048). (***Table 6*** *and* ***Supplement 7***).

Discussion

The results of this study indicate that intraoperative GDFT aiming to achieve near-maximal SV optimization compared to fluid therapy based on traditional principles does not reduce the incidence of PPOI in patients undergoing laparoscopic colorectal surgery in the context of a well-established ERAS program.

Several trials conducted in patients undergoing abdominal surgery but treated with conventional care have shown that inadequate fluid therapy delays the recovery of gastrointestinal function[22, 112-115]. Experimental and clinical studies have demonstrated that intestinal edema as a result of excessive fluid administration inhibits gastrointestinal transit and impairs anastomotic healing[112 113-115 19, 117 118, 119, 138]. In contrast, fluid restriction has been shown to accelerate the recovery of bowel function and facilitate early intake of oral diet[19, 22, 117]. However, due to the heterogeneity of the study designs, the lack of a universal definition characterizing a restrictive fluid management, and the absence of a standardized perioperative care[139], it remains difficult to establish the real impact of fluid restriction on postoperative morbidity[25, 140, 141].

Individualization of fluid therapy based on more objective measures of hypovolemia, commonly called GDFT, has shown not only to accelerate the recovery of gastrointestinal function[63,22] but also to reduce postoperative complications[50] and hospitalization[20, 50], especially in high-risk

patients[2, 121], and mainly when compared to liberal fluid administration[20]. Because of these benefits, it has been recommended in patients undergoing major abdominal surgery[17, 131, 142, 143].

The results of the present study do not support the use of GDFT to reduce the incidence of PPOI in this specific patient population and perioperative clinical context, despite a larger intraoperative volume of intravenous fluids in the Control group, and a more pronounced and sustained increase of SV and CO in the GDFT group during surgery.

Several reasons can explain these findings. First, patients were treated with several perioperative ERAS interventions that have shown to facilitate the recovery of gastrointestinal function after abdominal surgery, such as the use of preoperative carbohydrate drinks, laparoscopic surgery, thoracic epidural analgesia, opioid-sparing analgesia, and early feeding that might have contributed to minimize the occurrence of PPOI in both groups[109]. This has also been demonstrated by 2 recent meta-analyses, that have shown that when patients are treated with a more rational fluid management, and in the context of an ERAS program, the benefits of GDFT are offset by advancements in perioperative care[55, 123]. Second, patients in the Control group were able to eliminate fluid excess as indicated by a higher urine output the day of surgery and by a marginal weight gain (< 2.5 Kg) on day 1. This suggests that the volume of intravenous fluids received in the Control group might have not been high enough to cause sufficient interstitial edema to determine a high incidence of PPOI or postoperative complications. Finally, approximately two thirds of patients in both groups were at low-risk for postoperative complications and the benefits of GDFT have been mainly demonstrated in high-risk patients[2, 121]. Although postoperative systemic opioid consumption on day 1 and 2 was statistically higher in

patients of the Control group, the clinical relevance of this finding is questionable, as opioid consumption was minimal in both groups.

The main strength of this study is that specifically evaluates the impact of GDFT on the recovery of bowel function, in the context of a standardized and evidence-based perioperative care, limiting the risk of bias due to several perioperative confounding factors. However, it must be acknowledged that ERAS programs include variable interventions, different among institutions, potentially limiting the generalizability of these results in centers with different perioperative care. For example, the impact of GDFT on the recovery of bowel function might have produced favorable results in patients treated with systemic opioids and not with epidural analgesia, as it is well established that thoracic epidural analgesia facilitates the recovery of bowel function. It was decided to standardize the analgesia technique to minimize the risk of bias as patients undergoing laparoscopic rectal surgery, but not colonic surgery, in our institution frequently received epidural analgesia. This practice is based on the results of a previous study, showing better pain control with epidural analgesia in the first 48 h after laparoscopic rectal surgery than with systemic opioids plus intravenous lidocaine[132]. However, despite the use of epidural analgesia in laparoscopic surgery still remains controversial, it has been successfully reported in patients undergoing laparoscopic colorectal surgery and treated with a well-established ERAS program[142].

Several limitations must be acknowledged. First, patients in the Control group received a large volume of intravenous fluids, greater than what is currently recommended[131], Despite the fluid regimen used in the Control group is based on outdated perioperative fluid therapy principles[17, 25] it is consistent with what is recommended in widely used anesthesia textbooks[126]. The 2 groups also differed in the type of fluids, and this might have affected the primary outcome more than

the infusion regimen. However, to the best of our knowledge, colloids use has never been associated with postoperative gastrointestinal dysfunction.

Second, a more rational GDFT protocol based on SV optimization when clinically deemed, rather than on pre-emptive near-maximal SV optimization, might have led to better results, as many patients in the Control were able to maintain adequate systemic perfusion (CO), despite a sub-maximal SV. Third, despite randomization patients in the GDFT received more frequently MBP, and this might have positively influenced the recovery of bowel in this group[144]. However, by adjusting for the use of MBP, the risk of developing PPOI remained unchanged ($RR_{adjusted}$ = 1.00 95%CI= 0.53 to 1.86). Because the incidence of PPOI was similar between the 2 groups despite the unbalanced used of MBP, it might be argued that in the intervention group either GDFT might have not adequately compensated the intravascular deficit due to MBP, leading to splanchnic hypoperfusion and therefore to a higher incidence of PPOI, or that a large volume of fluids could have been administered because of a greater intravascular deficit, causing bowel edema and significant gastrointestinal dysfunction. However, none of these hypotheses can be confirmed, as a subgroup analysis in patients receiving MBP showed that during surgery the increase of SV and CO was more pronounced and sustained in the GDFT group (slope difference, $p< 0.001$ and $p<0.001$, respectively), and that the volume of fluids administered in the 2 groups was similar to what reported in the primary analysis. In this subgroup of patients the incidence of PPOI was 16.4% in the GDFT and 30.4% in the Control group (RR = 0.54, 95% CI = 0.21 to 1.43, p = 0.213) (data not submitted with the current manuscript). Fourth, in absence of a universal and validated definition of ileus, we used a definition based on an interdisciplinary consensus achieved among anesthesiologists and surgeons, which might have not accurately identified patients with PPOI. However, the incidence of PPOI was similar to what has been

previously reported in the context of an ERAS program[27]. Moreover, a secondary analysis including all patients of the study has shown that patients with PPOI, but without any other complications, had a median increase in length of hospital stay of 4 days, and that PPOI was an independent predictor of delayed readiness for discharge and prolonged hospital stay ($p<0.001$ and $p = 0.001$ respectively, data not submitted with the current manuscript). Although the sample size is limited and these results need further validation, these findings suggest that this definition of PPOI might accurately identify patients with a clinically meaningful gastrointestinal dysfunction in the context of an ERAS program. Finally, this study might have insufficient statistical power to determine whether GDFT can reduce PPOI, as its incidence was lower than expected. The expected incidence of PPOI in the control group might have been overestimated, probably because patients in the historical group used to calculate the sample size also received intravenous morphine patient-controlled analgesia and underwent open surgery, factors known to delay the recovery of bowel function after colorectal surgery[109]. In contrast, laparoscopy and thoracic epidural analgesia used in every patient of this study might have significantly reduced the occurrence of PPOI. It might be also possible that the volume of fluids received in the historical group was significantly higher than what infused in control group, causing a higher incidence of PPOI. Unfortunately we could not accurately retrieve this information, as the volume and type of fluids infused during surgery was poorly reported in the anesthetic charts. In addition, these results might be in part explained by the participation effect, as patients undergoing clinical trials tend to have better outcomes regardless of the treatment they receive[145].

In conclusion, within its limitations this study shows that intraoperative GDFT compared to fluid therapy based on traditional fluid management does not reduce the incidence of PPOI in patients undergoing laparoscopic colorectal surgery in the context of an ERAS program. Its previously

demonstrated benefits might have been offset by advancements in perioperative and surgical care. Nonetheless, fluid therapy should be always based on physiologic and scientific principles, to minimize the risk of complications associated with fluid overload and hypovolemia, especially in high-risk surgical patients.

Figure 1

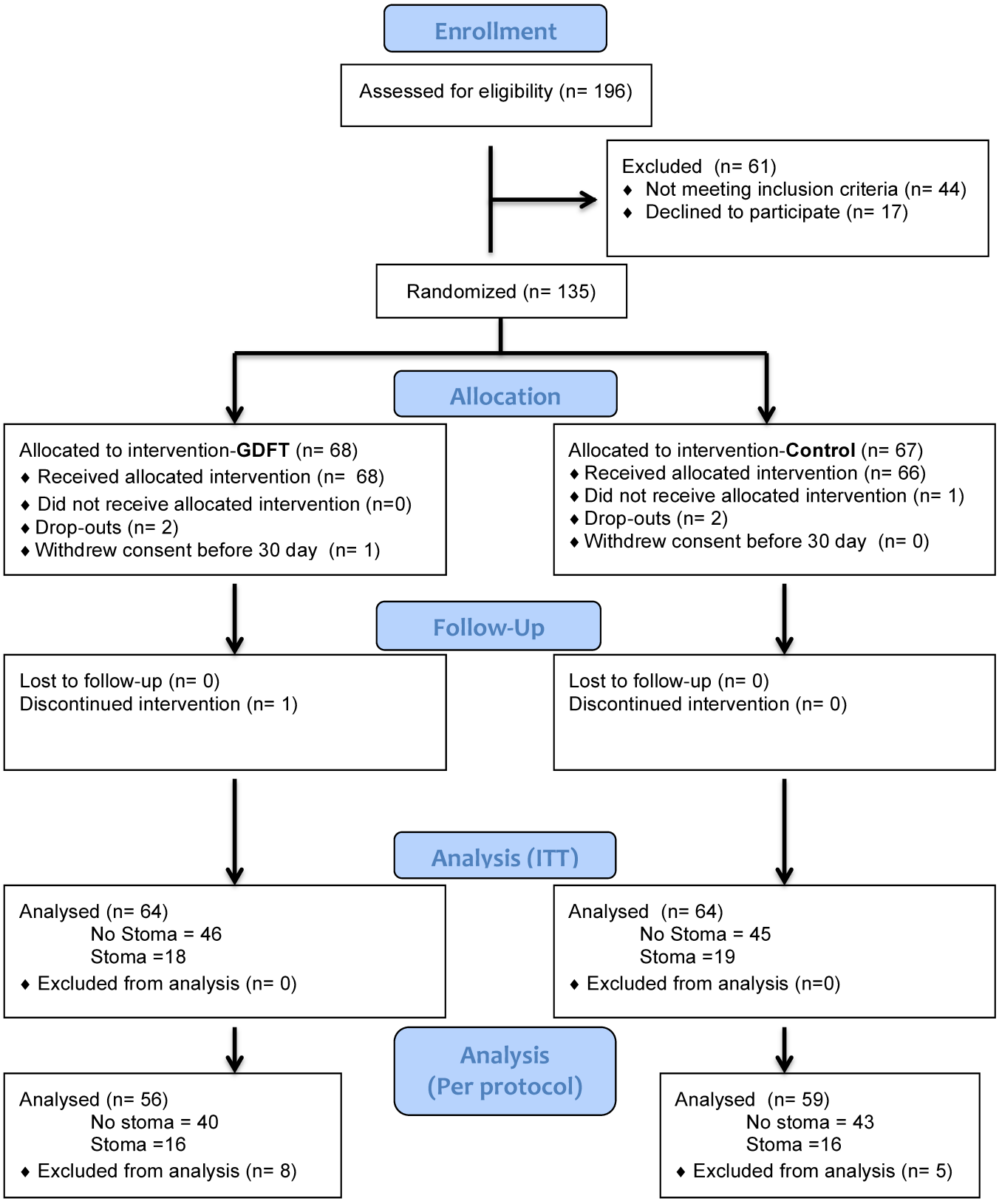

Table 1. Baseline patients' characteristics, operative data, and anesthesia care

	GDFT (n= 64)	**Control (n= 64)**	**p-value**
Age, *years*	62.7 ± 15.1	60.9 ± 15.3	
Gender M/F, *n*	31/33	40/24	
Weight, *Kg*	71.1 (62.2-85.1)	76.5 (67.6-84.7)	
BMI	24.9 (22.4-28.6)	26.1 (23.4-29.1)	
BSA, m^2	1.8 ± 0.2	1.9 ± 0.2	
ASA (I/II/III/IV), *n*	6/42/14/2	8/38/18/0	
CR-POSSUM			
Physiology	8 (7-10)	8 (7-9)	
Operative	7 (7-7)	7 (7-7)	
Predictive Mortality (%)	1.8 (0.9-9.3)	1.8 (0.9-2.6)	
Charlson comorbidity Index	2 (2-3)	2 (1-3)	
Preoperative hemoglobin, $g^{-1}\ dL^{-1}$	12.8	13.4	**0.049**
Indication for surgery, *n* (%)			
Colorectal cancer	48 (75.0)	43 (67.2)	
Inflammatory bowel disease	6 (9.4)	9 (14.1)	
Diverticulitis	4 (6.3)	7 (10.9)	
Others[a]	6 (9.4)	5 (7.8)	
Type of Surgery, *n (%)*			
Colonic	39 (61.0)	39 (60.1)	
Ileocecal resection	1 (1.6)	7 (10.9)	
Right hemicolectomy	20 (31.3)	19 (29.7)	
Left hemicolectomy	5 (7.8)	4 (6.3)	
Subtotal colectomy	0 (0)	3 (4.7)	
Sigmoidectomy	11 (17.2)	6 (9.4)	
Total colectomy	2 (3.1)	0 (0.0)	
Rectal	25 (39.0)	25 (39.0)	
Rectal anterior resection	10 (15.6)	8 (12.5)	
Rectal low anterior resection	8 (12.5)	9 (14.1)	
Proctocolectomy	6 (9.4)	5 (7.8)	
Abdominal perineal resection	1 (1.6)	3 (4.7)	
Stoma, *n (%)*	18 (28.1)	19 (29.7)	
Bowel preparation, *n (%)*			
4 L GoLYTELY®	36 (56.2)	23 (35.9)	**0.021**
2 Fleet enemas	12 (18.7)	17 (26.6)	
Preoperative carbohydrate drinks[*], *n (%)*			
Yes[†]	47 (73.4)	45 (71.4)	
Yes, according to the quantity indicated[††]	23 (35.9)	26 (41.9)	
Preoperative fasting time, *h*			
Solid[†††]	35.9 (19.0-40.0)	34.4 (16.7-38.0)	
Fluid[††††]	4.0 (3.1-5.7)	4.0 (3.2-6.3)	
Duration of surgery, *min*	189 (144-269.2)	183.5 (133.5-254.5)	0.564
Laparoscopic time, *min*	108 (68.2-146.2)	101 (71.2-143.2)	0.506
Conversion to open, *n (%)*	8 (12.5)	5 (7.8)	0.380
Final temperature, C°	36.1 ± 0.8	35.9 ± 0.6	0.269
Et Desflurane, %	4.4 ± 0.6	4.6 ± 0.7	0.103
Et Sevoflurane, %[**]	1.4 ± 0.3	1.3 ± 0.3	0.617
Remifentanil, $\mu g^{-1}\ Kg^{-1}\ min^{-1}$	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.083
Intraoperative ketorolac (30 mg), *n (%)*	49 (76.6)	50 (78.1)	0.754

[a] Benign adenoma (6 patients in the GDFT group and 3 patients in the Control group), fecal incontinence (1 patient in the Control group) terminal ileum stricture (1 patient in the Control group). [*] Morning dose. [†] Data from 1 patient in the Control group is missing. [††]Data from 2 patients in the Control group are missing[†††]Data from 2 patients in the Control group and 1 patient in the GDFT is missing. [††††] Data from 1 patient in the Control group is missing. [**]Eighteen patients received Sevoflurane (9 patients in the GDFT and 9 patients in the Control group). ASA= American Society of Anesthesiologists Physical Status. BMI= Body Mass Index; BSA= Body Surface Area; CR-Colorectal; Et= End Tidal; h= hours; M/F= Male/ Female; n= number; min= minutes. Data are presented as mean ± standard deviation, median (interquartile range), or absolute numbers (percentage); p-value *in Italic*: Fisher's exact test.

Table 2. Preoperative and intraoperative intravenous fluids, vasopressors, blood loss and transfusions

	GDFT group (n= 64)	Control (n=64)	p-value
Preoperative period			
Replacement of preoperative intravascular deficit due to MBP [a], *ml*	-	2093.6 ± 394.6	-
Intraoperative period			
Total volume of intravenous fluid, *ml*	1535.0 (1000.0-2271.7)	2370.0 (1779.0-3070.8)	**< 0.001**
Lactated Ringer's			
ml	500.0 (323-687.1)	2102.0 (1600.0-2528.0)	**< 0.001**
$ml^{-1}\ kg^{-1}\ h^{-1}$	2.0 (1.6-2.4)	8.6 (7.0 - 10.6)	**< 0.001**
Colloids, *ml*	900 (400.0-1400)	0 (0-500.0)	**< 0.001**
Pre-pneumoperitoneum ($\mathbf{T_B}$) boluses	400.0 (200.0-400.0)[*]	-[**]	-
NaCl 0.9%[***], *ml*	194.5 (150.0-268.0)	179.0 (145.7-234.2)	0.132
Total volume of intravenous fluids, *ml*			
Colonic surgery	1375.3 ± 667.5	2242.7 ± 873.9	**<0.001**
Rectal surgery	2342.1 ± 980.6	2957.9 ± 978.5	**0.031**
EBL, *ml*	175.0 (100.0-400.0)	150.0 (100.0-400.0)	0.708
Colonic Surgery	100 (100-200.0)	100 (100-200.0)	0.519
Rectal Surgery	400.0 (125.0-850.0)	400.0 (200.0-800.0)	0.914
PRBCs			
Patients receiving PRBCs, *n (%)*	5 (7.8)	1 (1.6)	0.094
Number of Units (2/4/8)	3/1/1	1/0/0	0.100
Volume, *ml*	0 (0-0)	0 (0-0)	na
Vasopressor, n (%)	53 (82.8)	58 (90.6)	0.193
Phenylephrine			
n (%)	39 (60.9)	51 (79.7)	**0.020**
µg	80.0 (0-300.0)	180.0 (80.0-440.0)	**0.016**
Ephedrine			
n (%)	40 (62.5)	43 (67.2)	0.496
mg	10.0 (0-25.0)	10.0 (0-20.0)	0.947
Phenylephrine continuous infusion, n (%)	0 (0)	0 (0)	na
Urine output, $ml^{-1}\ Kg^{-1}\ h^{-1}$	1.2 (0.8-1.8)	1.4 (0.8-2.6)	0.148

[a] Preoperative intravenous fluids were administered only in patients of the Control group who received Mechanical Bowel Preparation (35.9%). In 2 patients the preoperative deficit due to the use of mechanical bowel preparation could not be completed before surgery because the operating room schedule was changed at the last minute. [*]In the GDFT group, 35 patients (97.2%) needed stroke volume (SV) optimization before the pneumoperitoneum. [**]In the Control group 40 patients (62.5 %**)** increased SV_{T0} by more than 10% when positioned in steep Trendelemburg before the pneumoperitoneum (**T_B**) [***]Amount of normal saline solution used to dilute antibiotics, potassium chloride when needed, and remifentanil. EBL= Estimated Blood loss; Mechanical Bowel Preparation = MBP, 4 L GoLYTELY®; na= not applicable (no statistics were computed as there were not enough valid cases to perform the Mann-Whitney Test). NaCl 0.9%= Normal Saline; PRBCs= Packed Red Blood Cells. Data are presented as mean ± standard deviation, median (interquartile range), or absolute numbers (percentage).

Table 3. Postoperative fluid balance, weight balance, and postoperative hypotension

	GDFT (n= 64)	**Control (n= 64)**	**p-value**
Patients receiving intravenous infusion after day 0, *n(%)*	31 (48.4)	28 (43.8)	0.723
Input, *ml*			
Total intravenous crystalloids⌘, *ml*	318.75 (247.0-2967.4)	607.50 (291-3233.7)	0.269
Total oral fluid intake Ω, *ml*	7681.0 (5625.0- 10350.0)	6525 (3968.7-10050.0)	0.571
Output			
Urine output, day 0◆	700.0 (450.0-1440.0)	1450.0 (700.0-2000.0)	**0.004**
Total gastrointestinal losses ◆◆,*ml*	75.0 (0-1475.0)	50.0 (0-1912.5)	0.984
Weight balance†, *Kg*			
Day 1 - Day 0	1.08 ± 1.9	2.12 ±1.7	**0.002**
Day 2 - Day 1	0.61 ± 1.6	0.02 ± 1.7	0.054
Day 3 - Day 2	-0.76 ±1.4	-0.51 ± 1.4	0.321
Hypotension*, *n (%)*	15 (23.4)	16 (25)	1.000
Orthostatic hypotension**, *n (%)*	2 (3.2)	8 (12.5)	0.096

⌘Total amount of intravenous crystalloids received from surgical unit admission until hospital discharge; Ω Total oral fluid intake measured from surgical unit admission until hospital discharge. ◆Urine Output on day 0 measured from surgical unit admission until 8.00 AM of Day 1 (Foley catheters were removed on the morning of Day 1 as per ERAS protocol). Urine output on day 0 could not be measured in in 7 patients of the GDFT and in 10 patients of the Control group as Foley catheters were removed in PACU because of patients' discomfort. ◆◆ Total Gastrointestinal losses measured from surgical unit admission until hospital discharge. † Postoperative weight could not be measured in 12 patients of the GDFT and in 10 patients of the Control group because of patients' refusal or because patients were discharged early on Day 2 or day 3 (Day 1: 2 patients in GDFT and 1 patient in Control group; Day 2: 1 patient in the GDFT group; Day 3: 9 patients in GDFT and 5 patients in the Control group). * Systolic blood pressure less than 90 mmHg or less than 20% of the baseline value. ** A fall of at least 20 mmHg in systolic blood pressure upon assuming an upright posture from a supine position. Data are presented as mean ± standard deviation, median (interquartile range), or as absolute numbers (percentage).

Table 4. Postoperative pain intensity and management and time spent out of bed

	GDFT (n=64)	Control (n=64)	p-value
Pain, static			
NRS day 0	0 (0-2)	2 (0-3)	0.138
NRS day 1	2 (0-4)	2 (0-4)	0.486
NRS day 2	3 (1-4)	2 (1-4)	0.787
NRS day 3	1.5 (0-3.5)	1 (0-3)	0.617
Pain, coughing			
NRS day 0	1.5 (0-4)	3 (1.5-5)	**0.028**
NRS day 1	3.5 (2-5)	4 (2.5-6)	0.588
NRS day 2	4 (2-5.5)	4 (3-6)	0.457
NRS day 3	2 (0-5)	2 (0-5)	0.876
Pain, ambulating			
NRS day 0	0 (0-0)	0 (0-0)	0.806
NRS day 1	0 (0-3)	0 (0-2.5)	0.472
NRS day 2	2 (0-4)	2 (0-4)	0.608
NRS day 3	0 (0-2.5)	1 (0-3)	0.390
Days with thoracic epidural analgesia, *n (%)*	3 (2-3)	3 (2-3)	0.840
Systemic opioids†, *mg*			
Total	12 (3.30- 33.25)	18.30 (9.10-34.85)	0.072
Day 0	0	0	1.000
Day 1	0 (0-0)	0 (0-0)	**0.024**
Day 2	3.30 (0-9.95)	6.60 (3.30-13.20)	**0.035**
Day 3	3.30 (0-10)	5 (0-10)	0.803
Celebrex* with thoracic epidural analgesia, *n (%)*	9 (14.1)	10 (15.6)	1.000
Celebrex* after thoracic epidural analgesia, *n (%)*	48 (75.0)	51 (79.7)	0.673
No of patients receiving Milk of Magnesia, *n (%)*	52 (81.3)	45 (71.9)	0.297
Time spent out of bed, *min*			
Day 0	0 (0-10)	0 (0-3.75)	0.386
Day 1	65 (20-217.50)	127.50 (41.25-491.25)	0.063
Day 2	90 (45-256.25)	122.50 (67-375)	0.248
Day 3	120 (45-236.25)	180 (72.50-240)	**0.028**

† Intravenous morphine equivalents. * Celebrex 200 mg *per* os every 12 h. NRS= Numeric Rating Score (0-10); Data are presented as median (interquartile range), or as absolute numbers (percentage).

Table 5. Incidence of Primary Postoperative Ileus (PPOI) and recovery gastrointestinal function

	GDFT (n=64)	**Control (n=64)**	**RR (95%CI)**	**p-values**	**$RR_{adjusted}$ (95% CI)**	**p-values**
Incidence of PPOI*, *n (%)*						
ITT analysis	14 (21.9)	14 (21.9)	1.00 (0.52 to 1.92)	1.000	1.00 (0.53 to 1.86)	0.094
Per protocol	12 (21.4)	12 (20.3)	1.05 (0.52 to 2.15)	*1.000*	1.06 (0.53 to 2.12)	0.225
No Stoma, *n (%)*						
ITT analysis	9 (19.6)	7 (15.6)	1.25 (0.51 to 3.09)	0.615	1.29 (0.54 to 3.07)	0.316
Per protocol	7 (17.5)	7 (16.3)	1.07 (0.41 to 2.79)	0.882	1.09 (0.44 to 2.73)	0.272
Stoma, *n (%)*						
ITT analysis	5 (27.8)	(36.8)	0.75 (0.29 to 1.95)	0.556	0.81 (0.33 to 2.00)	0.226
Per protocol	5 (31.3)	5 (31.3)	1.00 (0.35 to 2.79)	1.000	1.10 (0.42 to 2.94)	0.477
Colonic surgery *n (%)*						
ITT analysis	9 (23.1)	6 (15.4)	1.50 (0.59 to 3.81)	0.389	1.42 (0.57 to 3.55)	0.370
Per protocol	7 (20.6)	6 (15.8)	1.30 (0.49 to 3.50)	0.597	1.24 (0.47 to 3.27)	0.385
Rectal surgery *n (%)*						
ITT analysis	5 (20.0)	8 (32.0)	0.62 (0.24 to 1.65)	0.333	0.69 (0.28 to 1.71)	0.147
Per protocol	5 (22.7)	6 (28.6)	0.79 (0.28 to 2.22)	0.661	0.90 (0.34 to 2.34)	0.298
PPOI						
Diagnosis, day 1/2/3/≥4, *n*						
ITT analysis	3/5/4/2	4/7/1/2	na	0.517	na	-
Per protocol	3/3/4/2	4/5/1/2	na	0.486	na	-
Duration, *days*						
ITT analysis	2 (1-3.5)	3 (1.7-3.2)	na	0.318	na	-
Per protocol	2 (1-3.7)	3 (1.2-3.7)	na	0.389	na	-
Time to first flatus, *h*						
ITT analysis	20.5 (12-26)	20 (12.5-24.5)	na	0.843	na	-
Per protocol	20 (13-26)	19 (13-24)	na	0.796	na	-
Time to first bowel movement, *h*						
ITT analysis	21.5 (16-36)	22 (16-28)	na	0.884	na	-
Per protocol	22 (16-36)	22 (15-28)	na	0.784	na	-
Nausea, *n (%)*						
ITT analysis	41 (64.1)	37 (57.8)	1.11 (0.83 to 1.47)	0.469	1.19 (0.90 to 1.56)	0.697
Per protocol	37 (66.1)	33 (55.9)	1.18 (0.88 to 1.59)	0.265	1.30 (0.97 to 1.74)	0.660
Vomiting, *n (%)*						
ITT analysis	25 (39.1)	25 (39.1)	1.00 (0.65 to1.54)	1.000	1.07 (0.70 to 1.64)	0.492
Per protocol	23 (41.1)	21 (35.6)	1.15 (0.72 to 1.84)	0.547	1.28 (0.80 to 2.07)	0.601
Abdominal distension, *n (%)*						
ITT analysis	49 (76.6)	55 (85.9)	0.89 (0.75 to 1.05)	*0.257*	0.91 (0.77 to 1.08)	0.938
Per protocol	43 (76.8)	51 (86.4)	0.89 (0.74 to 1.06)	*0.230*	0.91 (0.76 to 1.09)	0.856
Diet intolerance**, *n (%)*						
ITT analysis	15 (23.4)	17 (26.6)	0.88 (0.48 to1.61)	*0.839*	0.87 (0.48 to 1.59)	0.582
Per protocol	14 (25)	14 (23.7)	1.05 (0.55 to 2.01)	*1.000*	1.09 (0.56 to 2.11)	0.967

NGT insertion, *n (%)*						
ITT analysis	9 (14.1)	11 (17.2)	0.82 (0.36 to 1.84)	*0.808*	0.82 (0.37 to 1.82)	0.293
Per protocol	8 (14.3)	8 (13.6)	1.05 (0.42 to 2.61)	*1.000*	1.17 (0.47 to 2.90)	0.770
Number of skipped meals, n						
ITT analysis	1 (0-2)	1 (0-4.7)	na	0.551	na	-
Per protocol	1 (0-2)	1 (0-4)	na	0.770	na	-

The analysis was adjusted for the use of Mechanical Bowel Preparation. *Absence of gas but presence of stool was not considered a clinical indicator of gastrointestinal dysfunction. **Diet intolerance: at the end of the day patients were asked to judge whether they tolerated or not the meals they ate during the day. Patients who did not eat any meal during the day were considered not tolerating diet. ITT = Intention to treat; NGT = Nasogastric tube; na = not applicable; RR = Relative Risk. Data are presented as median (interquartile range), as absolute numbers (percentage), or as relative risk (95% confidence interval); p-values *in Italic*: Fisher's exact test.

Table 6. Perioperative morbidity and mortality

	GDFT (n=64)	Control (n=64)	RR (95%CI)	p-value
QoR on day 2	14 (13-16)	14 (13-16)	na	0.648
Readiness to be discharged, *days*	3 (2-4)	3 (3-5)	na	0.561
LOS, *days*	4 (3-5)	4 (3-5.7)	na	0.922
30-day Mortality, *n (%)*	0 (0)	0 (0)	na	na
Patients with at least one 30-day complication, *n (%)*	28 (43.8)	25 (39.1)	1.12 (0.74 to1.69)	0.590
In-hospital	22 (34.4)	20 (31.3)	1.10 (0.67 to1.80)	0.707
Post-discharge	9 (14.1)	8 (12.5)	1.12 (0.46 to 2.73)	0.795
Patients with at least one 30-day medical complication, *n (%)*	18 (28.1)	14 (21.9)	1.29 (0.70 to 1.35)	0.414
Cardiovascular	3 (4.7)	2 (3.1)	1.25 (0.26 to 8.68)	*1.000*
Respiratory	3 (4.7)	0 (0)	na	*0.244*
Infectious	12 (18.8)	8 (12.5)	1.50 (0.66 to 3.42)	0.330
Other	9 (14.1)	9 (14.1)	1.00 (0.42 to 2.35)	1.000
Patients with at least one 30-day surgical complication, *n (%)*	20 (31.3)	18 (28.1)	1.11 (0.651 to 1.90)	0.699
Primary postoperative ileus	14 (21.9)	14 (21.9)	1.00 (0.52 to 1.92)	1.000
Anastomotic leakage	3 (4.7)	0 (0)	na	*0.244*
Bleeding	3 (4.7)	3 (4.7)	1.00 (0.21-4.78)	*1.000*
Bowel perforation	1 (1.6)	0 (0)	na	*1.000*
Mechanical bowel obstruction	0 (0)	1 (1.6)	na	*1.000*
Wound dehiscence	0 (0)	1 (1.6)	na	*1.000*
Other	0 (0)	2 (3.1)	na	*0.496*
Patients admitted to ICU * *n (%)*	2 (3.1)	1 (1.6)	2.00 (0.19 to 21.50)	*1.000*
Patients reoperated within 30-days, *n (%)*	1 (1.6)	3 (4.7)	0.33 (0.04 to 3.12)	*0.619*
30-day Clavien, *n (%)*				
I	10 (15.6)	10 (15.6)	1.00 (0.44 to 2.28)	1.000
II	11 (17.2)	10 (15.6)	1.10 (0.50 to 2.40)	0.811
IIIa	5 (7.8)	2 (3.1)	2.50 (0.50 to 12.41)	*0.440*
IIIb-IVb	2 (3.1)	3(4.7)	0.66 (0.11 to 3.86)	0.648
30-day CCI	0 (0-20.9)	0 (0-11.3)	na	0.483
Patients visiting ED within 30 days, *n (%)*	13 (20.3)	9 (14.1)	1.44 (0.66 to 3.14)	0.349
Patients readmitted within 30 days, *n (%)*	8 (12.5)	6 (9.4)	1.33 (0.49 to 3.62)	0.571

Quality or recovery score, length of hospital stay, 30-day postoperative complications, 30-day Emergency Department visits and 30-day readmissions. *Intensive Care Unit admission during primary length of stay. CCI = Comprehensive Complication Index; ED = Emergency Department; ICU = Intensive Care Unit; LOS = Length of Hospital Stay; QoR = Quality of Recovery Score; RR = Relative Risk. Data are presented as median (interquartile range), as absolute numbers (percentages) or as relative risk (95% confidence interval); p-value in *Italic*: Fischer's exact test.

Chapter 3

"Sub-lingual microcirculatory effects of Goal-Directed Fluid Therapy as a surrogate measure of splanchnic perfusion: a mechanistic cohort study"

Conference paper

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Ph. D Experimental Surgery

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Sub-lingual microcirculatory effects of Goal-Directed Fluid Therapy as a surrogate of splanchnic perfusion

Preamble

Perioperative optimization of oxygen delivery is essential to prevent organ dysfunction. Several perioperative interventions, such as optimization of fluid therapy, perioperative use of inotropes, and adequate perioperative blood management can be used to ensure optimal oxygen delivery.

It can be hypothesized that optimization of systemic perfusion and oxygenation determines adequate tissue perfusion and oxygenation, resulting in better outcomes. Perioperative optimization of systemic perfusion and oxygenation have shown to improve outcomes after abdominal surgery, mainly in high-risk patients and in patients not treated with an ERAS program[68], probably as a result of better tissue perfusion[146]. However, it has been demonstrated that enhancing systemic perfusion does not necessarily increase tissue perfusion[147, 148], as the improvement of tissue microcirculation is "context sensitive" and it mainly depends on the severity of the tissue injury, on the basal state of tissue microcirculation[148], and on the increase in cardiac output[147]. Moreover, while several clinical and animal studies have shown an association between improvement of microcirculation and better postoperative outcomes[148-150], no studies have confirmed that this relationship is causal.

GDFT, by optimizing stroke volume and cardiac output, ensures adequate oxygen delivery and tissue perfusion[50, 146]. It also prevents both hypovolemia secondary to excessive fluid restriction[18]

and interstitial edema as a result of fluid overload, which are responsible of increased perioperative gastrointestinal morbidity[19, 36]. Impairment of splanchnic microcirculation contributes to the development of gastrointestinal complications after abdominal surgery[5, 30]. Commonly, efforts to improve splanchnic microcirculation are based on the optimization of hemodynamic variables such as cardiac output, mean arterial pressure and lactate levels, assuming that an improvement of macrocirculation variables determine better splanchnic perfusion. However, maintaining adequate splanchnic perfusion remains extremely challenging, because of the lack of adequate monitoring, and absence of gastrointestinal-specific biomarkers[28]. Moreover, it must be considered that even minimal blood loss (10-15%) can significantly decrease splanchnic perfusion, without altering common systemic hemodynamic measures[24].

The analysis of sub-lingual microcirculation has been proposed as a surrogate measure of splanchnic perfusion. Clinical and experimental trials conducted in the perioperative setting and in critically ill patients have shown that sub-lingual microcirculation alterations correlate with splanchnic microcirculatory changes[150, 151], and that impairment of sub-lingual microcirculation is associated with splanchnic hypoperfusion and increased mortality in septic patients[151, 152]. Finally, sub-lingual microcirculation shares the same embryological origins of the gastrointestinal tract, and it is easily accessible to be measured in the perioperative period[153].

Although the final results of the former randomized control trial have not demonstrated that GDFT reduce the incidence of PPOI and facilitate the recovery of gastrointestinal function after major colorectal surgery, the purpose of this *pre-planned* sub-group analysis is to elucidate the potential mechanisms through which GDFT might improve gastrointestinal perfusion, and

therefore attenuate postoperative gastrointestinal dysfunction, by measuring sub-lingual microcirculation as a surrogate measure of splanchnic tissue perfusion. It is hypothesized that GDFT leads to better sub-lingual microcirculation resulting in less PPOI and less postoperative gastrointestinal dysfunction. It was also hypothesized that sub-lingual microcirculation is significantly impaired in patients with primary postoperative ileus after major colorectal surgery.

Sub-lingual microcirculatory effects of Goal-Directed Fluid Therapy as a surrogate measure of splanchnic perfusion: a mechanistic cohort study

Introduction

PPOI is a significantly unpleasant postoperative complication after abdominal surgery, and it constitutes a huge economic burden for the healthcare system[3, 4]. Its pathogenesis is multifactorial as several perioperative factors affect the recovery of bowel function after abdominal surgery.

Inadequate perioperative fluid therapy has been recognized as one of the major determinants of postoperative gastrointestinal dysfunction. Indeed, both splanchnic hypoperfusion, as a result of hypovolemia, and excessive fluid administration, lead to an impairment of gastrointestinal motility. The splanchnic circulation is very sensitive to changes in the intravascular volume. In fact, subclinical reductions of only 10 to 15% of the circulating volume have demonstrated to cause splanchnic hypoperfusion[24], leading to an impairment of the gastrointestinal tract motility[30]. One of the mechanisms that determines the reduction of gastrointestinal contractility is the intracellular increase of CO_2 in the smooth muscle cells of the gastrointestinal tract secondary to splanchnic ischemia[28, 154]. Likewise, metabolic acidosis has demonstrated to increase the gastric fundus tone, disrupt the pyloric contractions and produce arrhythmic antral contractility[154]. Studies in vitro have also shown that a decreased pH level depresses the myoelectrical and contractile activity of the muscles of the gastrointestinal tract by impairing the muscular tone, muscle relaxation and decreasing the amplitude of the contractions[155]. Similarly, excessive fluid

administration causes bowel edema, which impairs tissue oxygenation and consequently bowel peristalsis[19]. Experimental studies have shown that mesenteric venous hypertension caused by excessive fluid resuscitation with crystalloids determined, interstitial edema, an increase of mucosal permeability, a decrease of epithelial resistance, and delayed intestinal transit[156,21, 31, 114]. As a result, intra-abdominal pressure increases reducing the mesenteric blood flow, which further impairs gastrointestinal motility. Clinical cohort and randomized controlled studies have also corroborated that fluid overload increased risk of PPOI[117 19, 22, 27].

Goal directed fluid therapy (GDFT) aims at optimizing oxygen delivery by administering fluids with or without inotropes based on stroke volume and cardiac output measurements[146]. Previous clinical trials and meta-analysis had shown that GDFT decreases the incidence of PPOI and accelerates the recovery of gastrointestinal function[20, 62, 63, 67], and these effects might be related to improvement of gastrointestinal microcirculation. Jhanji et al. demonstrated that stroke volume guided fluid administration and low dose inotropic therapy leads to better oxygen delivery, sublingual microcirculation and tissue oxygenation after major abdominal surgery[146]. However, improving systemic perfusion not always determines better tissue microcirculation as demonstrated in critically ill patients. In fact, in septic patients gastrointestinal and sub-lingual microcirculation seem to behave differently in response to improvements of systemic perfusion[147, 157]. These heterogeneous responses might be related to tissue specific autoregulatory mechanisms aiming at preventing organ dysfunction, independently from systemic perfusion. Although better gastrointestinal perfusion has been associated with lower postoperative morbidity and mortality[146, 150, 158, 159], it remains to explore whether or not interventions that directly improve tissue microcirculation lead to better clinical outcomes.

The analysis of sub-lingual microcirculation has been proposed as a surrogate measure of splanchnic perfusion in the surgical setting and in critically ill patients[150, 151] since the sublingual mucosa shares a common embryogenic origin with the bowel[153], and a strong correlation between sublingual and bowel microcirculatory measurements have been reported in different clinical contexts (r^2 between 0.74[151] and 0.92[152]), and using different type of technologies (e.g. Sidestream Dark Field (SDF) technology[151,152], or measurements of sub-lingual carbon dioxide tissue pressure[160, 161]). Moreover, sublingual microcirculation is easily accessible[153], and does not required invasive technology to be measured.

Sidestream Dark Field (SDF) technology allows to non-invasively evaluate tissue microcirculation at the patient's bedside[162]. SDF technology is based on the principle that a beam generated by light-emitting diodes with a length wave of 530 nanometers is absorbed by the hemoglobin of the red cells in small vessels[162]. Then, pulsed illumination allows acquisition of stroboscopic imagining of the red cells through the use of a microscope connected to a camera, making possible to measure blood flow velocities[162]. This technology is able to provide information about at least three different microcirculation indices: Proportion of perfused vessels (PPV), Perfused vessel density (PVD) and microvascular flow index (MFI). PPV provides information about tissue flow heterogeneity; PVD reflects functional capillary density, and MFI adds information about the quality of the flow[163]. SDF has been successfully utilized to measure tissue microcirculation in surgical and critically ill patients[149-151] and it has shown to predict anastomotic leakage[149], the likelihood of developing postoperative complications[150], and to differentiate survivors from non-survivors in severe sepsis[100].

The purpose of this *pre-planned* sub-group analysis is to elucidate the potential mechanisms through which GDFT might improve gastrointestinal perfusion, and therefore attenuate postoperative gastrointestinal dysfunction, by measuring sub-lingual microcirculation as a surrogate index of splanchnic perfusion. It is hypothesized that GDFT leads to better sub-lingual microcirculation resulting in less PPOI and less postoperative gastrointestinal dysfunction. It was also hypothesized that sub-lingual microcirculation is significantly impaired in patients with PPOI after major colorectal surgery.

Methods

This trial was approved by the Research Ethics Board of the McGill University Health Centre, Montreal, Quebec, Canada (12-214-SDR) and the study procedures were carried out in accordance with ethical standards. A cohort of patients, enrolled in the previous randomized controlled trial (Chapter 2) (ClinicalTrials.gov registration: NCT01818375), and undergoing laparoscopic colorectal surgery within an ERAS program at the Montreal General Hospital, were consecutively recruited in three different periods: between February and April 2013, between September and October 2013 and in February 2014. Patients were excluded from the analysis if developed secondary postoperative ileus, or if surgery was converted to laparotomy.

Perioperative anesthesia and surgical care

All patients received the same perioperative care based on the ERAS program implemented at the Montreal General Hospital (page 52-55). Anesthesia and analgesia care was standardized as per protocol. Intraoperatively, patients received either GDFT (GDFT Group) or fluid therapy

based on standard perioperative fluid principles (Control group), according to the original study randomization (please refer to the methods section of the randomized controlled trial, page 52).

Sub-lingual microcirculation assessment

Sub-lingual microcirculation measurements*:* sublingual microcirculatory flow was evaluated preoperatively (before epidural insertion, and infusing intravenous fluids in the Control group), 10 min after induction of anesthesia, 10 min after establishment of pneumoperitoneum, 30 min after arrival in the Post Anesthesia Care (PACU) and every evening (before supper) on each postoperative day, using a sidestream darkfield (SDF) imaging camera, equipped with a 5x objective lens (Microvision Medical, Amsterdam, the Netherlands). Image acquisition and analysis were performed according to published consensus guidelines by trained personal[163]. To prevent motion and pressure artifacts and for training purposes, sub-lingual microcirculation measurements were obtained first in surgical patients not involved in the study by the research personal supervised by an experienced researcher familiar with this technology[164], until the research personal was able to independently acquire accurate sub-lingual microcirculation images.

Before each microcirculation measurements, patients were asked to rinse their mouths with water. In presence of air bubbles in the saliva patients were asked again to rinse their mouth more than once to avoid interference with imaging acquisition. At each time point, the microcirculation was recorded for 30 sec at three different sublingual locations. The 30 sec recording with the least pressure artifacts and best focus, contrast, stability and overall quality was chosen for off-line analysis[163]. When pressure artifacts were identified, the microscope probe was slowly pulled

back until contact with the mucosa was lost and then gently re-advanced until contact was regained[100, 163].

Sub-lingual microcirculation analysis*:* videos were recorded and stored using a portable computer and they were labeled according to the timing and coded for every patient. Videos were stored full size as DV-AVI files to allow the analysis of the videos using the software provided by the manufacturer of the microscope. Videos were recorded in high-quality digital videotape mode, and were analyzed once all patients recruited in the study were discharged from the hospital. Using Automated Vascular Analysis Software version 3.0 (Microvision Medical), the microcirculatory parameters for vessels <20 μm was analyzed for each 30 sec recording. First, the perfusion in each vessel was categorized as present (continuous flow for at least 20 sec), intermittent (no flow at least 50% of the time) or absent (no flow for at least 20 sec), making possible to calculate the number of perfused vessels (PV), and then the proportion of perfused vessels (PPV). Subsequently, a grid pattern, containing three equidistant horizontal and vertical lines, was superimposed onto the recording. Perfused vessel density (PVD) was calculated by dividing the number of perfused vessels crossing this grid pattern by the total length of the grid pattern lines (***Table 1***). PPV and PVD calculation is highly reproducible when performed by the same evaluator, with a reported intra-observer variability ranging between 2.5% and 4.7% for PVD, and between 0.9 and 4.5% for PPV[165]. The microvascular flow index (MFI) at each time point was determined by dividing the recording into four equal quadrants, quantifying the flow in each quadrant using an ordinal scale of 0-3 (with 0 representing no flow, 1 representing intermittent flow, 2 representing sluggish flow and 3 representing continuous flow), then calculating the average score of all four quadrants. Kappa coefficients for the measurement of the MFI show substantial intra-observer and inter-observer agreement (0.78 and 0.85,

respectively)[166]. Each 30 sec recording was analyzed in this manner by one researcher who was blinded to the patient group allocation. Patients with postoperative abdominal complications (secondary postoperative ileus) were excluded from the analysis.

Macrocirculatory assessment

Intraoperative mean arterial pressure, heart rate, oxygen saturation; temperature, intraoperative stroke volume (SV), cardiac output (CO), cardiac index (CI), oxygen delivery (DO_2) and hemoglobin (Hb) concentration, were measured according to the protocol described in Chapter 2 (please refer to pages 52-54).

Assessment of bowel function

Bowel function was assessed blindly as reported in the methods section of the randomized controlled trial (page 56-57).

Outcomes

- Sub-lingual microcirculatory measurements[162, 163] (***Table 1***):
    - MFI
    - PVD
    - PPV
- Recovery of bowel function:
    - PPOI: patients with PPOI were identified by the presence of 2 or more clinical indicators of gastrointestinal dysfunction, at least 1 for each of the 2 following criteria 1) presence of vomiting, OR abdominal distension and 2) absence of

passing gas or stool, OR not tolerating oral diet in absence of any precipitating complications.

- Comparison of microcirculatory and macrocirculatory measurements between patients who developed PPOI and patients who did not develop PPOI (non-PPOI).
- Postoperative morbidity:
    - Postoperative complications: complications were defined *a priori* (please refer to ***Supplement 4***, page 131)
    - Length of hospital stay (LOS)
    - Intensive care unit (ICU) admission.

Statistical analysis

Nominal variables were analyzed using the χ^2 or Fisher test. Normality was assessed with the Shapiro-Wilk test. Continuous normally distributed data was analyzed using the two independent samples T test and continuous non-normally distributed data using the Mann-Whitney U test. The independent groups repeated measures ANOVA, mixed ANOVA model, was used to compare continuous variables measured over time between the 2 groups. The two-way ANOVA was used to compare hemodynamic variables from the beginning and the end of the surgery. Bonferroni test was used as post-hoc analysis. To determine the relation between microcirculation, macrocirculation and PPOI, the overall mean value throughout the perioperative period for both macro and microcirculatory measures was compared between patients who developed PPOI and patients who did not develop PPOI (non-PPOI).

Results

In total 24 patients were recruited. One patient was excluded because of secondary postoperative ileus (ileus secondary to portal venous thrombosis caused by an infectious portal phlebitis). Twenty-three patients were evaluated and analyzed (***Figure 1***), 9 were randomized to GDFT group and 14 to the Control group. In total 432 sub-lingual microcirculatory measurements, 168 in the GDFT, and 264 in the Control group were performed and analyzed.

Demographics, medical and surgical characteristics

Demographic characteristics and preoperative morbidity were similar between the 2 groups, except for the BMI that was higher in the Control group (p = 0.016) (***Table 2***), and for the Colorectal (CR) Possum severity score that was higher in the GDFT group (p = 0.019) (***Table 3***). Preoperative surgical care did not differ between the 2 groups (***Table 3***).

Intraoperative data

Patients in the Control group received a larger volume of intravenous fluids than patients in the GDFT group (2681.50 ml (1661.50 - 4576), versus 1160 ml (819.50 - 2159.12), p = 0.016). However, patients in the GDFT group received less crystalloids but more colloids than the Control group (547 ml, 371.50 - 859.12, versus 2362.70 ml, IQR 1368.50 - 4149, p = 0.001, and 600 ml, IQR 400 - 1400, versus 0 ml, IQR 0 - 500, p = 0.005, respectively). The proportion of patients requiring blood products, estimated blood loss, duration of surgery, and opioid and vasopressor requirements were similar between the 2 groups (***Table 4***).

Intraoperative stroke volume, cardiac output, mean arterial pressure, hemoglobin concentration and oxygen delivery.

Stroke volume (SV) and Stroke Volume Index (SVI) increased over time ($p = 0.005$ and $p = 0.005$, respectively), but they were not different between the 2 groups ($p = 0.477$ and $p = 0.379$, respectively). In the GDFT, SV and SVI significantly increased at the end of surgery, compared to baseline values ($p = 0.001$ and $p = 0.002$, respectively) (***Figures 2 and 3***). Cardiac output (CO) and Cardiac Index (CI) were not statistically different over time or between the 2 groups (***Figures 4 and 5***). Mean arterial pressure (MAP) was significantly higher in the GDFT group ($p = 0.021$), but did not differ overtime ($p = 0.093$) (***Figure 6***). Hemoglobin concentration dropped in both groups over time ($p<0.002$ in the GDFT group, and $p<0.001$ in the Control group). Similarly, oxygen delivery (DO_2) significantly dropped over time ($p = 0.001$), mainly in the Control group ($p = 0.001$), but it did not differ between the 2 groups (***Figure 7***).

Postoperative data

- Post anesthesia care unit (PACU): there were no differences in the total amount of intravenous fluids administered ($p = 0.914$). The amount of crystalloids ($p = 0.760$) and colloids ($p = 0.600$) received was also similar between the 2 groups. The incidence of postoperative hypotension, nausea and vomiting, vasopressor and opioid requirements, and length of stay in PACU were not different between the groups (***Table 5***).
- Fluids and opioids requirements: overall the volume of intravenous fluids administered in the postoperative period was significantly smaller in the GDFT group than in the Control group (292.50 ml versus 1536 ml, $p = 0.047$). However, the amount of intravenous fluids administered in the first 3 days, when the microcirculation measurements were acquired

and PPOI mostly occurred, was not significantly different between the 2 groups (GDFT 292.50 versus Control 1262, p = 0.072). Indications triggering fluid administration after day 0 were hypotension (50% of patients in the Control group and 33.3% in the GDFT group) and NPO status associated with vomiting (7.1% of patients in the Control group and 0% in the GDFT group). The incidences of orthostatic intolerance and hypotension and postoperative opioid requirements were similar between the 2 groups (***Table 6***).

- Postoperative morbidity: postoperative complications and length of hospital stay did not differ between the 2 groups. No patients required ICU admission (***Table 7***).

Sub-lingual microcirculation, perioperative hemodynamics, oxygenation and body temperature

- Sub-lingual microcirculation: Although PVD was higher intraoperatively and postoperatively in the GDFT group over time, this difference was not statistically significant (p = 0.057) (***Figure 8***). PPV, intraoperatively and postoperatively, was higher in patients treated with GDFT than in patients of the Control group (p = 0.023) (***Figure 9***). There were no differences in MFI between the 2 groups (p >0.05).
- Perioperative MAP, heart rate, oxygenation and body temperature: although remaining always within normal values, MAP significantly changed over time (p <0.001), but it was not different between the 2 groups (p = 0.485), at any time point. Post-hoc analysis demonstrated that MAP significantly dropped after the induction of anesthesia in both groups (p = 0.006 in the GDFT group, and p = 0.001 in the Control group). MAP significantly increased in the GDFT on day 2 (p = 0.031) (***Figure 10***). Similarly, although remaining always within normal values heart rate (HR) changed over time, but it was not different between the 2 groups (p = 0.581). HR was higher in the Control group

on day 1 (p = 0.032), and post-hoc analysis showed a significant increase in HR between pneumoperitoneum and PACU arrival in patients of the Control group (p = 0.034). Peripheral oxygen saturation changed over time (p = 0.004), and it slightly decreased from when patients arrived into PACU to day 1 in both groups (p = 0.048 in the GDFT group, and p = 0.048 in the Control group) (***Figure 11***). Body temperature also changed over time (p<0.001), but not between the 2 groups at any time point. Post-hoc analysis indicated a statistically significant increase in temperature between pneumoperitoneum and PACU arrival in patients of the Control group (p = 0.004).

Recovery of bowel function

PPOI occurred in 33.3% of patients in GDFT versus 21.4% of the Control group (p = 0.643); PPOI lasted a median of 1 day in both groups (p = 1.00). The time to first bowel motion was shorter in the Control group (26.23 ± 11.21 h versus 38.67 ± 15.77 h in GDFT, p = 0.042). Symptoms and clinical indicators of gastrointestinal dysfunction were similar between the 2 groups, but the incidence of abdominal distension was higher in Control group (p = 0.047) (***Table 8***).

Microcirculation, macrocirculation and PPOI

• Microcirculation and PPOI: PPV was lower in patients who developed PPOI than in patients without PPOI, non-PPOI (82.76 ± 3.19 vs 87.29 ± 4.20, p = 0.026). There were no statistically significant differences in MFI and PVD between PPOI and non-PPOI patients (***Table 9***).

• Macrocirculation and PPOI: There were no statistically significant differences in

macrocirculation measurements between PPOI and non-PPOI patients (p>0.05) (***Table 9***)

Discussion

The results of this sub-group analysis showed that GDFT using colloids increased the PPV, possibly indicating better splanchnic tissue perfusion. However, these effects did not translate into better recovery of bowel function. Patients who developed PPOI exhibited a lower sub-lingual PPV, which might demonstrate suboptimal splanchnic perfusion.

Previous studies have shown that GDFT facilitates the recovery of gastrointestinal function[20, 107, 99,167, 168], and decreases the incidence of PPOI[66], possibly by improving splanchnic tissue microcirculation and oxygenation[51]. Based on this consideration, it was hypothesized that colorectal surgery patients intraoperatively exposed to GDFT could experience less PPOI as a result of a better splanchnic tissue microcirculation, indirectly assessed by measuring sub-lingual microcirculation.

Sub-lingual microcirculation has been proposed as a surrogate measure of splanchnic microcirculation as it shares the same embryologic origin with the bowel mucosa[153]. Moreover, a moderate to strong correlation has been observed between the two microcirculation beds, even using different technologies[152, 161]. It might be argued that intestinal microcirculation was not directly measured, thereby limiting the validity of sub-lingual microcirculation to assess splanchnic tissue perfusion. In fact, recent evidence has shown lack of correlation between sub-lingual and intestinal microcirculation measurements in patients with abdominal sepsis, probably

as the consequence of redistribution of tissue perfusion caused by septic shock[147]. Under these circumstances blood flow from the splanchnic circulation is redistributed to vital organs such as the brain and heart, possibly explaining the lack of correlation between these two microcirculatory beds[151, 169]. In fact, in patients with septic shock it is not surprising to observe normal sub-lingual microcirculation, but splanchnic microcirculatory alterations as blood supply of the tongue originates from the carotid artery, which also irrigates the brain[153]. However, when profound systemic hemodynamic alterations occur, severe microcirculatory changes (less than 30% of the small vessels perfused) occur in both territories[147, 152]. Indeed, a trial in animals with hypodynamic endotoxemic shock (cardiac output reduced by 50% from baseline values), showed a strong correlation between sub-lingual microcirculation and splanchnic microcirculation[170]. As microcirculatory measurements were taken in uncomplicated surgical patients, without abdominal sepsis or septic shock, it could be assumed that in this clinical context sub-lingual microcirculation represents an adequate indirect measurement of splanchnic tissue perfusion.

The PPV identifies the proportion of vessels from where oxygen diffuses into the cells, and it provides information about tissue flow heterogeneity within the analyzed area[163]. It represents the capability of the tissue to extract oxygen[163]. In this study, the PPV was significantly better in the GDFT compared to the Control group, suggesting that GDFT might produce a vessel-recruiting effect and therefore enhances the oxygen extraction capacity of the tissue[171-174], a physiologic effect associated with reduced organ dysfunction[163, 175]. Intraoperative MAP was significantly higher in the GDFT, independently from the use of vasopressors. Since MAP is the most important determinant of bowel perfusion[176-178], it can be hypothesized that the vessel-recruiting effect of the GDFT was in part generated by higher intraoperative MAP values in the

GDFT group, resulting in better postoperative PPV. Similarly, higher SV and CO values in the GDFT group might have also contributed to better PPV. Moreover, a less pronounced decline of DO_2 was observed at the end of surgery in patients treated with GDFT. Physiologically, a higher PPV in combination with better oxygen delivery at the end of surgery would result in better tissue oxygen diffusion[175, 179].

PVD is considered an estimate of functional capillary density, representing capillaries with continuous flow in an area of tissue, regardless if the flow in those capillaries is sluggish or normal[162, 163]. Although not statistically significant, PVD was higher in the GDFT group throughout the entire postoperative period.

PPV and PVD are more important than flow since tissues can adapt their oxygen extraction capabilities to slow flow velocities as long as the flow in the capillaries is homogeneous and continuous[180-182]. These two measurements are also markedly affected in severely ill patients. Septic patients and animal models of abdominal sepsis have demonstrated decreased PVD and PPV during states of systemic hypoperfusion[100, 152, 165], but reversible after adequate fluid resuscitation[183]. MFI is an indicator of the quality of the flow; and it is similar between patients treated with GDFT and patients in the Control group and it remains within optimal values in both groups in the entire postoperative period. Previous studies have shown that MFI is significantly altered (absent or intermittent) in severely ill patients, as demonstrated in patients with septic shock and severe abdominal sepsis[100, 151, 152], anastomotic leakage[149] and in those developing significant postoperative complications[184], but rarely in patients with minor complications. In fact, in this cohort study the number of postoperative complications was limited, and patients in

the Control group were able to maintain adequate systemic perfusion in the entire perioperative period.

In this study, although CO and SV during surgery increased in a more pronounced manner in the GDFT group; and the PPV was higher in the GDFT, these effects did not translate into better recovery of bowel function. Several factors can explain these results. First, systemic hemodynamics in the control group were probably sufficient to determine adequate splanchnic tissue microcirculation and therefore satisfactory bowel function. In fact, although lower PPV values were observed in the Control group, splanchnic tissue microcirculation was not compromised to an extent to impair bowel function as the PPV was not different from baseline in both groups. Second, this study was performed in the context of and ERAS program which integrates several perioperative strategies that facilitate the recovery bowel function[3, 109, 7, 185, 186], and that might have offset the microcirculatory benefits observed in the GDFT. Similarly, as the pathogenesis of PPOI is multifactorial, more determinant perioperative factors than fluid therapy, might have contributed to the development of PPOI. For example, patients in the GDFT underwent more complex surgical procedures as indicated by a higher CR-POSSUM severity score[187], and a greater inflammatory state caused by more complex surgery might have influenced the incidence of PPOI, independently from the type fluid regimen received, and from the microcirculatory changes observed.

Despite these results, this cohort study, performed in a clinical setting where several perioperative elements influencing bowel function were well standardized, gave the opportunity to adequately investigate the impact of macro and microcirculatory changes on the incidence of

PPOI. Independently from the type of fluid regimen received, sub-lingual microcirculatory alterations were associated with PPOI. In fact, patients who developed PPOI exhibited a worse PPV, likely indicating worse splanchnic perfusion. These results are physiologically plausible if it is considered that bowel perfusion is one of the major determinants of bowel motility[154]. There was no difference in macrocirculatory measurements such as SV, CO, CI between PPOI and non-PPOI patients, suggesting that perhaps targeting splanchnic microcirculatory perfusion might be more important than targeting standard systemic hemodynamic variables[188]. These findings offer new perspectives for future research specifically investigating the efficacy of perioperative strategies aiming at enhancing splanchnic microcirculation with the ultimate goal of decreasing postoperative gastrointestinal dysfunction. These results will clarify the role of splanchnic microrcirculation on the pathogenesis of PPOI.

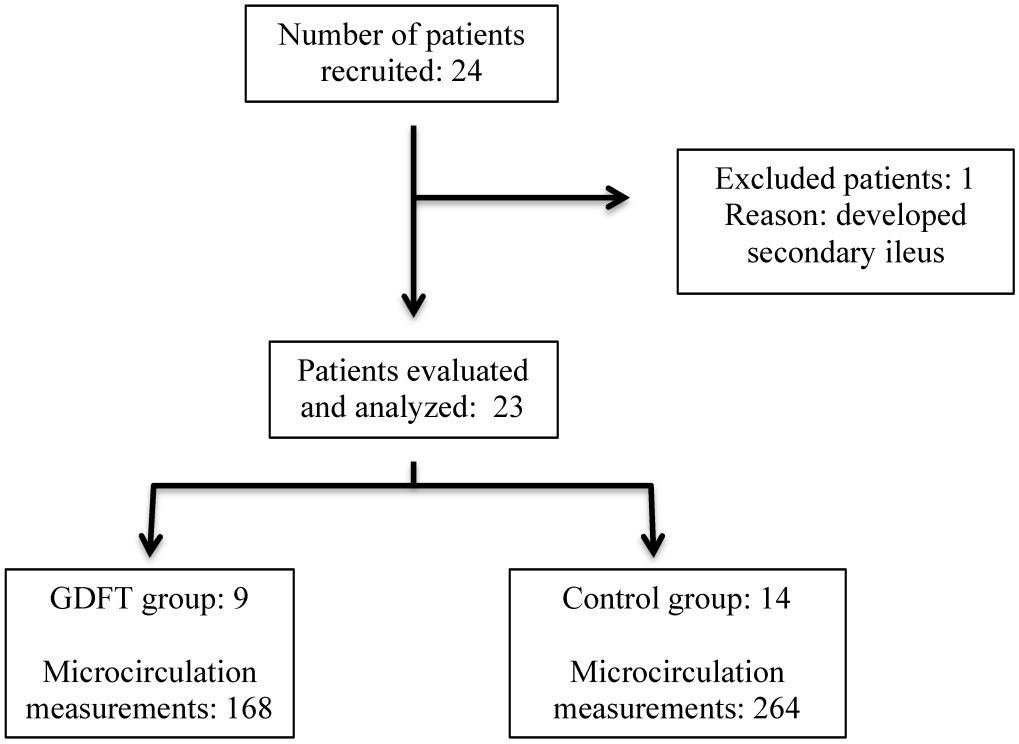
The following limitations must be also acknowledged. First, although a moderate to strong correlation has been reported between the sublingual and splanchnic circulation[151, 152], microcirculatory measurements were not directly acquired from the splanchnic circulation[153, 161]. Second, the PPV may have been lower in the Control group, independently from the type of fluid regimen received, as patients in the Control group received a larger amount of crystalloids during and after surgery[189]. However, the difference in the amount of fluids infused in the first 3 postoperative days between the two groups was not statistically significant, and this period is when the microcirculation measurements were acquired and the presentation of PPOI took place. Similarly, patients in the control group also had a negligible bowel dysfunction (low incidence of PPOI, PPOI started within the first 2 postoperative days and had a median duration of 1 day), which indicates that they were most likely able to compensate the extra amount of crystalloids

given in the postoperative period. The fact that the weight gain the day after the surgery is less than 2.5 kilos in the control group and the weight balance is zero on postoperative day 2 and 3 supports the statement that they compensated well for the excess of crystalloids. Third, the sample size was limited and the study was not powered to observed changes in sub-lingual microcirculations associated with bowel dysfunction. It was not possible to determine *a priori* the sample size because of the lack of previous studies investigating this association in surgical patients. Moreover, having calculated the sample size based on pre-determined and arbitrary reductions in any microcirculation measurement in the Control group would have been methodologically incorrect.

In conclusion, the results of this sub-group analysis show that intraoperative GDFT improves PPV, possibly indicating better splanchnic tissue perfusion. However, these effects did not translate into better recovery of bowel function. Patients who developed PPOI exhibited a lower sub-lingual PPV, which might demonstrate suboptimal splanchnic perfusion.

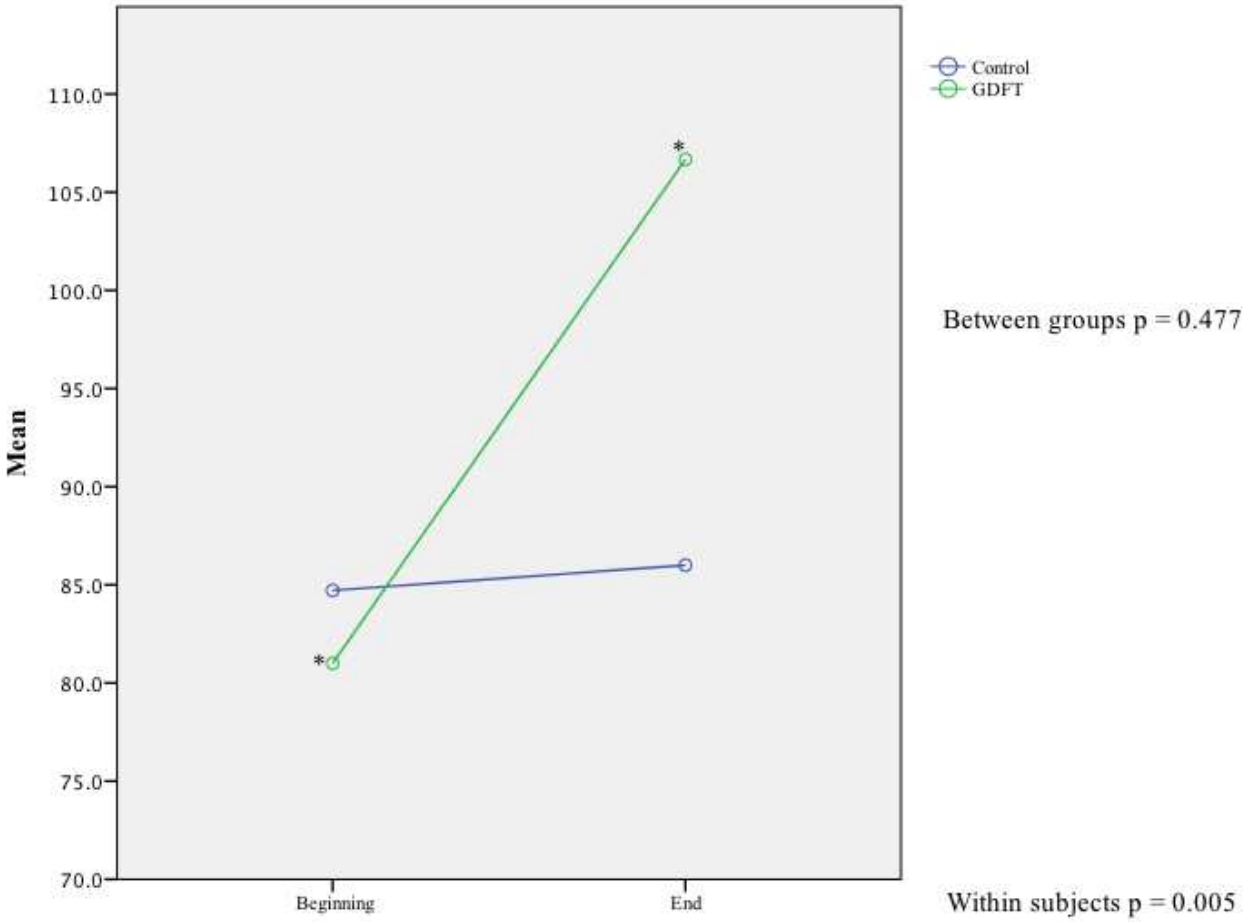
Figures

Figure 1. Flow diagram of recruited and analyzed patients



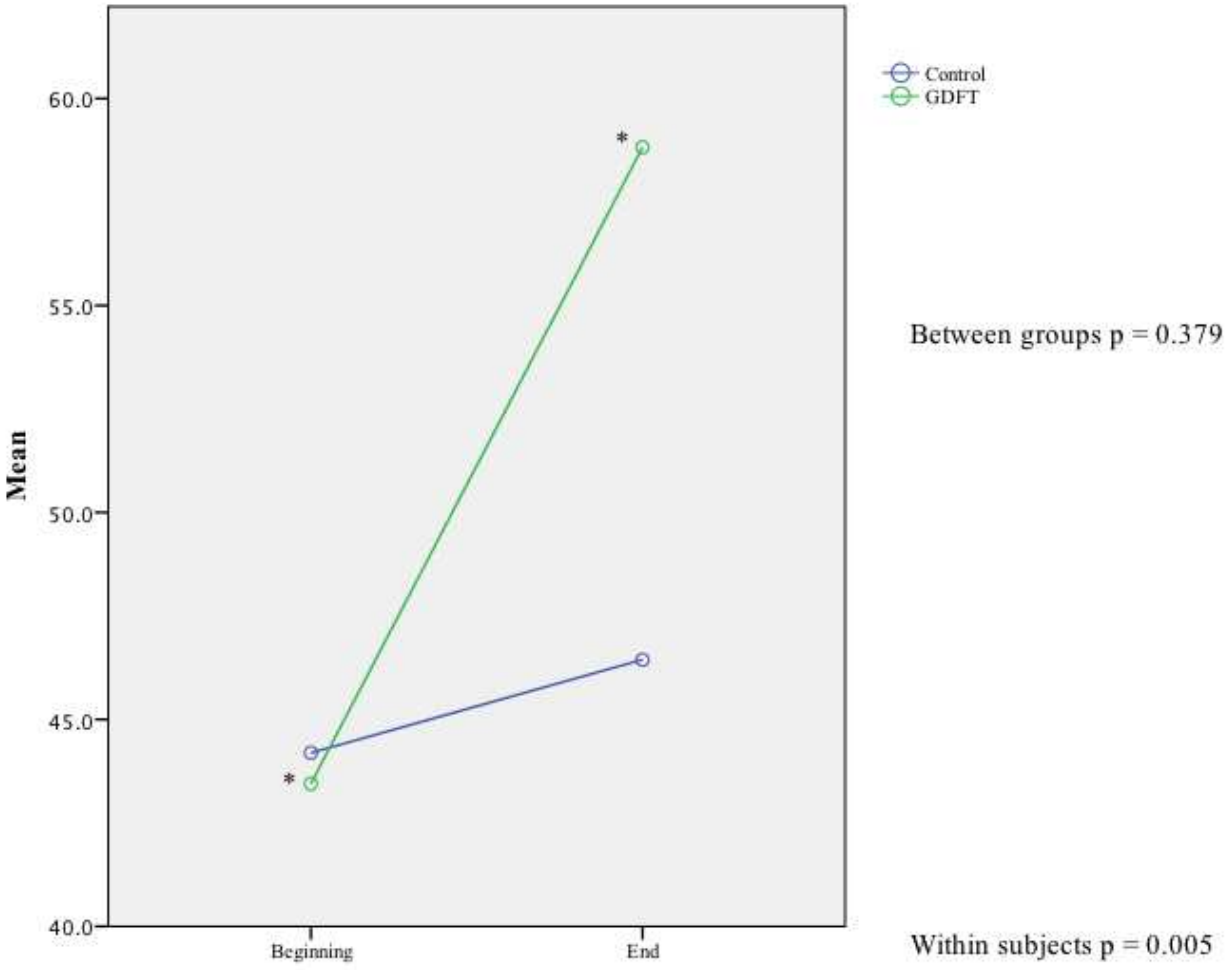
GDFT: goal directed fluid therapy

Figure 2. Stroke Volume (SV) at the beginning and end of the surgery



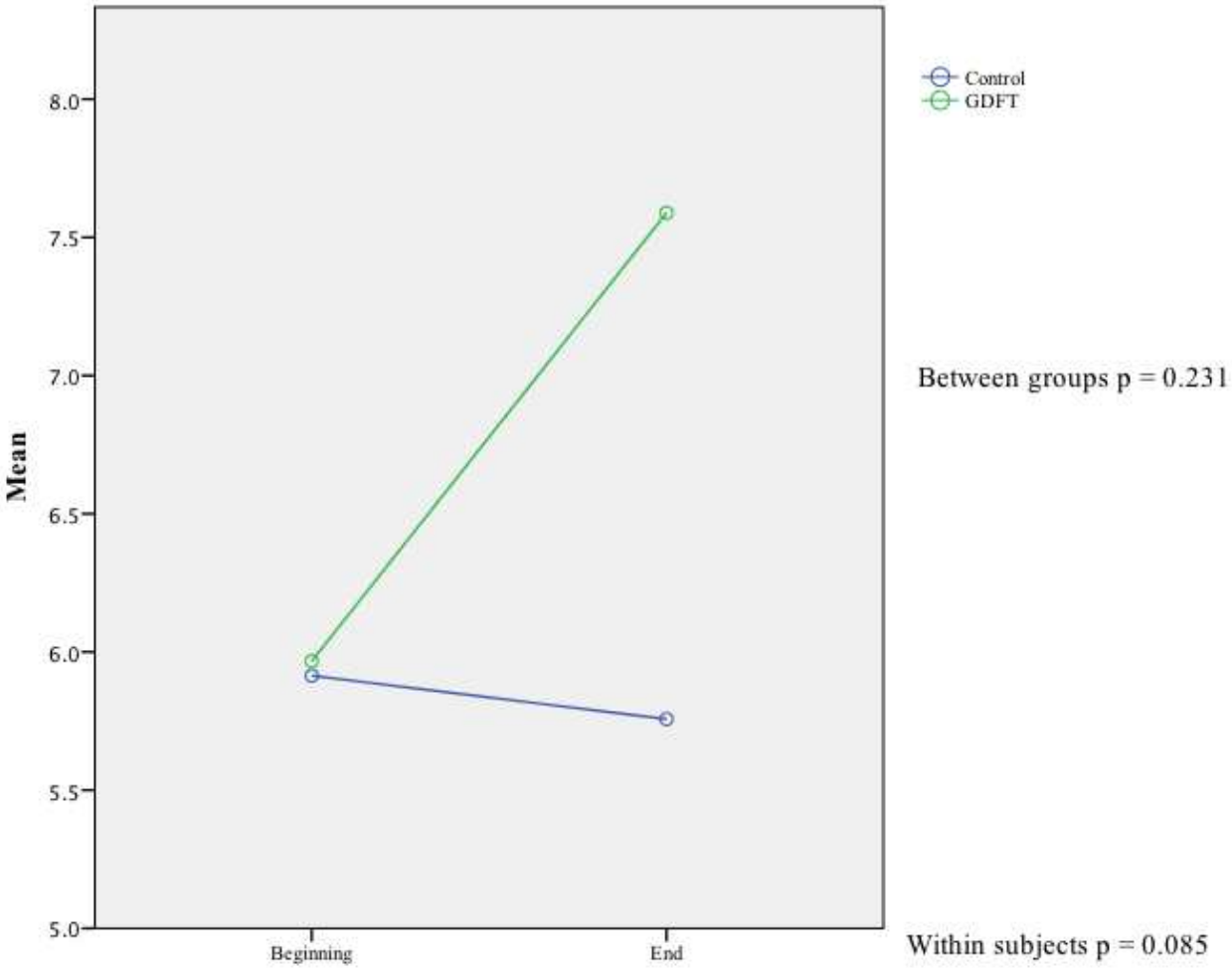
Two way ANOVA. Between time points within groups *p = 0.001

Figure 3. Stroke Volume Index (SVI) at the beginning and end of the surgery



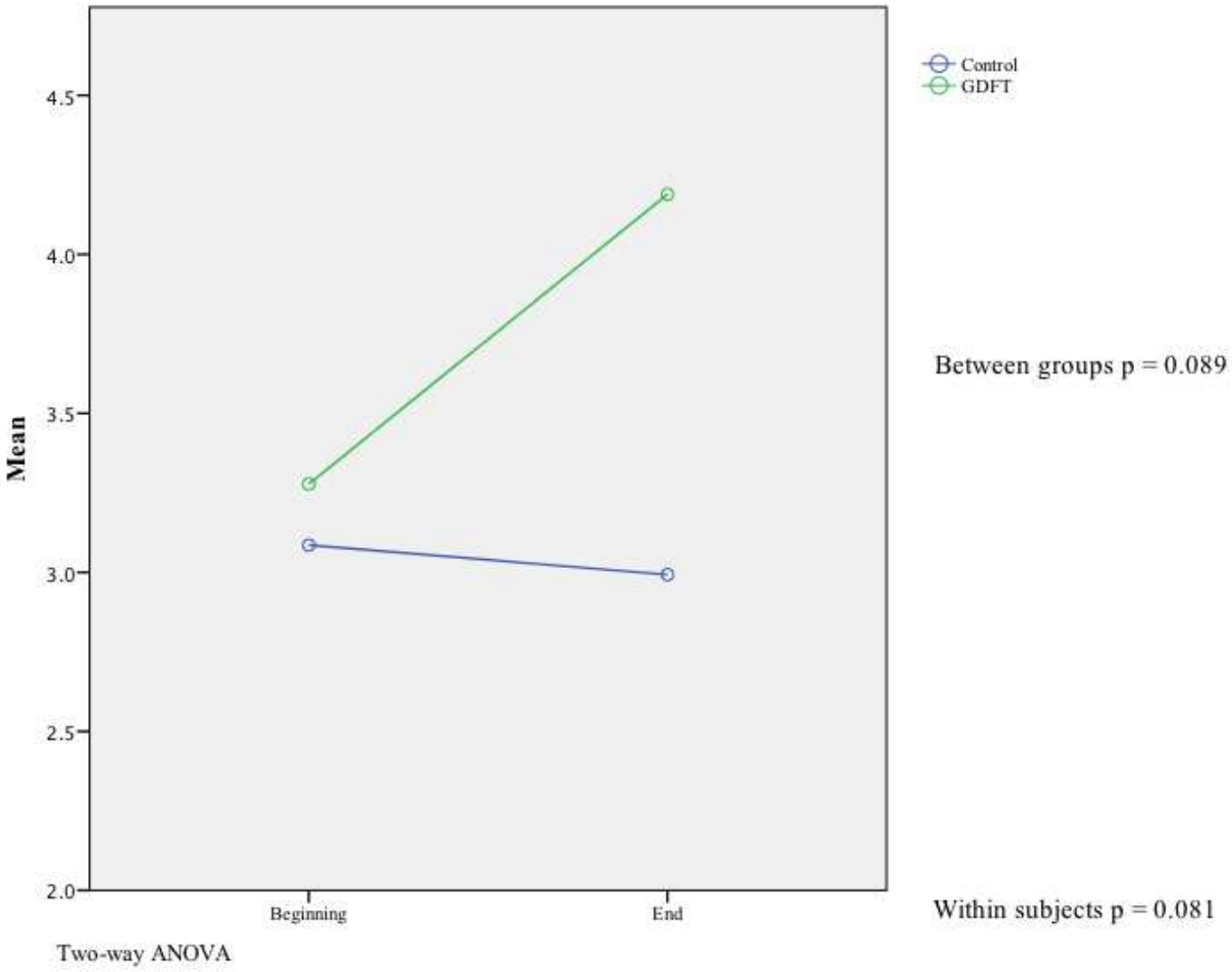
Two way ANOVA. Between time points within groups *p = 0.002

Figure 4. Cardiac Output (CO) at the beginning and end of the surgery



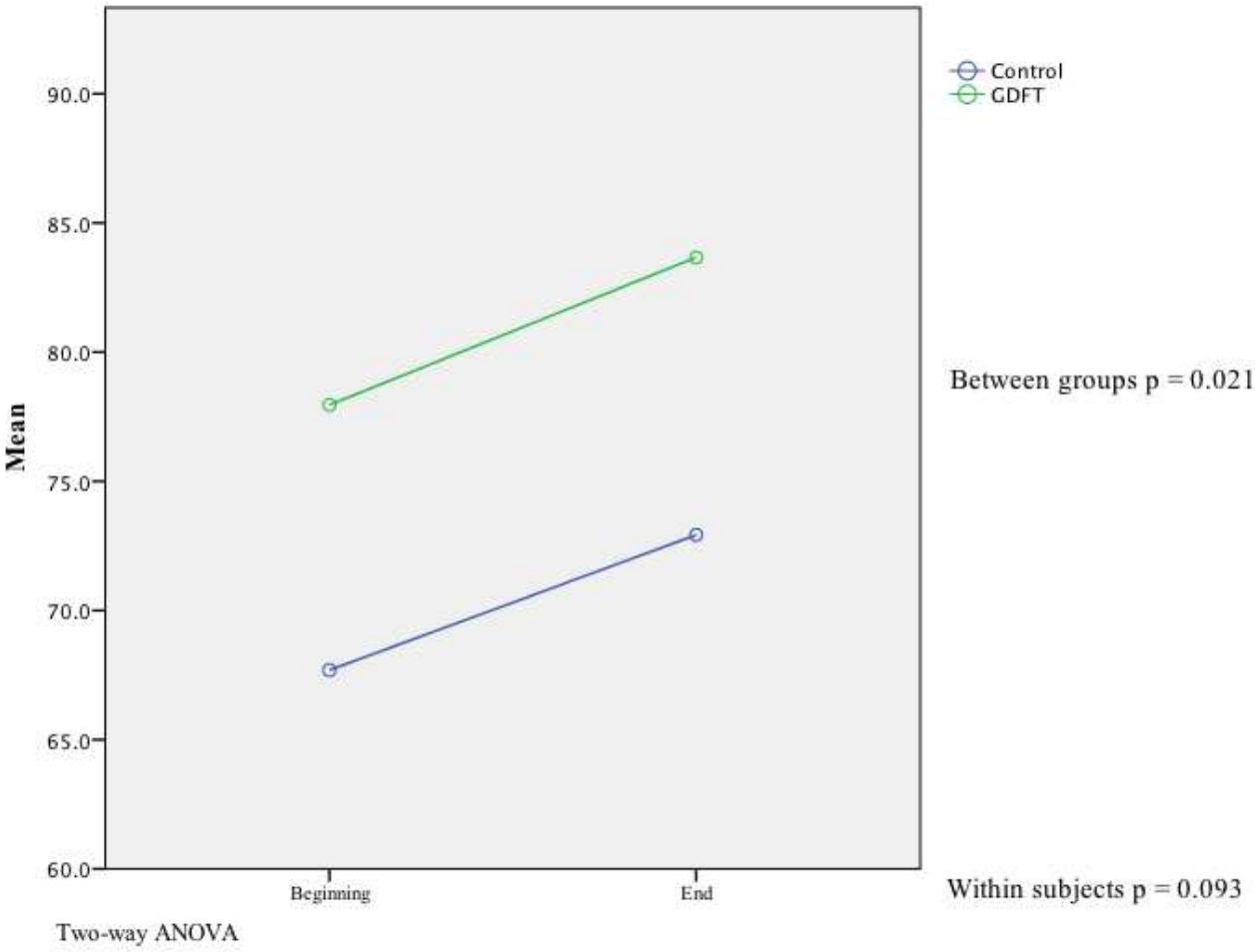
Two-way ANOVA

Figure 5. Cardiac Index (CI) at the beginning and end of the surgery



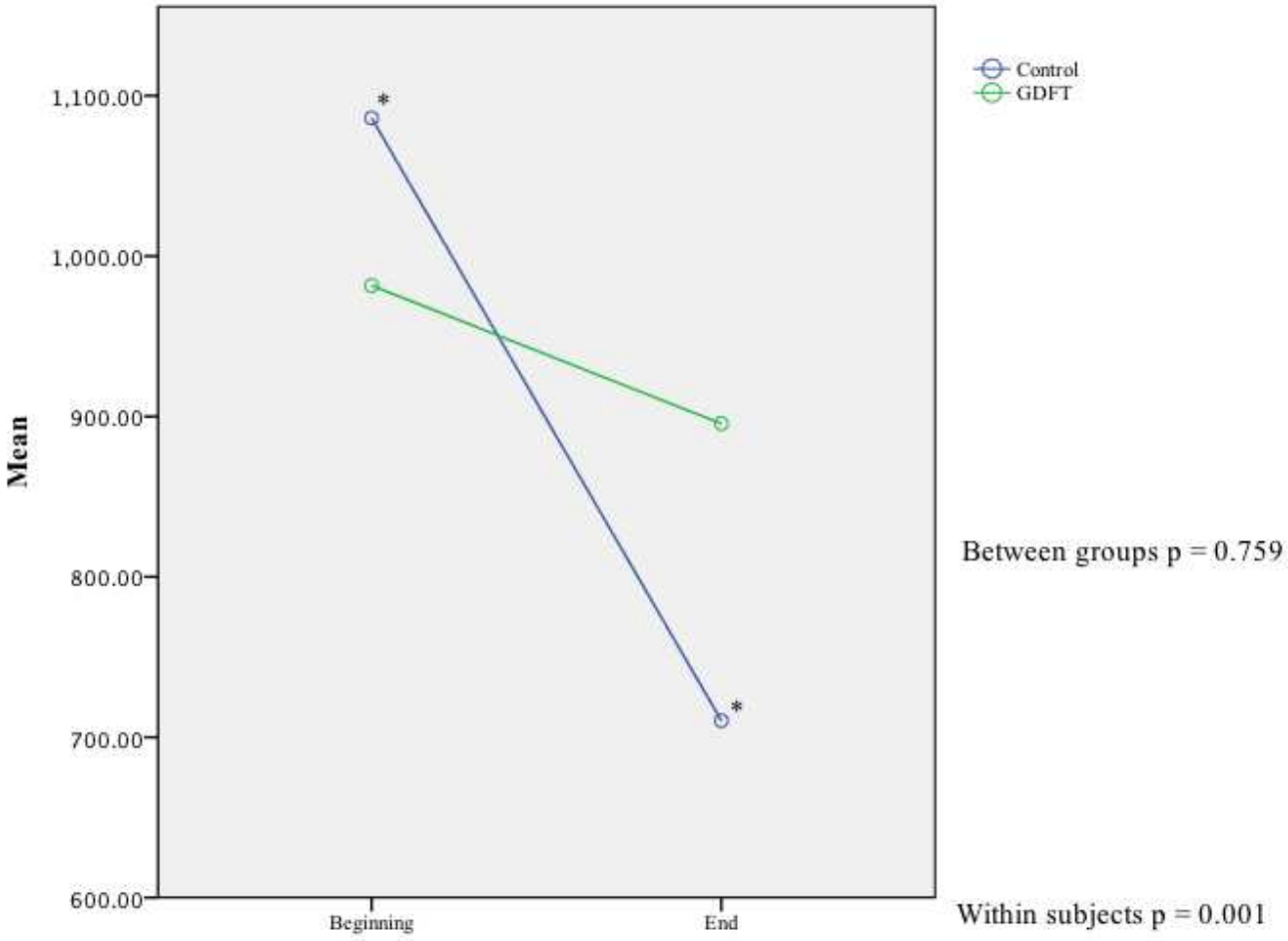
Two-way ANOVA

Figure 6. Mean arterial pressure (MAP) at the beginning and end of the surgery



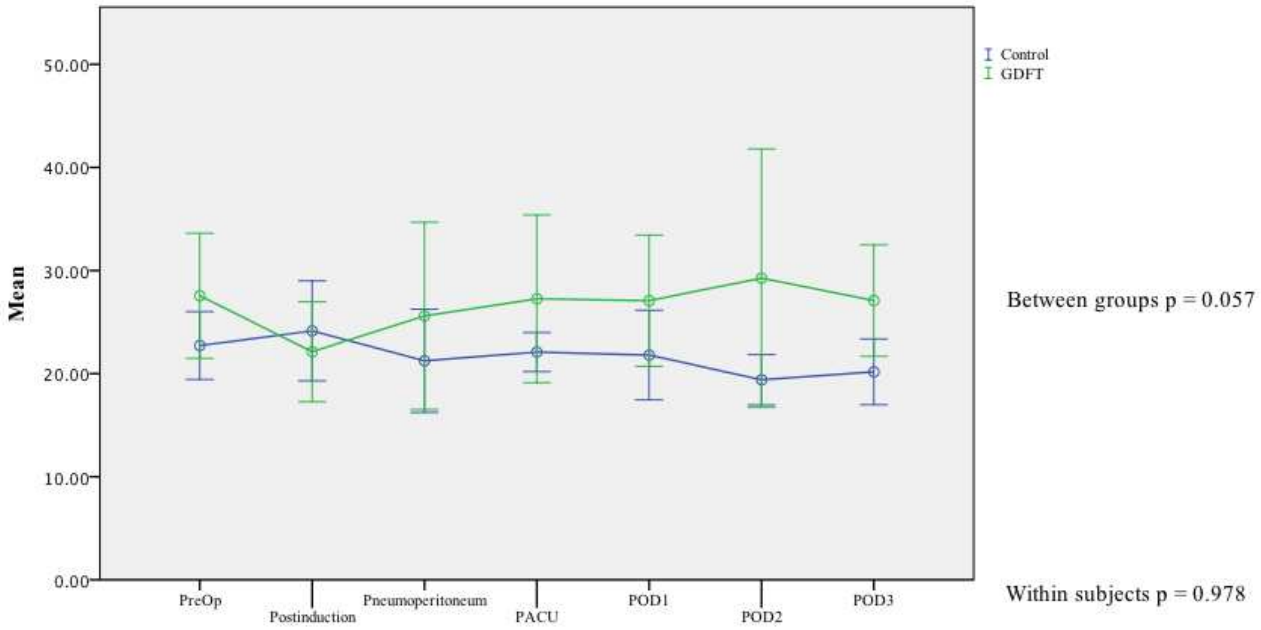
Two-way ANOVA

Figure 7. Oxygen Delivery (DO2) at the beginning and end of the surgery



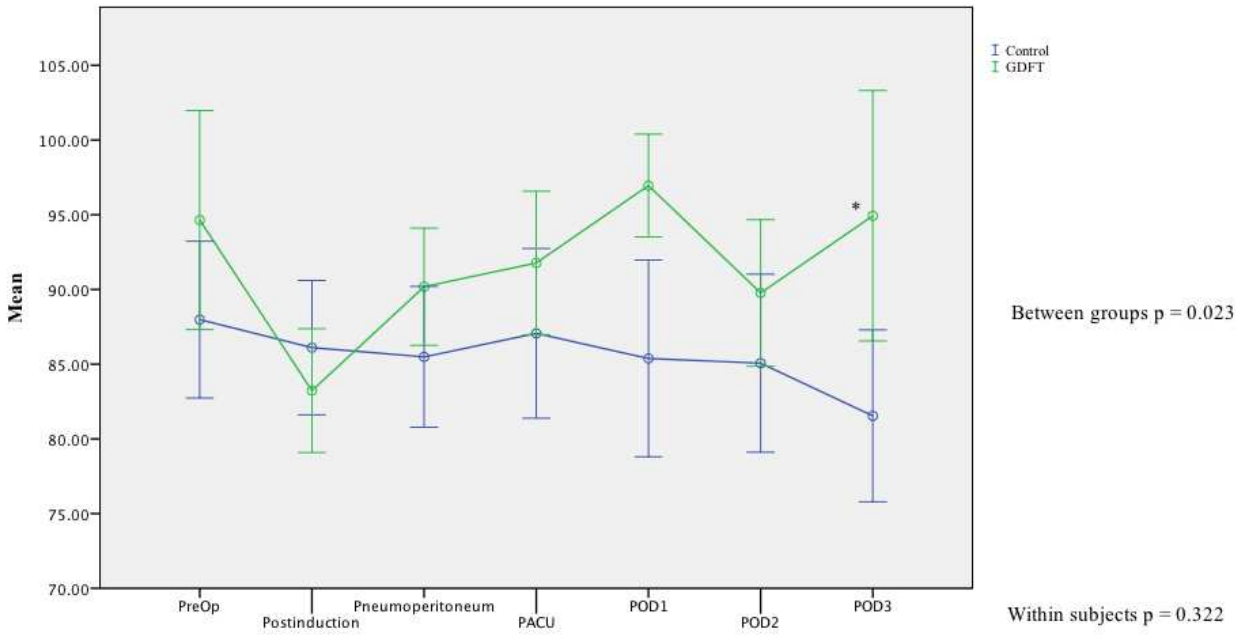
Two-way ANOVA. Between time points within groups: *p <0.001

Figure 8. Perfused Vessel Density (PVD) over time



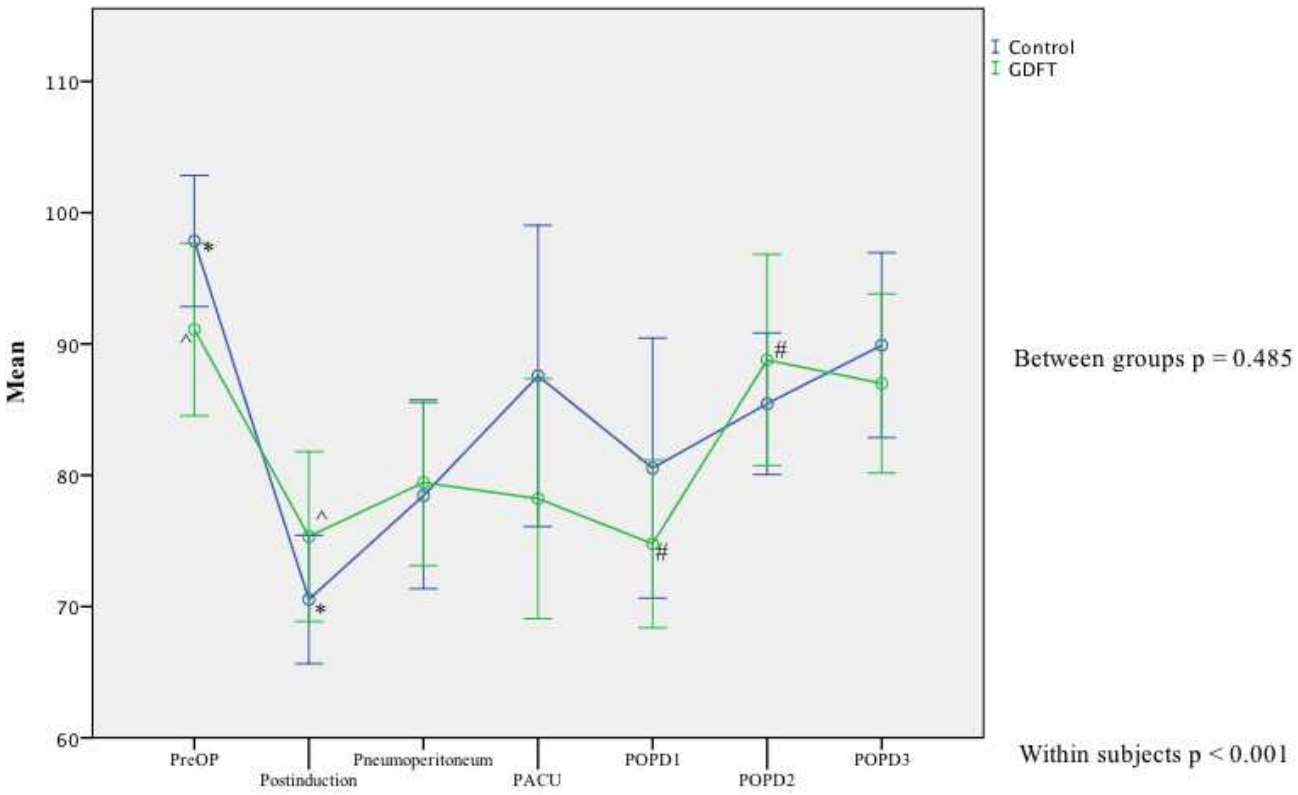
Independent groups repeated measures ANOVA; Error Bars: Standard Error of the mean

Figure 9. Proportion of Perfused Vessels (PPV) over time



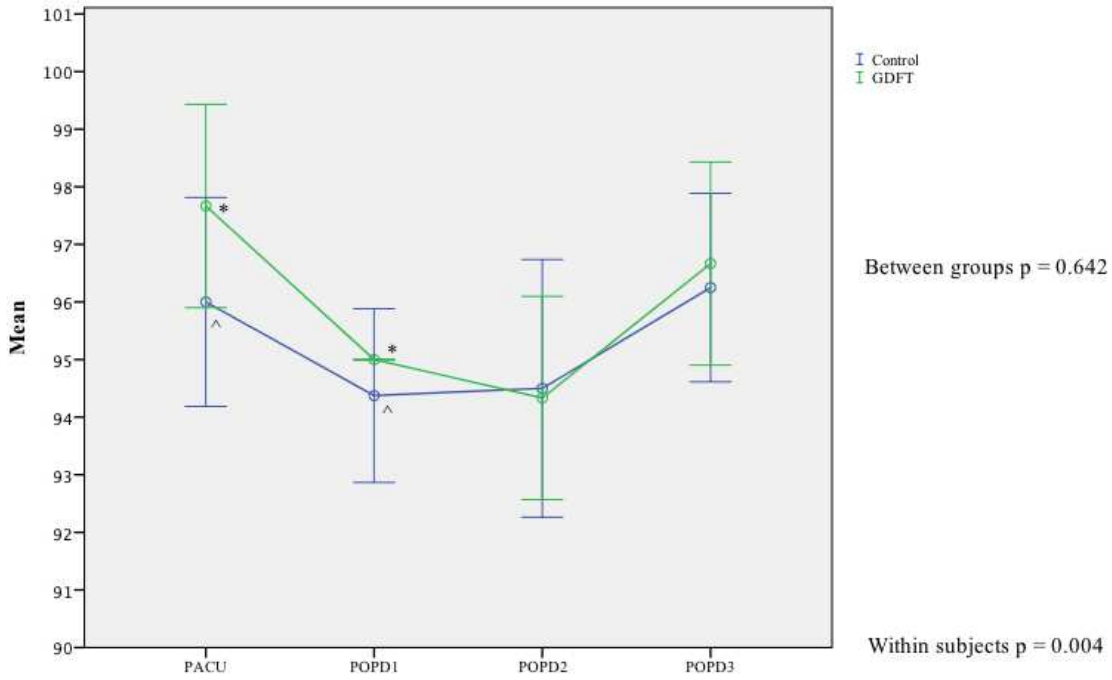
Independent groups repeated measures ANOVA. * GDFT vs Control at specific time point p = 0.032; Error Bars: Standard Error of the mean

Figure 10. Mean Arterial Pressure (MAP) over time



Independent groups repeated measures ANOVA. Between time points per exposure: *p = 0.001; ^p= 0.006; #p= 0.031; Error Bars: Standard Error of the mean

Figure 11. Blood Oxygen Saturation (SaO2%) over time



Independent groups repeated measures ANOVA. Between time points per exposure: *p = 0.048 and ^ p= 0.048; Error Bars: Standard Error of the mean

Tables

Table 1. Microcirculatory measurements

Measurement	**Definition and calculation**
Microvascular Flow Index (MFI)	0 = Absent 1 = Intermittent 2 = Sluggish 3 = Normal
Perfused vessels (PV)	PV = Total number of vessels - (number of vessels with no flow + number of vessels with intermittent flow)
Perfused Vessels Density (PVD)	Three horizontal and three vertical lines divides the image in 16 quadrants. PVD = Number of PV crossing the lines / Total length of the lines
Proportion of Perfused Vessels	PPV= (PV / total number of capillaries) X 100

Table 2. Demographics

		Overall (n = 23)	GDFT group (n = 9)	Control group (n = 14)	p value*
Age (years)		59.57 ± 19.16	59.11 ± 21.12	58.15 ± 18.20	0.957
Gender	Male	13 (56.5)	5 (55.6)	8 (57.1)	1.00
	Female	10 (43.5)	4 (44.4)	6 (42.9)	
Weight (kg)		78.7 [67.3 - 85]	69 [63.2 – 81.8]	80.6 [72.3 – 85.8]	0.124
Height (m)		1.67 ± 0.10	1.71 ± 0.11	1.65 ± 0.92	0.231
BMI		25.90 [24.2 - 32.86]	24.29 [21.94 - 25.66]	28.86 [25.59 - 33.42]	**0.016**
BSA		1.90 ± 0.21	1.84 ± 0.23	1.94 ± 0.20	0.291
Baseline Hb		12.74 ± 2.16	11.93 ± 2.55	13.26 ± 1.78	0.155
Diagnosis n (%)	Cancer	13 (56.5)	6 (66.7)	7 (50)	0.512
	Polyps	3 (13)	2 (22.2)	1 (7.1)	
	Crohn's	1 (4.3)	0	1 (7.1)	
	Diverticulosis	5 (21.7)	1 (11.1)	4 (28.6)	
	Fecal incontinence	1 (4.3)	0	1 (7.1)	
Procedure n (%)	Ileocecal resection	2 (8.7)	1 (11.1)	1 (7.1)	0.109
	Left hemicolectomy	4 (17.4)	3 (33.3)	1 (7.1)	
	Right hemicolectomy	6 (26.1)	0	6 (42.9)	
	Sigmoid resection	4 (17.4)	1 (11.1)	3 (21.4)	
	Hartmann's procedure	1 (4.3)	0	1 (7.1)	
	Low Anterior resection	6 (26.1)	4 (44.4)	2 (14.3)	
Ostomy		3 (13)	1 (11.1)	2 (14.3)	1.00
ASA, n (%)	1	3 (13)	2 (22.2)	1 (7.1)	0.558
	2	15 (62.5)	5 (55.6)	10 (71.4)	
	3	5 (21.7)	2 (22.2)	3 (21.4)	
Previous abdominal surgery		13 (56.5)	5 (55.6)	8 (57.1)	1.00
Chronic use of opioids, n (%)		1 (4.3)	0	1 (7.1)	1.00

*GDFT vs Control. Mean ± SD, median [IQR]; kg = kilograms; m = meters; BMI = body mass index, BSA = body surface area; hb = hemoglobin; ASA = American society of anesthesiologist score. Dichotomous outcomes are presented as absolute values and proportion (%). Data was

analyzed using χ^2 or Fisher test for nominal variables, two samples t-test for continuous normally distributed data, Mann-Whitney U test for non-normally distributed data

Table 3. Preoperative morbidity

		Overall (n = 23)	**GDFT group (n = 9)**	**Control group (n = 14)**	**p value***
Mechanical bowel preparation, n (%)		10 (43.5)	6 (66.7)	4 (20.6)	0.102
Fleet enema, n (%)		9 (39.1)	3 (33.3)	6 (42.9)	1.00
Duration of preoperative fasting, clear fluids, (h)		4 [3 – 6.25]	4.5 [3.6 - 8.12]	3.5 [2.5 - 4.62]	0.91
Duration of preoperative fasting, solid food, (h)		28.41 ± 14.57	33.37 ± 10.87	25.22 ± 16.08	0.197
CR Possum Physiology		8 [7 – 10]	8 [6 – 11.50]	8.5 [7 – 9.25]	0.441
CR Possum Severity		7 [7 – 8]	8 [7 - 11]	7 [7 - 7]	**0.019**
Comorbidities	Hypothyroidism	5 (21.7)	2 (22.2)	3 (21.4)	1.00
	COPD/Asthma	4 (17.4)	1 (11.1)	3 (23.1)	1.00
	CAD	1 (4.3)	0	1 (7.1)	1.00
	GERD	4 (17.4)	1 (11.1)	3 (21.4)	1.00
	Hepatitis B	1 (4.3)	1 (11.1)	0	0.391
	CVA	1 (4.3)	0	1 (7.1)	1.00
	Smoking history	3 (13)	0	3 (21.4)	0.253

*GDFT vs Control. Median [IQR]. n = absolute count; h = hours; CR = colorectal; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; GERD = gastroesophageal reflux disease; CVA = cerebrovascular accident. Dichotomous outcomes are reported as absolute values and proportion (%). Data was analyzed using χ^2 or Fisher test for nominal variables, Mann-Whitney U test for non-normally distributed data

Table 4. Intraoperative data

	Overall (n = 23)	**GDFT group (n = 9)**	**Control group (n = 14)**	**p value***
Total intravenous fluids (ml)	2034 [1160 - 3252]	1160 [819.50 - 2159.12]	2681.50 [1661.50 - 4576]	**0.016**
Crystalloids (ml)	1372 [560 - 2910]	547 [371.50 – 859.12]	2362.70 [1368.50 - 4149]	**0.001**
Colloids (ml)	400 [0-600]	600 [400 – 1400]	0 [0 – 500]	**0.005**
Blood transfusion, n (%)	1 (4.3)	1 (11.1)	0	0.391
Urine output (ml)	400 [327 - 550]	400 [300 - 550]	400 [368 – 674.50]	0.416
Patients requiring vasopressors, n (%)	21 (91.3)	7 (77.8)	14 (100)	0.142
Phenylephrine (µg)	120 [0 - 200]	80 [0-180]	120 [80 - 440]	0.212
Ephedrine (mg)	10 [0 - 20]	5 [0 – 22.5]	15 [5 – 23.75]	0.275
Duration of surgery (min)	170 [130 - 237]	170 [112.50 - 254.50]	169.50 [130 - 240.25]	0.963
Laparoscopic time (min)	99.57 ± 40.30	104.33 ± 43.82	96.50 ± 39.25	0.66
Duration of anesthesia (min)◆	200 [145 - 277]	200 [137 - 284.5]	197 [145.75 - 279.50]	0.989
Estimated blood loss (ml)	100 [100 - 400]	300 [100 - 800]	100 [100 - 300]	0.178
Remifentanil (µg)	1650 [1250 - 2650]	1500 [975 - 2500]	1900 [1537.5 - 2675]	0.178

*GDFT vs Control. ◆From induction to extubation. Mean ± SD, median [IQR]; BP = blood pressure. ml = milliliters; min = minutes; mg = milligrams; µg = micrograms. Dichotomous outcomes are reported absolute values or proportion (%). Data was analyzed using χ^2 or Fisher test for nominal variables, two samples t-test for continuous normally distributed data, Mann-Whitney U test for non-normally distributed data.

Table 5. Post anesthesia care unit (PACU) data

		Overall (n = 23)	GDFT group (n = 9)	Control group (n = 14)	p value*
Total intravenous fluids (ml)		300 [200 - 570]	231 [185 - 643]	304.50 [195 – 517.50]	0.914
Colloids (ml)		0 [0 – 0]	0	0 [0 - 0]	0.600
Crystalloids (ml)		355.26 ± 220.99	373.44 ± 236.68	343.57 ± 218.63	0.760
BP (mmHg)	Systolic	126.43 ± 27.34	114.89 ± 26.11	113.86 ± 26.34	0.106
	Diastolic	62.04 ± 13.35	59.89 ± 9.58	63.43 ± 15.49	0.547
	Mean	83.51 ± 16.30	78.22 ± 13.70	86.90 ± 17.39	0.220
Hypotension, n (%)◆		8 (34.8)	4 (44.4)	4 (28.6)	0.657
Number of patients requiring vasopressors n, (%)		5 (21.7)	3 (33.3)	2 (14.3)	0.343
PONV, n (%)		8 (34.8)	4 (44.4)	4 (28.6)	0.657
Number of patients requiring antiemetics, n (%)		9 (39.1)	3 (33.3)	6 (42.9)	1.00
Number of patients requiring > 1 antiemetic agent		2 (8.7)	0	2 (14.3)	0.502
Fentanyl (μg)		28.26 ± 47.25	25 ± 41.45	30.36 ± 52.05	0.798
Meperdine (mg)		0 [0 – 0]	0 [0 – 12.50]	0 [0 – 0]	0.260
PACU length of stay (min)		145 [99 - 245]	130 [95 - 260]	160 [96.75 – 219.25]	0.865

*GDFT vs Control. ◆Hypotension: SBP<90mmhHg or drop >20% from baseline. Mean ± SD, median [IQR]; ml = milliliters; μg = micrograms; mg = milligrams; min = minute. BP = blood pressure. Dichotomous outcomes are reported as absolute values (n) or proportion (%). Data was analyzed using χ^2 or Fisher test for nominal variables, two samples t-test for continuous normally distributed data, Mann-Whitney U test for non-normally distributed data.

Table 6. Postoperative fluids and opioids

		Overall (n = 23)	GDFT group (n = 9)	Control group (n = 14)	p value*
Total IV fluids (ml)		1187 [255 – 1785]	292.50 [194.25 – 1617.50]	1536 [270 – 2480.62]	**0.047**
IV fluids (ml) during the first 3 POP days		954.50 [262.50 – 1742.50]	292.50 [195-1565]	1262 [270-1942.50]	0.072
Oral water intake (ml)		6025 [3850 – 8250]	6075 [4725 - 9562]	5750 [3543.75 - 8550]	0.403
Total output (ml)		6609.42 ± 4265.47	1387.74 ± 801.21	4238.08 ± 1412.69	0.088
Weight balance, Kg	POP D1◆	1 [0.20 – 1.70]	0.90 [-0.15 – 1.40]	1.2 [0.40 – 1.85]	0.446
	POP D2◆◆	0.43 ± 2.05	1.54 ± 2.21	0.01 ± 1.73	0.078
	POP D3◆◆◆	-0.75 ± 1.85	-1.80 ± 1.41	0.00 ± 1.62	**0.014**
IV fluids restarted, n (%)		11 (47.8)	3 (33.3)	8 (57.1)	0.400
Reasons for restarting IV fluids	Hypotension	10 (43.5)	3 (33.3)	7 (50)	0.439
	NPO + vomiting	1 (4.3)	0	1 (7.1)	
Blood transfusion, n (%)		2 (8.7)	0	2 (14.3)	0.502
Orthostatic intolerance, n (%)		1 (4.3)	1 (11.1)	0	0.391
Orthostatic hypotension		5 (21.7)	0	5 (35.7)	0.116
Morphine IV equivalent (mg)		13.20 [8.3 – 26.40]	9.90 [6.60 - 18.85]	17.45 [9.97 – 41.00]	0.051
TEA (days)		2 [2 - 2]	2 [2 - 2]	2 [2 - 2]	1.00
Systemic opioid (days)		1.74 ± 1.13	1.33 ± 1	2 ± 1.17	0.175

*GDFT vs Control. ◆7 patients in GDFT and 12 in control group. ◆◆9 patients in GDFT and 14 in control group. ◆◆◆9 patients in GDFT and 13 in control. IV= intravenous. Median [IQR]. ml = milliliters; mg = milligrams; IV = intravenous; NPO = nil per os; TEA= thoracic epidural analgesia. Total output = urinary output plus output from nasogastric tube and drains. POP D= postoperative, day. Dichotomous outcomes reported as counts (n) and percentage (%). Data was analyzed using χ^2 or Fisher test for nominal variables, Mann-Whitney U test for non-normally distributed data

Table 7. Postoperative morbidity

		Overall (n = 23)	GDFT group (n = 9)	Control group (n = 14)	p value*
Patients with at least one postoperative complication	Hypoxemia⌘	1 (4.3)	0	1 (7.1)	1.00
	Urinary retention∞	1 (4.3)	0	1 (7.1)	1.00
	C. Difficile¶	1 (4.3)	0	1 (7.1)	1.00
	Total patients	9 (39.1)	2 (22.2)	7 (50)	0.228
Clavien	I	7 (30.4)	2 (22.2)	5 (35.7)	0.315
	II	2 (8.7)	0	2 (14.3)	
Quality of recovery score (POD 2)		14 [13 - 16]	14 [12.50 – 15.50]	15.5 [13 - 16]	0.452
Readiness to be discharged		3 [3 - 4]	3 [2 - 3]	3 [3 - 4.25]	**0.010**
Length of Hospital Stay (days)		3 [3 - 4]	3 [3 - 3.5]	4 [3 - 4.5]	0.156
ICU admission, (n)		0	0	0	

*GDFT vs Control. ⌘Oxygen saturation per pulse oximetry < 90%. ∞Urinary retention requiring the insertion of a catheter for bladder evacuation. ¶Diarrhea with a positive stool culture reporting C. Difficile. ICU = Intensive care unit. Dichotomous outcomes are reported as counts (n) and percentage (%)

Table 8. Bowel function in the postoperative period

		Overall (n = 23)	GDFT group (n = 9)	Control group (n = 14)	p value*
PPOI		6 (26.1)	3 (33.3)	3 (21.4)	0.643
Onset time	POD 1	4 (66.4)	3 (100)	1 (33.3)	0.400
	POD 2	2 (33.3)	0	2 (66.7)	
Duration of PPOI		1 [1 - 1.25]	1 [1 - 1]	1 [1 - 1.50]	1.00
Time to first bowel motion (h)		31.32 ± 14.34	38.67 ± 15.77	26.23 ± 11.21	**0.042**
Time to first flatus (h)		21 [16 - 26]	21 [18 - 34]	20 [10.50 - 24]	0.467
Bowel function symptoms n, (%)	Nausea	14 (60.9)	7 (77.8)	7 (50)	0.228
	Vomiting	9 (39.1)	3 (33.3)	6 (42.9)	1.00
	Intolerance of oral intake	4 (17.4)	1 (11.1)	3 (21.4)	1.00
	Abdominal distension	20 (87)	6 (66.7)	14 (100)	**0.047**
Clear fluids diet for at least 24 h, n (%)		7 (30.4)	3 (33.3)	4 (28.6)	1.00
NPO, n (%)		1 (4.3)	0	1 (7.1)	1.00
Number of Skipped meals		1 [0 - 3]	1 [0 - 1]	1.5 [0.75 - 4.50]	0.065
NGT, n (%)		1 (4.3)	0	1 (7.1)	1.00

*GDFT vs Control. Mean ± SD, median [IQR]; BP = blood pressure. Dichotomous outcomes are reported as counts (%). Data was analyzed using χ^2 or Fisher test for nominal variables, two samples t-test for continuous normally distributed data, Mann-Whitney U test for non-normally distributed data. NPO = nil per os as per surgical team, NGT = nasogastric tube; PPOI = Primary Postoperative Ileus.

Table 9. *Microcirculation, macrocirculation and PPOI*

		PPOI (n = 6)	Non-PPOI (n = 17)	p-value
Microcirculation	MFI	3 [3 - 3]	3 [3 - 3]	0.865★
	PVD	23.15 ± 5.13	24.62 ± 4.11	0.488*
	PPV	82.76 ± 3.19	87.29 ± 4.20	**0.026***
Macrocirculation	MAP	84.89 ± 4.34	85.62 ± 7.26	0.822*
	CO	5.67 [4.47 - 6.10]	5.95 [4.92 - 7.35]	0.286★
	CI	2.92 [2.28 - 3.12]	3.35 [2.67 - 3.77]	0.101★
	SV	74.50 [69.25 - 86.75]	82.50 [73 - 107.50]	0.227★

★Mann-Whitney U; *2 independent samples t-test. The overall mean value throughout the perioperative period for both macro and microcirculatory measurements was used for analyses. PPOI = postoperative primary ileus; non-PPOI = patients who did not develop PPOI; PVD = perfused vessel density; PPV = proportion of perfused vessels; MFI = microvascular flow index; SV = stroke volume; CO = cardiac output; CI = cardiac index; MAP = mean arterial pressure

Overall conclusions

Even though previous small and underpowered randomized controlled trials have demonstrated that GDFT attenuated postoperative gastrointestinal dysfunction[63, 167, 168], the results of the performed meta-analysis (Chapter 1) have supported the benefits of this intervention only in colorectal patients and in patients not treated with ERP[107].

These findings are in agreement with the results of the randomized controlled trial comparing intraoperative GDFT versus fluid therapy based on traditional fluid therapy principles (Chapter 2). In fact, it was found that the incidence of PPOI in patients undergoing elective laparoscopic colorectal surgery within an ERP was similar in the 2 groups, even if the overall amount of intravenous fluids received (mainly crystalloids) was higher in the Control group, and the increase in systemic perfusion (stroke volume and cardiac output) was more pronounced and sustained in the GDFT group. These findings are in keeping with the results of a recent meta-analysis that suggests that the previously demonstrated benefits observed in surgical patients treated with GDFT are offset by advancements in perioperative and surgical care[68]. Moreover, patients in the Control group were able to eliminate fluid excess as demonstrated by a higher urine output. Finally, the weight gain observed on day 1 in the Control group was less than 2.5 kg, threshold associated with an increased postoperative morbidity and mortality[57, 122]. Absence of evidence does not mean evidence of absence, and fluid therapy should be always based on physiologic and scientific principles, to minimize the risk of complications associated with fluid overloading and hypovolemia, especially in high-risk surgical patients.

The microcirculation study (Chapter 3) showed that GDFT improved the sub-lingual PPV and this effect was sustained until postoperative day 3. A better PPV was interpreted as a vessel-recruiting effect of GDFT, leading to better tissue oxygen extraction. It was also observed that oxygen delivery was lower in the Control group at the end of surgery. Overall, these findings suggest better splanchnic tissue perfusion and oxygenation in patients receiving GDFT. Nevertheless, these physiological benefits did not translate into better recovery of bowel function, as also demonstrated by the overall results of the randomized controlled trial. Patients who developed PPOI exhibited a lower sub-lingual PPV, which might demonstrate suboptimal splanchnic perfusion. It suggests that therapeutic interventions targeting splanchnic microcirculatory perfusion might be more effective than targeting standard systemic hemodynamic variables.

As future directions, studies investigating the role of GDFT as a perioperative strategy to minimize postoperative gastrointestinal dysfunction in high-risk patients, sensitive to both fluid overload and hypovolemia, and undergoing more complex and invasive surgeries are warranted. The results of this thesis also offer new perspectives for future research specifically investigating the efficacy of perioperative strategies aiming at directly enhancing splanchnic tissue microcirculation with the ultimate goal of decreasing postoperative gastrointestinal dysfunction. These results will also serve to elucidate the role of splanchnic microcirculation on the pathogenesis of PPOI.

Supplementary material

Chapter 1

A) Medline Search Strategy

exp Fluid Therapy/
exp Body Fluids/
exp Echocardiography, Doppler/
exp Echocardiography, Transesophageal/
exp Ultrasonography, Doppler/
exp Cardiac Output/
exp Monitoring, Intraoperative/
exp Blood Flow Velocity/
exp Hemodynamics/
exp Stroke Volume/
exp Blood Pressure/
exp Pulmonary Artery/
exp Catheterization, Swan-Ganz/
exp Thermodilution/
exp Monitoring, Physiologic/
exp Pulse/
exp Intraoperative Care/ or exp Intraoperative Period/
exp Oximetry/
Oxygen/ or exp Oxygen Consumption/
exp Critical Care/
exp Biological Oxygen Demand Analysis/
exp Vascular Access Devices/
exp Arterial Pressure/
exp Central Venous Catheters/
exp Venous Pressure/
exp Manometry/
exp Models, Cardiovascular/
exp Cardiography, Impedance/
exp Cardiopulmonary Resuscitation/
exp Plethysmography, Impedance/ or Plethysmography/
exp Heart Function Tests/
exp Indicator Dilution Techniques/
exp Radioisotope Dilution Technique/
exp Lithium Chloride/
exp Microdialysis/
exp Colloids/
exp Heart Rate/
exp Aorta/
exp Spectrum Analysis/
exp Spectroscopy, Near-Infrared/

exp Electric Impedance/
goal directed therapy.tw.
goal.tw.
exp Carbon Dioxide/
exp Pulsatile Flow/
exp Cardiac Volume/
exp Cardiac Output, Low/
exp Cardiac Output, High/
exp Diagnostic Techniques, Cardiovascular/
exp Plasma Substitutes/
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
exp Intestinal Mucosa/
exp Gastric Mucosa/
exp Splanchnic Circulation/
exp anastomosis, roux-en-y/ or exp appendectomy/ or exp biliary tract surgical procedures/ or exp biliopancreatic diversion/ or exp colectomy/ or exp endoscopy, digestive system/ or exp enterostomy/ or exp fundoplication/ or exp gastrectomy/ or exp gastroenterostomy/ or exp gastropexy/ or exp gastroplasty/ or exp gastrostomy/ or exp hemorrhoidectomy/ or exp hepatectomy/ or exp jejunoileal bypass/ or exp liver transplantation/ or exp pancreas transplantation/ or exp pancreatectomy/ or exp pancreaticoduodenectomy/ or exp pancreaticojejunostomy/ or exp peritoneovenous shunt/
exp Abdomen/
exp Laparoscopy/ or exp Hand-Assisted Laparoscopy/
exp Laparotomy/
exp Colostomy/
exp Ileostomy/
exp Colonic Pouches/
exp Proctocolectomy, Restorative/
intermediate risk patients.mp.
high risk patients.mp.
abdominal surgery.mp.
52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
51 and 66
exp Cohort Studies/
exp Randomized Controlled Trial/
68 or 69
67 and 70

exp= explode

B) Excluded studies due to poor quality

	Random sequence generation	Allocation concealment	Blinding of patients and surgeons	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources*
Buettner, 2008[190]	?	?	?	-	?	-	-
Cohn, 2010[191]	+	?	+	+	+	-	-
Concha, 2011[192]	?	?	?	?	+	?	?
Conway, 2002[193]	?	?	?	-	+	-	+
Donati, 2007[194]	+	?	?	-	+	+	+
Pillai, 2011[195]	?	?	+	?	+	-	+

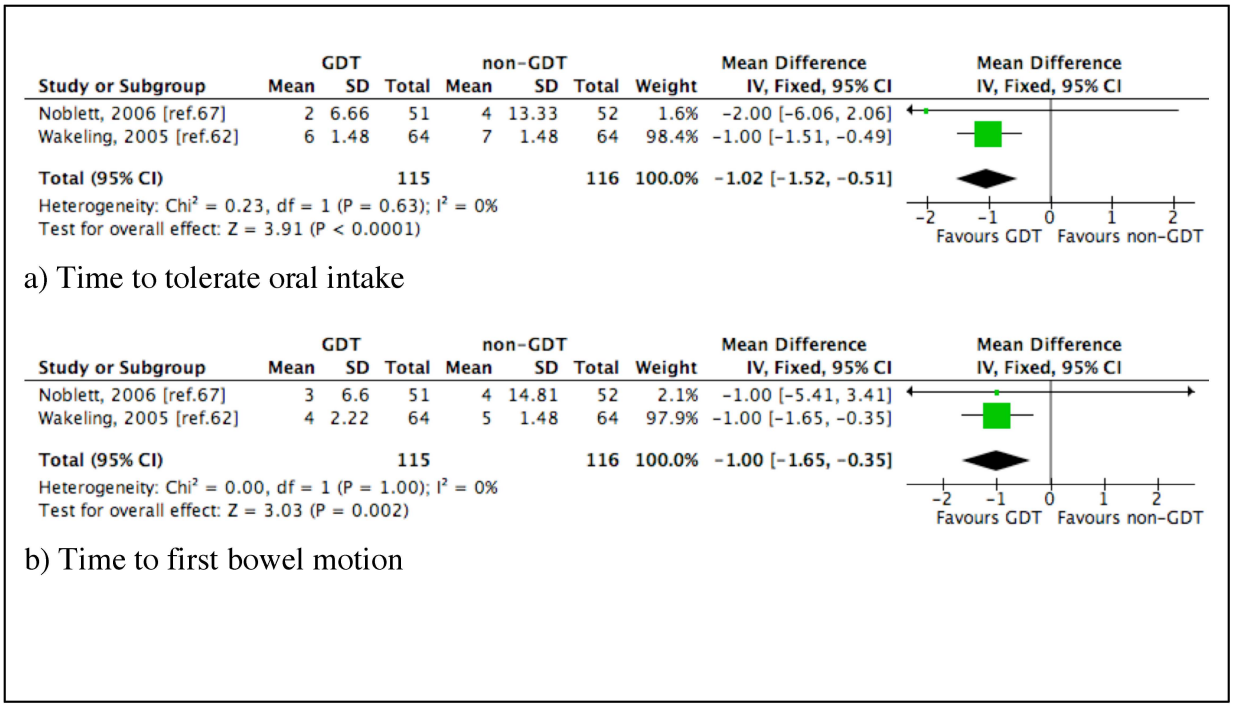
+ ; low risk of bias, ? ; unclear risk of bias; - ; high risk of bias. *For example, the study design was inappropriate, the study was stopped earlier, extreme baseline imbalance.

C) Reasons for exclusion of studies

Study	Reasons
Abdullah, 2012[196]	Patients in each arm of the study were treated with GDT
Buettner, 2008[197]	Detection bias (blinding of outcome assessment): no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Sample size was not calculated All patients were transferred to intensive care unit
Cohn, 2010[191]	Sample size was not calculated
Concha, 2011[192]	Selecting reporting
Conway, 2002[193]	Detection bias (blinding of outcome assessment): no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Performance bias (blinding of participants and personal): incomplete blinding, and the outcome is likely to be influenced by lack of blinding
Davies, 2011[198]	Patients in each arm of the study were treated with GDT
Donati, 2007[194]	Detection bias (blinding of outcome assessment): no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Performance bias (blinding of participants and personal): no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding GDT was continued in the postoperative period All patients were transferred to intensive care unit
Feldheiser, 2013[199]	Patients in each arm of the study were treated with GDT
Futier, 2010[200]	Patients in each arm of the study were treated with GDT
Futier, 2010[201]	Patients in each arm of the study were treated with GDT
Jhanji, 2010[146]	Patients in each arm of the study were treated with GDT
Lee, 2012[202]	Patients in each arm of the study were treated with GDT
Li, 2013[203]	Patients in each arm of the study were treated with GDT
Lobo, 2011[204]	Patients in each arm of the study were treated with GDT
Mayer, 2010[205]	Patients in each arm of the study were treated with GDT
Pillai, 2011[195]	Sample size was not calculated; Detection bias (blinding of outcome assessment): blinding of outcome assessment is not reported, and the outcome measurement is likely to be influenced by lack of blinding
Senagore, 2009[206]	Patients in each arm of the study were treated with GDT
Sondergaard, 2012[207]	Patients in each arm of the study were treated with GDT
Stone, 2003[208]	Patients in each arm of the study were treated with GDT
Szakmany, 2005[209]	Patients in each arm of the study were treated with GDT
Wang, 2012[210]	Patients in each arm of the study were treated with GDT

GDT; goal directed therapy

D) Forest plots: Effect of goal directed therapy on bowel function after colorectal surgery



Chapter 2

Supplement. 1 Perioperative fluid management in the Goal Directed Fluid Therapy (GDFT) group and in the Control group

GDFT-group	Control-group [126]
Preoperative *Bowel preparation* - *Fasting (LR): replacement for each hr of fasting* -	**Preoperative** *Bowel preparation (if received)* 27 ml^{-1} Kg^{-1} * *Fasting (RL): replacement for each hr of fasting* 4 ml^{-1} Kg^{-1} h^{-1} first 10 Kg BW 2 ml^{-1} Kg^{-1} h^{-1} second 10 Kg BW 1 ml^{-1} Kg^{-1} h^{-1} each additional Kg BW
Intraoperative *Compensatory intravascular volume expansion (LR)* - *Maintenance* 1.5 ml^{-1} Kg^{-1} h^{-1} *Third space* - *SV optimization* 200 ml Voluven® based on the GDFT algorithm	**Intraoperative** *Compensatory intravascular volume expansion (LR)* 5 ml^{-1} Kg^{-1} *Maintenance* 4 ml^{-1} Kg^{-1} h^{-1} first 10 kg BW 2 ml^{-1} kg^{-1} h^{-1} second 10 Kg BW 1 ml^{-1} Kg^{-1} h^{-1} each additional Kg BW *Third space* 4 ml^{-1} Kg^{-1} hr^{-1} *Hemodynamic optimization* LR or Voluven based on standard hemodynamic variables
PACU 1.5 ml^{-1} Kg^{-1} h^{-1}	**PACU** 1.5 ml^{-1} Kg^{-1} h^{-1}
Surgical Unit Standardized orders as per colorectal ERAS program: LR 15 ml^{-1} h^{-1} until morning day 1 LR discontinued on day 1	**Surgical Unit** Standardized orders as per colorectal ERAS program: 15 ml^{-1} h^{-1} until morning day 1 LR discontinued on day 1

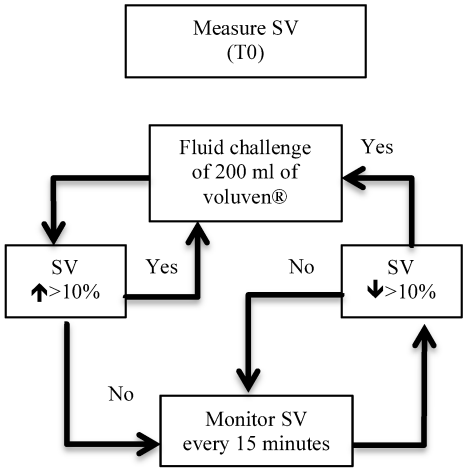
BW = body weight; ERAS = Enhanced Recovery After Surgery program; GDFT = Goal Directed Fluid Therapy; LR = Lactated Ringer's®; SV = stroke volume.

Supplement. 2 Montreal General Hospital Enhanced Recovery After Surgery program for colorectal surgery

	ERAS element
Preoperative period	Patient education: Oral and written explanations about the perioperative pathway, diet and ambulation plan, presence of drains, expectation about duration of hospital stay (3-4 days) Medical optimization of risk factors Pre-habilitation (research only) Carbohydrate loading beverages 100 g the night before and 50 g the morning of surgery Adherence to preoperative fasting guidelines[*211] Selective use of oral Mechanical Bowel Preparation (4 L of GoLytely®): If diverting ileostomy or intraoperative colonoscopy was planned. 2 Fleet enemas® the morning of surgery In patients undergoing sigmoid resection and proctocolectomy without ileal pouch-anal anastomosis Preoperative short-acting sedative in selected patients (younger than 65 years old)
Intraoperative period	Antibiotic and DVT prophylaxis as per guidelines[212**] DVT pharmacological prophylaxis as per guidelines and Peristaltic pneumatic compression of the legs[***] Maintain normothermia (core T > 36º C) Thoracic epidural analgesia, mainly for open or laparoscopic rectal procedures T_8-T_9 Ileocecal and right hemicolectomy T_9-T_{12} transverse, left and sigmoid resections; rectal resection No routine nasogastric or abdominal drainage Routine prophylactic antiemetic
Postoperative period	Intravenous fluids discontinued the morning of day 1 Oral Fluids (including 2 cans of Ensure®) on day 0, diet as tolerated on day 1 Patients encouraged to sit in a chair on day 0; Mobilization goal of at least 6 h on day 1 Milk of magnesia (30 ml every 12 h) in patients without an ileostomy, started on day 1 Thoracic epidural analgesia or patient controlled analgesia for 48 h Multimodal analgesia

*Solid food was allowed up to 6 h before surgery, and clear fluids up to 2 h before surgery. A liquid diet during the 24 h preceding surgery was prescribed if patients received Mechanical Bowel Preparation. **Cefazolin (2 g) and metronidazole (500 mg) were administered as per antibiotic guidelines, and repeated when indicated. ***Until discharge to the surgical). DVT = Deep Venous Thrombosis.

Supplement 3, Figure A. Goal Directed Fluid Therapy algorithm[64]



Stroke volume (SV). A maximum administration of 33 ml^{-1} Kg^{-1} of hydroxyethyl starch (VoluvenTM®; Fresenius Kabi Ltd, Cheshire, UK) was allowed. Further fluids challenges were performed with 500 ml of Lactated Ringer's

Supplement 4. Definitions of postoperative complications after colorectal surgery

MEDICAL

Cardiovascular

- *Heart failure:* clinical or radiological signs of congestive heart failure and specific treatment initiated.[213]
- *Acute myocardial infarction:* increase in cardiac biomarker values or characteristic ECG changes or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[214]

- *Cardiac arrhythmia:* ECG diagnosis of new arrhythmia requiring at least a pharmacologic intervention.[215]
- *Cardiac arrest:* cardiopulmonary resuscitation performed.
- *Deep vein thrombosis:* radiological confirmation of deep vein thrombosis or anticoagulation started due to clinical findings.
- *Pulmonary embolism:* radiological evidence of pulmonary embolism.
- *Cerebrovascular accident:* new focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h.[216]

Respiratory

- *Pneumonia:* Hospital acquired pneumonia, defined as presence of lung infiltrate at chest x-ray accompanied with signs of infection and initiation of antibiotic treatment. [217]
- *Lobar atelectasis:* radiological finding of at least one lobar collapse.[215]
- *Pleural fluid:* pleural effusion requiring drainage of the pleural cavity.
- *Respiratory failure:* delayed extubation > 24 hours after primary surgery, or reintubation at any time for ventilatory support.[215]
- *Pulmonary edema:* clinical signs and radiological confirmation.[218]

Infection

- *UTI:* upper or lower urinary symptoms and urine culture with no more than two species of organisms, at least one of which is a bacteria of $\geq 10^5$ CFU^{-1} ml^{-1}.[219]
- *Wound infection:* Purulent drainage, with or without positive culture, from the superficial incision or any sign or symptom of infection (e.g. pain or tenderness, localized swelling, redness) and superficial incision is deliberately opened by the surgeon or attending physician. Not included if part of intra-peritoneal abscess.[220]
- *Intra- or retroperitoneal abscess:* Radiologic finding of deep collection of pus associated with systemic signs of infection or finding during reoperation.
- *Sepsis*: at least two SIRS criteria positive and a documented or suspected infection. SIRS criteria are the following: Temperature < 36 or >38 °C; heart rate >90 beats per minute,

respiratory frequency >20 breath per minute, leukocytosis (WBC>12) or leukopenia (WBC<4) AND documented or suspected infection.[221]

- *Other infectious complications:* any other documented infectious complication (e.g. Clostridium difficile colitis).

Other medical

- *Acute Kidney Injury:* increase in serum creatinine ×2 from baseline or reduction of glomerular filtration rate greater than 50%.[222]
- *Urinary retention:* Reinsertion of indwelling urinary catheter after removal attempt or patient discharged with urinary drainage (excluding patients with permanent indwelling urinary catheter).
- *Anemia:* low serum hemoglobin requiring transfusion of PRBC, unrelated to any identified source of bleeding.
- *Hepatic dysfunction:* Increased serum bilirubin concentration > 34 $\mu mol^{-1}\ l^{-1}$ (2 $mg^{-1}\ dl^{-1}$) compared to preoperative value AND elevated liver enzymes AND has NOT undergone a pancreaticobiliary procedure.[215]
- *Acute Pancreatitis:* diagnosis requires 2 of the following: upper abdominal pain of acute onset often radiating through to the back; increase in serum amylase or lypase (x3 normal value); cross-sectional abdominal imaging consistent with acute pancreatitis.[223]
- *Other gastrointestinal complications:* any other complication of the gastrointestinal tract requiring treatment (e.g. blood per rectum, diarrhea, high stoma output).
- *Neurological complications:* any neurological complication excluding cerebrovascular events or anesthesia-related injuries (e.g. epileptic seizure).
- *Psychiatric complications:* new psychiatric symptoms including delirium and depression, requiring pharmacological treatment.

SURGICAL

- *Anastomotic leak: d*ocumentation at reoperation OR documentation by imaging technique (e.g. radiologically, endoscopically) of leakage from the surgical connection between the two bowel ends into the abdomen or pelvis with either spillage and/or fluid collection around the

anastomotic site or extravasation through a wound, drain site, or anus.[224] In the case of rectal surgery, a pelvic abscess close to the anastomosis is also considered as anastomotic leakage.[225]

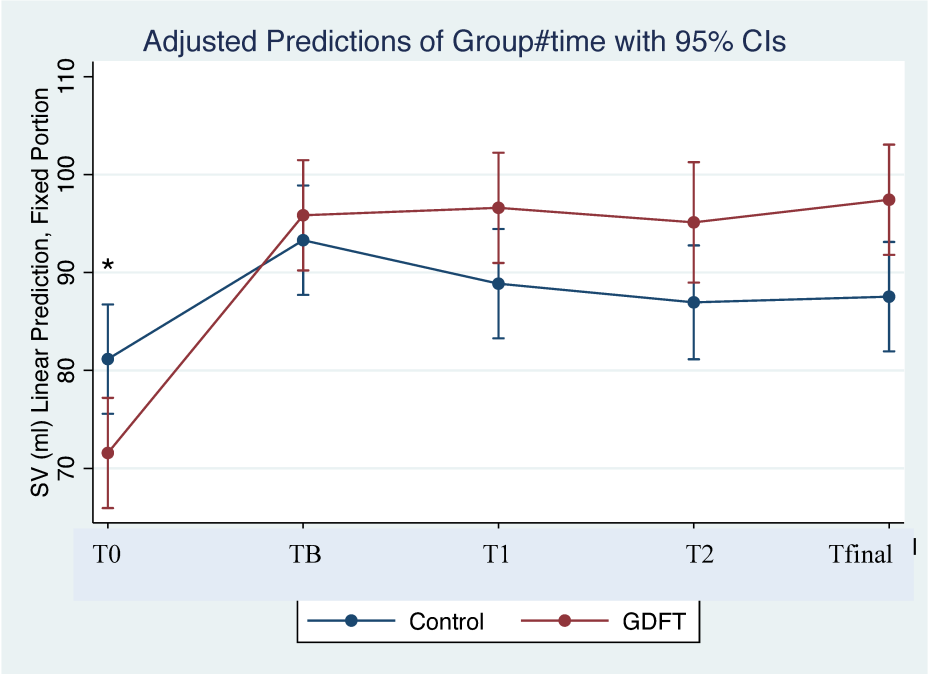
- *Bowel perforation:* documentation at reoperation OR radiologically of perforation of small or large bowel.[218]
- *Mechanical bowel obstruction:* documentation at reoperation OR radiologically of mechanical small or large bowel obstruction.
- *Wound dehiscence:* separation of the abdominal wall muscle fascia large enough to necessitate operative closure of the wound OR incisional hernia diagnosed after primary discharge.[218]
- *Bleeding:* any postoperative bleeding (e.g. intra-abdominal, gastrointestinal) requiring transfusion of at least 2 PRBC after surgery.[226]
- *Other surgical complications:* any other surgical complication necessitating treatment or delaying discharge (e.g. abdominal wall hematoma).

Supplement 5. Patients' comorbidities

	GDFT (n = 64)	Control (n = 64)	p-value
Co-morbidities, *n (%)*			
Arterial hypertension	22 (34.4)	15 (23.4)	0.172
Coronary heart disease	5 (7.8)	1 (1.6)	0.094
Congestive heart failure	0 (0.0)	0 (0.0)	-
Cerebrovascular disease	1 (1.6)	0 (0.0)	0.315
Peripheral vascular disease	2 (3.1)	1 (1.6)	0.559
Diabetes type II	6 (9.4)	10 (15.6)	0.285
Arrhythmia	0 (0.0)	0 (0.0)	-
Chronic obstructive pulmonary diseases	0 (0.0)	3 (4.7)	0.080
Asthma	3 (4.7)	4 (6.3)	0.697
Thyroid disorders	1 (1.6)	1 (1.6)	1.000
Dyslipidemia	4 (6.3)	6 (9.4)	0.510
Anemia	33 (51.6)	25 (39.1)	0.155
Chronic Kidney Diseases	1 (1.6)	0 (0.0)	0.315
Gastric esophageal reflux disease	0 (0.0)	1 (1.6)	0.315
Other cancer	3 (4.7)	1 (1.6)	0.310
Osteoporosis/Arthritis	4 (6.3)	0 (0.0)	**0.042**
Depression	1 (1.6)	1 (1.6)	1.000
Obstructive sleep apnea	0 (0)	1 (1.6)	0.315
Human Immunodeficiency Virus	0 (0)	1 (1.6)	0.315
Liver disease	1 (1.6)	1 (1.6)	0.315

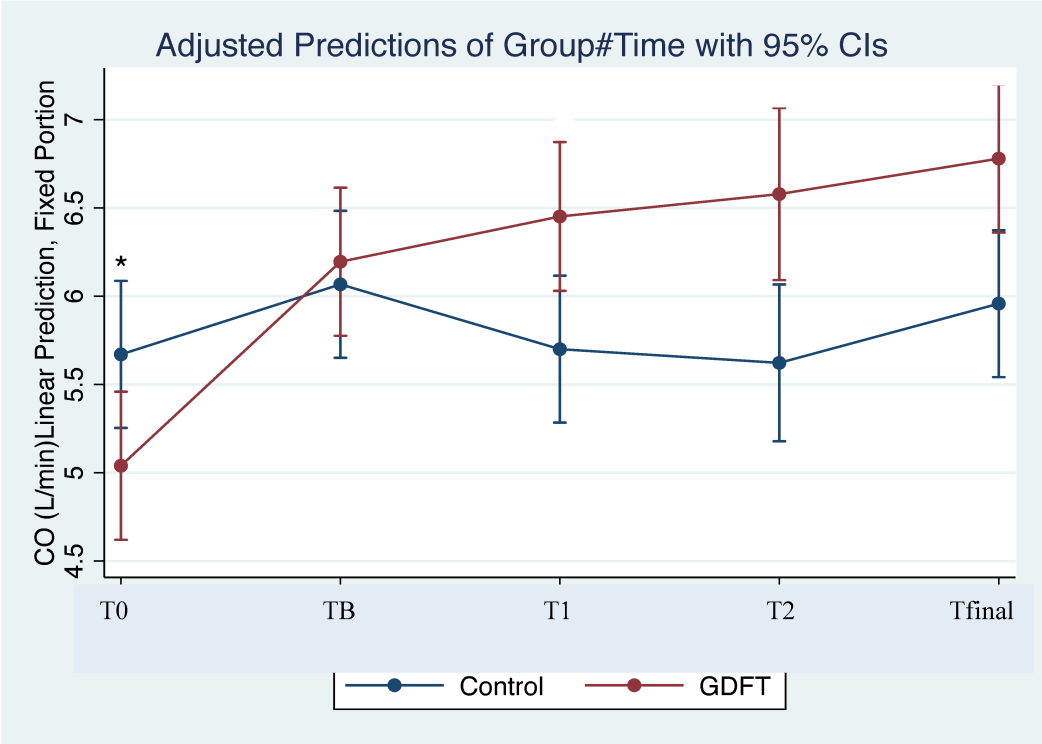
Supplement 6. Intraoperative hemodynamics

Figure B, Stroke Volume (SV)



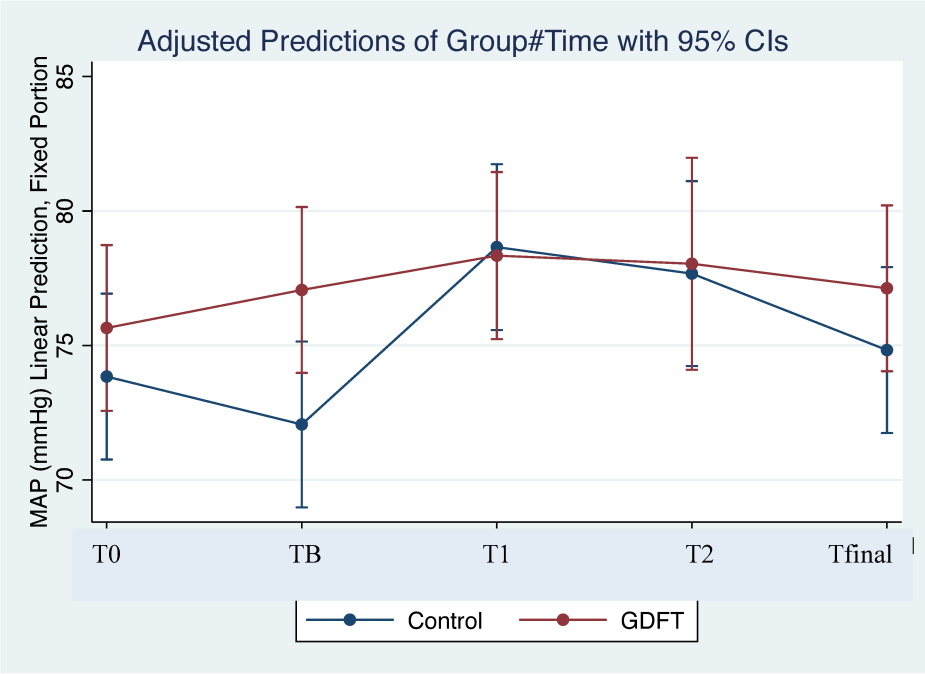
T_0 = 5 minutes after induction of anesthesia; T_B = in steep Trendelemburg (GDFT group = the final measurement in Trendelenburg position that did not result in an increase in SV by more than 10%; Control group = cardiovascular response after positioning the patient in steep Trendelenburg); T_1 = 1 h after beginning of surgery; T_2 = 2 h after the beginning of surgery); Tfinal = end of the surgery; *p <0.05.

Figure C, Cardiac Output (CO)



T_0 = 5 minutes after induction of anesthesia; T_B = in steep Trendelemburg (GDFT group = the final measurement in Trendelenburg position that did not result in an increase in SV by more than 10%; Control group = cardiovascular response after positioning the patient in steep Trendelenburg); T_1 = 1 h after beginning of surgery; T_2 = 2 h after beginning of surgery; T_{final} = end of surgery; *p <0.05.

Figure D, Mean Arterial Pressure (MAP)



T_0 = 5 minutes after induction of anesthesia; T_B = in steep Trendelemburg (GDFT group = the final measurement in Trendelenburg position that did not result in an increase in SV by more than 10%; Control group = cardiovascular response after positioning the patient in steep Trendelenburg); T_1 = 1 h after beginning of surgery; T_2 = 2 h after beginning of surgery; T_{final} = end of surgery.

Supplement 7. **30-day medical complications**

	GDFT (n = 64)	Control (n = 64)	RR (95% CI)	p-value
Patients with at least one 30-day cardiovascular complication, *n (%)*				
Heart failure	1 (1.6)	0 (0)	na	*1000*
Myocardial infarction	0 (0)	0 (0)	-	-
Cardiac Arrhythmia	1 (1.6)	0 (0)	na	*1.000*
Cardiac arrest	1 (1.6)	0 (0)	na	*1.000*
Deep venous thrombosis	1 (1.6)	2 (3.1)	0.50 (0.05 to 5.38)	0.559
Pulmonary embolism	0 (0)	0 (0)	na	-
Cerebrovascular accident	0 (0)	0 (0)	na	-
Patients with at least one 30-day respiratory complication, *n (%)*				
Pneumonia	1 (1.6)	0 (0)	na	*1.000*
Lobar atelectasis	1 (1.6)	0 (0)	na	*1.000*
Pleural effusion	2 (3.1)	0 (0)	na	*0.496*
Respiratory failure	1 (1.6)	0 (0)	na	*1.000*
Pulmonary edema	1 (1.6)	0 (0)	na	*1.000*
Patients with at least one 30-day infectious complication, *n (%)*				
UTI	2 (3.1)	3 (4.7)	0.67 (0.11 to 3.86)	*1.000*
Wound infection	1 (1.6)	3 (4.7)	0.33 (0.04 to 3.12)	*0.619*
Intra-or-retroperitoneal abscess	8 (12.5)	2 (3.1)	4.00 (0.89 to 18.11)	**0.048**
Sepsis	4 (6.3)	0 (0)	na	*0.119*
Other infectious complications	1 (1.6)	1 (1.6)	1.0 (0.06 to 15.64)	*1.000*
Patients with at least one 30-day other medical complication, *n (%)*				
AKI	3 (4.7)	0 (0)	na	*0.244*
Urinary Retention	2 (3.1)	4 (6.3)	0.50 (0.09 to 2.63)	*0.680*
Anemia	3 (4.7)	5 (7.8)	0.60 (0.15 to 2.40)	*0.718*
Hepatic dysfunction	0 (0)	0 (0)	-	-
Pancreatitis	0 (0)	0 (0)	-	-
Other GI complications	1 (1.6)	2 (3.1)	0.50 (0.05 to 5.38)	*1.000*
Psychiatric complications	1 (1.6)	0	na	*1.000*

One patient with PPOI in the GDFT group had a cardiac arrest on day 2 after a massive pulmonary aspiration of gastrointestinal content. He required intensive care unit admission and prolonged postoperative care and hospitalization; AKI = Acute Kidney injury; CI = Confidence Interval; GI = Gastrointestinal; RR = Relative risk; UTI: Urinary Tract Infections. Data are presented as numbers (percentage) or relative risk (95% confidence interval); p-value *in Italic*: Fisher's exact test.

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