Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery

A Randomized Controlled Trial

Juan C. Gómez-Izquierdo, M.D., Alessandro Trainito, M.D., David Mirzakandov, R.R.T., B.Sc., Barry L. Stein, M.D., Sender Liberman, M.D., Patrick Charlebois, M.D., Nicolò Pecorelli, M.D., Liane S. Feldman, M.D., Franco Carli, M.D., Gabriele Baldini, M.D., M.Sc.

ABSTRACT

Background: Inadequate perioperative fluid therapy impairs gastrointestinal function. Studies primarily evaluating the impact of goal-directed fluid therapy on primary postoperative ileus are missing. The objective of this study was to determine whether goal-directed fluid therapy reduces the incidence of primary postoperative ileus after laparoscopic colorectal surgery within an Enhanced Recovery After Surgery program.

Methods: Randomized patient and assessor-blind controlled trial conducted in adult patients undergoing laparoscopic colorectal surgery within an Enhanced Recovery After Surgery program. Patients were assigned randomly to receive intraoperative goal-directed fluid therapy (goal-directed fluid therapy group) or fluid therapy based on traditional principles (control group). Primary postoperative ileus was the primary outcome.

Results: One hundred twenty-eight patients were included and analyzed (goal-directed fluid therapy group: n = 64; control group: n = 64). The incidence of primary postoperative ileus was 22% in the goal-directed fluid therapy and 22% in the control group (relative risk, 1; 95% CI, 0.5 to 1.9; P = 1.00). Intraoperatively, patients in the goal-directed fluid therapy group received less intravenous fluids (mainly less crystalloids) but a greater volume of colloids. The increase of stroke volume and cardiac output was more pronounced and sustained in the goal-directed fluid therapy group. Length of hospital stay, 30-day postoperative morbidity, and mortality were not different.

Conclusions: Intraoperative goal-directed fluid therapy compared with fluid therapy based on traditional principles does not reduce primary postoperative ileus in patients undergoing laparoscopic colorectal surgery in the context of an Enhanced Recovery After Surgery program. Its previously demonstrated benefits might have been offset by advancements in perioperative care. **(Anesthesiology 2017; 127:36-49)**

POSTOPERATIVE gastrointestinal dysfunction that occurs in absence of surgical complications, frequently defined as primary postoperative ileus, is one of the major determinants of in-hospital recovery after colorectal surgery.[1,2] Despite advancements in surgical and perioperative care, primary postoperative ileus remains an unpleasant complication that not only delays early enteral feeding and increases caregivers' workload but also increases morbidity,[3] prolongs hospitalization,[4] and increases medical costs.[5,6]

Experimental and clinical trials have shown that both fluid excess[7–15] and hypovolemia[16] can significantly affect the recovery of bowel function and impair anastomotic healing.[11,17,18] Early studies have shown that individualization of fluid therapy based on more objective measures of

What We Already Know about This Topic

- Individualization of intraoperative fluid administration (goal-directed fluid therapy) has been shown to be of benefit in many studies
- The majority of these studies were uncontrolled, and confounding factors might have affected the results

What This Article Tells Us That Is New

- This randomized blinded trial assessed effects of goal-directed fluid therapy on primary postoperative ileus after laparoscopic colorectal surgery, within a well-established Enhanced Recovery After Surgery program
- The incidence of primary postoperative ileus was identical (22%) in the goal-directed fluid therapy control groups
- Previous benefits of goal-directed fluid therapy may have been offset by subsequent improvements in perioperative and surgical care

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast.

Submitted for publication July 23, 2016. Accepted for publication April 3, 2017. From the Department of Anesthesia (J.C.G.-I., A.T., D.M., F.C., G.B.), Department of Surgery (B.L.S., A.S.L., P.C., N.P., L.S.F.), and Steinberg–Bernstein Centre for Minimally Invasive Surgery and Innovation, Department of Surgery (N.P., L.S.F.), McGill University Health Centre, Montreal, Quebec, Canada.

 Anesthesiology 2017; 127:36-49

<zdoi;10.1097/ALN.0000000000001663>

hypovolemia (goal-directed fluid therapy) accelerates the recovery of bowel function[19,20] and reduces hospitalization[21,22] and overall complications,[22] especially in high-risk patients.[23,24] 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[25–29] has not confirmed these results in patients treated with Enhanced Recovery After Surgery programs, especially when the laparoscopic approach is used. In these patients, the implementation of several integrated evidence-based perioperative interventions, each shown to improve clinical outcomes after colorectal surgery, may provide similar benefits as those observed with goal-directed fluid therapy.[25–29] It also must be considered that the number and type of interventions included in the Enhanced Recovery After Surgery programs vary between different centers, making it difficult to determine and generalize the impact of a single intervention on postoperative outcomes.

In light of this controversial evidence, the impact of goal-directed fluid therapy on specific postoperative complications and in a context of an Enhanced Recovery After Surgery program remains unknown. Specifically, there is a lack of high-quality studies primarily investigating the effect of goal-directed fluid therapy on the recovery of bowel function[28] in a controlled clinical setting in which perioperative interventions influencing bowel function are standardized.

The aim of this study was to determine the impact of goal-directed fluid therapy on the incidence of primary postoperative ileus in patients undergoing laparoscopic colorectal surgery and treated with a well-established, center-specific Enhanced Recovery After Surgery program. It was hypothesized that patients treated with goal-directed fluid therapy would experience less primary postoperative ileus than patients receiving fluid therapy based on traditional principles.

Materials and Methods

Trial 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 No. 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 the research investigators (A.T., D.M., J.C.G.-I.) at the preoperative clinic, and written consent was obtained from eligible patients. Patients were excluded if they were younger than 18 yr 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 assigned randomly by a stratified computer-based block randomization to receive goal-directed fluid therapy based on near-maximal stroke volume optimization (goal-directed fluid therapy group)[30] or fluid therapy based on traditional principles[31] (control group). These include the replacement of preoperative fasting deficit (4/2/1 rule), volume expansion after the induction of anesthesia, and the replacement of insensible blood loss and third-space loss (Supplemental Digital Content 1, http://links.lww.com/ALN/B446, which includes a table that describes the fluid management in the two groups). 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 (A.T. and D.M.).

Perioperative Care

Patients were treated according to a well-established Enhanced Recovery After Surgery program specific for patients undergoing elective colorectal surgery initially implemented at our institution in 2008[32] and subsequently modified (Supplemental Digital Content 2, http://links.lww.com/ALN/B447, which includes a table that describes the Montreal General Hospital Enhanced Recovery After Surgery program for colorectal surgery).

Anesthesia and Analgesia Management. On the day of surgery, patients were transferred to the preoperative anesthesia area, where preoperative weight was measured and an intravenous catheter was inserted. After the recording of baseline hemodynamic variables, lactated Ringer's 27 ml/kg[33] was infused before induction of anesthesia in patients of the control group who received mechanical bowel preparation (4 l polyethylene glycol electrolyte lavage; GoLytely®, Braintree Laboratories, USA). A thoracic epidural catheter was inserted between T8 and T12 and a test dose of 3 ml lidocaine 2% with epinephrine (5 μg/ml) 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/kg) and remifentanil (1 μg/kg) and maintained with desflurane or sevoflurane in a mixture of 40% oxygen and 60% air. Intraoperatively, analgesia was provided with remifentanil infusion (0.05 to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) 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 count less than 2). Lungs were ventilated with a tidal volume of 8 ml/kg and with a positive end-expiratory pressure of 5 cm H_2O. End-tidal carbon dioxide was maintained between 35 and 40 mmHg by adjusting the respiratory rate. Postoperative nausea and vomiting prophylaxis was achieved with dexamethasone (8 mg) and droperidol (0.625 mg). At the end of surgery, remifentanil was discontinued, 10 ml lidocaine 2% was bolused in the epidural catheter, and ketorolac (30 mg) was administered if not contraindicated. Then, an epidural mixture of bupivacaine (0.1 mg/ml) and fentanyl (3 μg/ml) was started and infused for 48 h. Celebrex and acetaminophen also were 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. After induction of anesthesia, a disposable esophageal Doppler probe (DP12 Probe; Deltex Medical Ltd., United Kingdom) 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 esophageal Doppler monitor (CardioQ-ODM; Deltex Medical Ltd.) by the treating anesthesiologist in the goal-directed fluid therapy group and by two research investigators (A.T. and D.M.) in the control group. The machine was calibrated to provide data averaged more than 10 cycles.[34]

In the goal-directed fluid therapy group, the patient was positioned in steep Trendelenburg, and after 30 s from the change in position esophageal Doppler–derived hemodynamic variables and standard cardiovascular parameters were recorded. If stroke volume 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., United Kingdom) was administered in 5 min, and a new stroke volume measurement obtained. This process was repeated until changing in position did not result in an increase of more than 10% in stroke volume. At this point, it was assumed that stroke volume had reached the plateau of the Frank-Starling curve (near-maximal stroke volume), and the patient was considered volume optimized. The final head-down cardiovascular measurement that did not result in an increase in stroke volume by more than 10% was recorded (Trendelenburg), the patient was repositioned flat, and surgery commenced. This method was described previously to minimize the cardiovascular effects of the pneumoperitoneum and of the changes in position during surgery.[35] After having established the pneumoperitoneum and positioned the patient in Trendelenburg, near-maximal stroke volume was maintained during surgery[30] (Supplemental Digital Content 3, http://links.lww.com/ALN/B448, which includes the goal-directed fluid therapy algorithm). A background maintenance infusion of lactated Ringer's 1.5 ml · kg^{-1} · h^{-1} was administered until the end of surgery.[36]

In the control group, the esophageal Doppler monitor was turned away from the anesthesia care provider, and the screen was covered with a surgical towel soon after the induction of anesthesia. The cardiovascular response obtained 30 s after positioning the patient in steep Trendelenburg and before starting the pneumoperitoneum was measured and recorded (Trendelenburg). Anesthesiologists were blinded to the measurements obtained with the esophageal Doppler 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.[19] Vasopressors and inotropes also were administered based on the clinical judgment of the treating anesthesiologist.

Surgical Technique. Surgery was performed by three experienced fellowship-trained colorectal surgeons (S.L., P.C., and B.L.S.) as previously described[37]

Postoperative Care. At the end of surgery, patients were transferred into the postanesthesia care unit, and an intravenous infusion of lactated Ringer's 1.5 ml · kg^{-1} · h^{-1} was started. After meeting the postanesthesia care unit discharge criteria, patients were discharged to the surgical unit and lactated Ringer's infusion was reduced to 15 ml/h (to keep the vein open) until 8:00 AM the following morning, when intravenous fluids were discontinued. Additional intravenous fluids were administered by the anesthesiologist in charge in the postanesthesia care unit 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/day), and a solid diet as tolerated was started the morning after surgery. The acute pain service visited patients daily to optimize pain control. The surgical team and the acute pain service were blinded to patients' randomization. Patients were discharged if they were afebrile, they tolerated an oral diet, their pain was well controlled (Numeric Rating Score less than 4), and they ambulated independently.

Study Outcomes, Measurements, and Data Collection

The primary outcome was the incidence of primary postoperative ileus during the hospital stay. There is a lack of a standard and validated definition of primary postoperative ileus. Traditional criteria used to define primary postoperative ileus 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 Enhanced Recovery After Surgery program, as after colorectal surgery patients are fed as tolerated in the immediate postoperative period, independently of 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 Enhanced Recovery After Surgery program. It was found that primary postoperative ileus in the absence of postoperative complications was associated with a median increase of 2 days in length of hospital stay. Beginning on postoperative day 1, patients with primary postoperative ileus were identified by the presence of two or more clinical indicators of gastrointestinal dysfunction, at least one for each of the two following criteria: (1) presence of vomiting OR abdominal distension and (2) absence of flatus/stool OR not tolerating oral diet, in the absence of any precipitating complications. Secondary outcomes included Quality of Recovery score,[38] 30-day complications, readiness to be discharged, length of hospital stay, and readmission rates. Postoperative complications were defined *a priori* (Supplemental Digital Content 4, http://links.lww.com/ALN/B449, which includes the definitions of postoperative complications) and their severity graded by using the Clavien–Dindo classification[39] and the Comprehensive Complication Index.[40]

Hemodynamic variables were measured by the treating anesthesiologist in the goal-directed fluid therapy group and by the two research investigators (A.T. and D.M.) in the control group, all well trained on how to obtain and interpret esophageal Doppler–derived hemodynamic measurements. The esophageal Doppler probe was refocused if necessary, and esophageal Doppler–derived hemodynamic variables were measured 5 min after induction of anesthesia (baseline), in steep Trendelenburg (Trendelenburg), and every 15 min until the end of surgery (end of surgery), before the epidural was bolused. Postoperatively, patients were instructed to drink from a specific 250-ml cup to measure daily oral fluid intake. Patients also were weighed every morning before breakfast. Postoperative gastrointestinal function was assessed by the research investigator (J.C.G.-I.) after dinner was served to the patient. The amount of systemic opioid consumption was measured daily and converted to intravenous morphine equivalents.[41]

Preoperative and intraoperative data were collected by two study investigators (A.T. and D.M.), whereas postoperative data were collected by a third study investigator (J.C.G.-I.), 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 recorded initially on specific data-collection sheets and then transferred into two separate databases, one containing preoperative and intraoperative data and the other postoperative data. The two databases were merged only when the study was terminated.

Sample Size Calculation and Statistical Analysis

Based on 40% incidence of primary postoperative ileus observed in 114 patients who underwent elective colorectal surgery in the context of an Enhanced Recovery After Surgery program at the Montreal General Hospital, by 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% primary postoperative ileus reduction in patients treated with goal-directed fluid therapy (one-sided Student's *t* test), with a power of 0.8 and a type 1 error (α) = 0.05. The hypothesis that goal-directed fluid therapy would reduce to 20% the incidence of primary postoperative ileus was based on the observation that in 2012, the incidence of primary postoperative ileus at our institution was higher (40%) than that reported in other centers,[42] despite a well-established Enhanced Recovery After Surgery program that included several perioperative interventions shown to accelerate the bowel recovery (*e.g.,* selective use of mechanical bowel preparation, carbohydrate-rich beverage, early feeding, laparoscopic surgery, epidural, chewing gum, opioid-sparing strategies, and others). At that time, perioperative fluid management was the only element that was not standardized. We therefore hypothesized that goal-directed fluid therapy, by administering intravenous fluids based on more objective measures of hypovolemia, would significantly reduce the incidence of primary postoperative ileus.

Analysis was performed on an intention-to-treat basis and as per protocol. The primary outcome was evaluated with the chi-square test or Fisher exact test if appropriate. A preplanned subgroup analysis of the primary outcome was conducted in patients not receiving a stoma, in patients undergoing colonic surgery, and in patients undergoing rectal surgery. As the proportion of patients who received mechanical bowel preparation was significantly different between the two groups ($P = 0.021$), a nonplanned adjusted analysis was conducted to calculate the relative risk (RR) of primary postoperative ileus, by adjusting for the use of mechanical bowel preparation. Secondary outcomes were evaluated with the Student's *t* test for normally distributed data, the Wilcoxon–Mann–Whitney U test for not normally distributed, and the chi-square test or Fisher exact test when appropriate. Repeated-measures linear mixed model analysis was used to assess and compare intraoperative hemodynamic variables, postoperative pain intensity, opioid consumption, and time spent out of bed over time and between groups. The Tukey *post hoc* test was used for *post hoc* analysis.

Continuous variables are reported as mean ± SD or median (interquartile range), and categorical and ordinal variables as absolute number (percentage). RR with 95% CI also is reported for categorical variables.

Statistical analysis was performed with SPSS, version 23 (IBM Corp., USA) or STATA, version 14 (StataCorp, USA). All statistical tests were two-sided, and $P < 0.05$ was considered to indicate statistical significance.

Results

Patients' Characteristics, Operative Data, and Anesthesia Care

A total of 196 patients were assessed for eligibility, of whom 135 were randomized, 68 to the goal-directed fluid

therapy group and 67 to the control group. One patient in each group did not receive the allocated intervention (goal-directed fluid therapy group: one patient withdrew the consent before starting surgery; control-group: in one patient planned laparoscopic surgery was changed to laparotomy). Two patients in each group dropped out as surgery was aborted because of intraperitoneal carcinomatosis. The intervention was discontinued in one patient in the goal-directed fluid therapy group because the intravenous catheter through which intravenous fluids were administered was disconnected accidentally during the intervention, and this was recognized only at the end surgery. A total of 128 patients were analyzed on an intention-to-treat basis (64 in the goal-directed fluid therapy and 64 in the control group) and 115 patients were analyzed per protocol (56 in the goal-directed fluid therapy and 59 in the control group), as in eight patients in the goal-directed fluid therapy group and in five patients in the control group laparoscopic surgery was converted to laparotomy (fig. 1). Baseline patients' characteristic, operative data, and anesthesia care were similar between the two groups, except for the use of mechanical bowel preparation that was more frequent in the goal-directed fluid therapy group (P = 0.021; table 1 and Supplemental Digital Content 5, http://links.lww.com/ALN/B450, which includes a table reporting patients' comorbidities in the two groups).

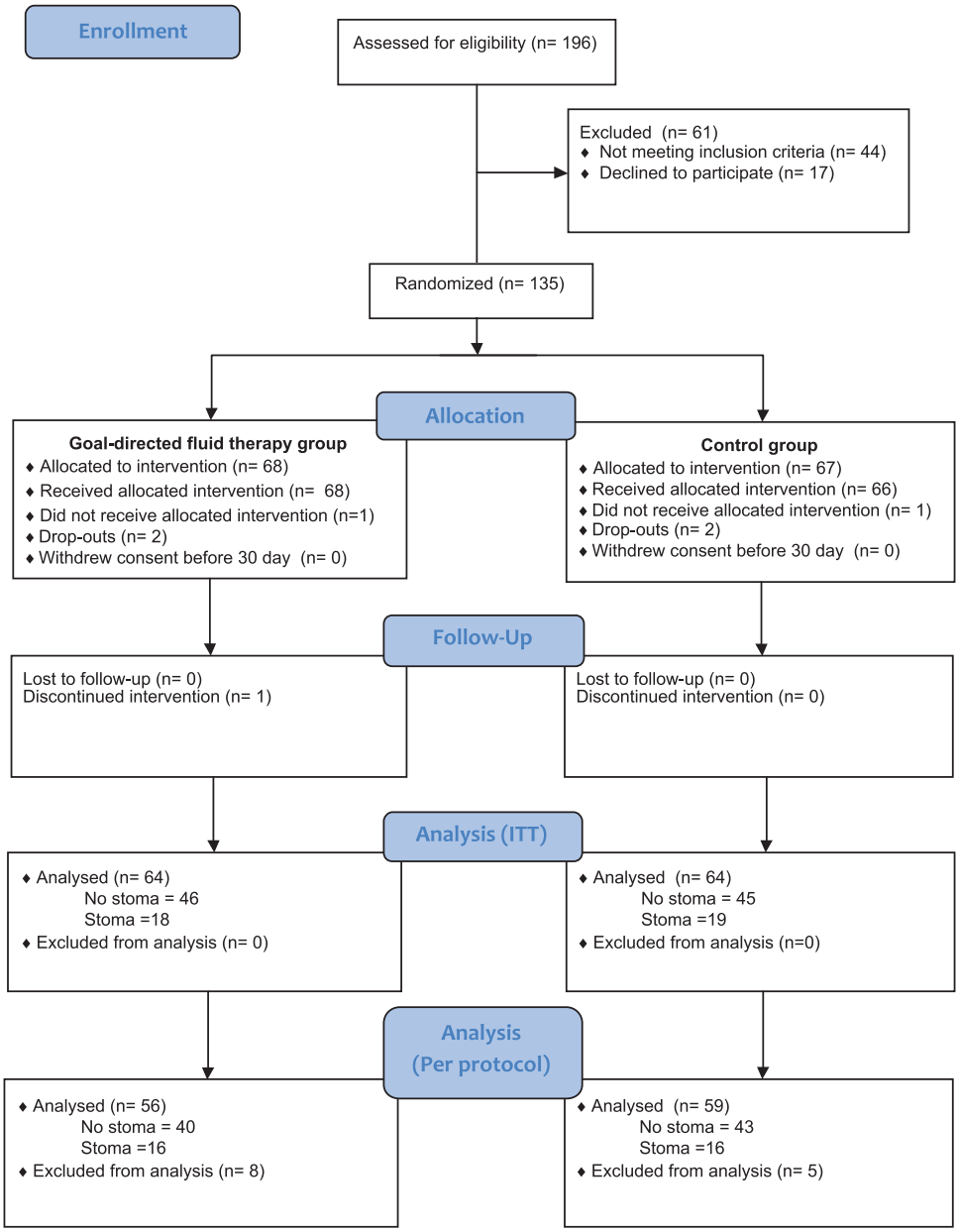

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. ITT = intention to treat.

Table 1. Baseline Patients' Characteristics, Operative Data, and Anesthesia Care

	Goal-directed Fluid Therapy (n = 64)	Control (n = 64)	*P* Value
Age, yr	63 ± 15	61 ± 15	
Sex 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 physical status (I/II/III/IV), n	6/42/14/2	8/38/18/0	
CR-POSSUM score			
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/dl	12.8	13.4	
Indication for surgery, n (%)			
Colorectal cancer	48 (75)	43 (67)	
Inflammatory bowel disease	6 (9.4)	9 (14)	
Diverticulitis	4 (6.3)	7 (10)	
Others*	6 (9.4)	5 (7.8)	
Type of surgery, n (%)			
Colonic	39 (61)	39 (60)	
Ileocecal resection	1 (1.6)	7 (10.9)	
Right hemicolectomy	20 (31)	19 (30)	
Left hemicolectomy	5 (7.8)	4 (6.3)	
Subtotal colectomy	0 (0)	3 (4.7)	
Sigmoidectomy	11 (17)	6 (9.4)	
Total colectomy	2 (3.1)	0 (0)	
Rectal	25 (39)	25 (39)	
Rectal anterior resection	10 (16)	8 (12)	
Rectal low anterior resection	8 (12)	9 (14)	
Proctocolectomy	6 (9.4)	5 (7.8)	
Abdominal perineal resection	1 (1.6)	3 (4.7)	
Stoma, n (%)	18 (28)	19 (30)	
Bowel preparation, n (%)			
4 l GoLYTELY®	36 (56)	23 (36)	
2 Fleet enemas	12 (19)	17 (27)	
Preoperative carbohydrate drinks,† n (%)			
Yes‡	47 (73)	45 (71)	
Yes, according to the quantity indicated§	23 (36)	26 (42)	
Preoperative fasting time, h			
Solid‖	36 (19–40)	34 (17–38)	
Fluid#	4 (3–6)	4 (3–6)	
Duration of surgery, min	189 (144–269)	183.5 (133–254)	0.564
Laparoscopic time, min	108 (68–146)	101 (71–143)	0.506
Conversion to open, n (%)	8 (12)	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, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.083
Intraoperative ketorolac (30 mg), n (%)	49 (77)	50 (78)	0.754

Data are presented as mean ± SD, median (interquartile range), or absolute numbers (percentage).

*Benign adenoma (six patients in the goal-directed fluid therapy group and three patients in the control group), fecal incontinence (one patient in the control group) terminal ileum stricture (one patient in the control group). †Morning dose. ‡Data from one patient in the control group is missing. §Data from two patients in the control group are missing. ‖Data from two patients in the control group and one patient in the goal-directed fluid therapy is missing. #Data from one patient in the control group is missing. **Eighteen patients received sevoflurane (nine patients in the goal-directed fluid therapy and nine patients in the control group).

ASA = American Society of Anesthesiologists; BMI = body mass index; BSA = body surface area; CR-POSSUM = Colorectal-Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; Et = end-tidal; M/F = male/female.

Intraoperative Fluid Administration, Vasopressors, and Hemodynamic Data

Patients in the goal-directed fluid therapy 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). At baseline, stroke volume and cardiac output were higher in the control group (differences of least squares means, −9.6 ml; 95% CI, −16.6 to −2.6; $P = 0.008$, and differences of least squares means, −0.6 l/min; 95% CI, −1.2 to −0.1; $P = 0.024$, respectively). Overall, stroke volume and cardiac output changes over time significantly differed between the two groups ($P < 0.001$). This difference was driven mainly by a more pronounced increase of stroke volume and cardiac output from baseline to Trendelenburg position in the goal-directed fluid therapy group (stroke volume goal-directed fluid therapy group: differences of least squares means, 24.3 ml; 95% CI, 18 to 30.5; stroke volume control group: differences of least squares means, 12.1 ml; 95% CI, 6 to 18.3; cardiac output goal-directed fluid therapy group: differences of least squares means, 1.1 l/min; 95% CI, 0.7 to 1.6; cardiac output control group: differences of least squares means, 0.4 l/min; 95% CI, −0.1 to 0.86). Only in the goal-directed fluid therapy group did stroke volume and cardiac output remain significantly higher compared with baseline throughout surgery ($P < 0.001$). Intraoperative stroke volume and cardiac output values were higher in the goal-directed fluid therapy group; however, the differences between the two groups did not reach statistical significance at any of the other time intervals (Supplemental Digital Content 6, http://links.lww.com/ALN/B451, which includes two figures reporting stroke volume and cardiac output between groups during surgery). Mean arterial pressure changes over time were similar between the two groups.

Table 2. Preoperative and Intraoperative Intravenous Fluids, Vasopressors, Blood Loss, and Transfusions

	Goal-directed Fluid Therapy (n = 64)	Control (n = 64)	*P* Value
Preoperative period			
Replacement of preoperative intravascular deficit due to MBP,* ml	—	2,094 ± 395	—
Intraoperative period			
Total volume of intravenous fluid, ml	1,535 (1,000–2,272)	2,370 (1,779–3,071)	**< 0.001**
Lactated Ringer's			
ml	500 (323–687)	2,102 (1,600–2,528)	**< 0.001**
ml · kg^{-1} · h^{-1}	2 (2–2)	8.6 (7–11)	**< 0.001**
Colloids, ml	900 (400–1,400)	0 (0–500)	**< 0.001**
Prepneumoperitoneum boluses	400 (200–400)†	—‡	—
NaCl 0.9%,§ ml	194 (150–268)	179 (146–234)	0.132
Total volume of intravenous fluids, ml			
Colonic surgery	1,375 ± 667	2,243 ± 874	**< 0.001**
Rectal surgery	2,342 ± 981	2,958 ± 978	**0.031**
EBL, ml	175 (100–400)	150.0 (100–400)	0.708
Colonic surgery	100 (100–200)	100 (100–200)	0.519
Rectal surgery	400 (125–850)	400 (200–800)	0.914
Erythrocytes			
Patients receiving erythrocytes, 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 (%)			
Phenylephrine	53 (83)	58 (91)	0.193
n (%)	39 (61)	51 (80)	**0.020**
µg	80 (0–300)	180 (80–440)	**0.016**
Ephedrine			
n (%)	40 (62)	43 (67)	0.496
mg	10 (0–25)	10 (0–20)	0.947
Phenylephrine continuous infusion, n (%)	0 (0)	0 (0)	na
Urine output, ml · kg^{-1} · h^{-1}	1.2 (0.8–1.8)	1.4 (0.8–2.6)	0.148

Data are presented as mean ± SD, median (interquartile range), or absolute numbers (percentage). *P* values in bold represent statistically significant results ($P < 0.05$).

*Preoperative intravenous fluids (4 l GoLYTELY®) were administered only in patients of the control group who received mechanical bowel preparation (35.9%). In two 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 goal-directed fluid therapy group, 55 patients (86%) needed stroke volume optimization before pneumoperitoneum. ‡In the control group, 40 patients (62.5%) increased stroke volume at baseline by more than 10% when positioned in steep Trendelenburg before pneumoperitoneum. §Amount of normal saline solution used to dilute antibiotics, potassium chloride when needed, and remifentanil. ‖No statistics were computed because there were not enough valid cases to perform the Mann–Whitney U test.

EBL = estimated blood loss; MBP = mechanical bowel preparation; na = not applicable; NaCl 0.9% = normal saline.

Postoperative Data

In the postanesthesia care unit, the two groups were comparable with regard to the amount of intravenous fluids, systemic opioids, and vasopressors received. Postoperative nausea and vomiting, the number of hypotension episodes, urine output, and length of stay in the postanesthesia care unit also were 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 at rest and while ambulating, systemic opioid consumption, and time spent out of bed were similar between the two groups. Postoperative pain scores were significantly lower in the goal-directed fluid therapy group on day 0 (P = 0.018), but this difference was not clinically significant (table 4).

Outcomes

Primary Outcome and Gastrointestinal Function. Overall, the incidence of primary postoperative ileus was similar between the two groups, on intention-to-treat analysis (22% in the goal-directed fluid therapy group and 22% in the control group, RR, 1; 95% CI, 0.5 to 1.9; P = 1.000) and per protocol (P = 1.000). By adjusting for the use of mechanical bowel preparation, the risk of developing primary postoperative ileus did not change ($RR_{adjusted}$, 1; 95% CI, 0.5 to 1.9; P = 0.094). Recovery measures of gastrointestinal function and gastrointestinal symptoms also were 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 goal-directed fluid therapy developed intra- or retroperitoneal abscesses (P = 0.048; table 6 and Supplemental Digital Content 7, http://links.lww.com/ALN/B452, which includes a table that describes medical morbidity in the two groups).

Discussion

The results of this study indicate that intraoperative goal-directed fluid therapy aiming to achieve near-maximal stroke volume optimization compared with fluid therapy based on traditional principles does not reduce the incidence of primary postoperative ileus in patients undergoing laparoscopic colorectal surgery in the context of a well-established Enhanced Recovery After Surgery 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.[7–11] Experimental and clinical studies have demonstrated that intestinal edema as a result of excessive fluid administration inhibits gastrointestinal transit and impairs anastomotic healing.[7–10,13,14,17,18,43] In contrast, fluid restriction has been shown to accelerate the recovery of bowel function and to facilitate the early intake of oral diet.[11,13,14] However, due to the heterogeneity of the study designs, the

Table 3. Postoperative Fluid Balance, Weight Balance, and Postoperative Hypotension

	Goal-directed Fluid Therapy (n = 64)	Control (n = 64)	*P* Value
Patients receiving intravenous infusion after day 0, n (%)	31 (48)	28 (44)	0.723
Input, ml			
Total intravenous crystalloids,* ml	319 (247–2,967)	607 (291–3,234)	0.269
Total oral fluid intake,† ml	7,681 (5,625–10,350)	6,525 (3,968–10,050)	0.571
Output			
Urine output, day 0‡	700 (450–1,440)	1,450 (700–2,000)	**0.004**
Total gastrointestinal losses,§ ml	75 (0–1,475)	50 (0–1,912)	0.984
Weight balance,‖ kg			
Day 1 – day 0	1.1 ± 1.9	2.1 ± 1.7	**0.002**
Day 2 – day 1	0.6 ± 1.6	0 ± 1.7	0.054
Day 3 – day 2	–0.8 ± 1.4	–0.5 ± 1.4	0.321
Hypotension,# n (%)	15 (23)	16 (25)	1.000
Orthostatic hypotension,** n (%)	2 (3.2)	8 (12)	0.096

Data are presented as mean ± SD, median (interquartile range), or as absolute numbers (percentage). *P* values in bold represent statistically significant results (P < 0.05).

*Total amount of intravenous crystalloids received from surgical unit admission until hospital discharge. †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 Enhanced Recovery After Surgery protocol). Urine output on day 0 could not be measured in seven patients of the goal-directed fluid therapy group and in 10 patients of the control group as Foley catheters were removed in postanesthesia care unit because of patients' discomfort. §Total gastrointestinal losses measured from surgical unit admission until hospital discharge. ‖Postoperative weight could not be measured 11 times in the goal-directed fluid therapy group and six times in the control group because of patients' refusal or because patients were discharged early on day 2 or day 3 (day 1: two patients in goal-directed fluid therapy group and 1 patient in control group; day 2: one patient in the goal-directed fluid therapy group and one patient in the control group; day 3: eight patients in goal-directed fluid therapy group and four patients in the control group). #Systolic blood pressure less than 90 mmHg or less than 20% of the baseline value. **A decrease of at least 20 mmHg in systolic blood pressure on assuming an upright posture from a supine position.

Table 4. Postoperative Pain Intensity and Management and Time Spent Out of Bed

	Goal-directed Fluid Therapy (n = 64)	Control (n = 64)	*P* Value
Pain, static			0.189
NRS day 0	1 ± 2	2 ± 2	
NRS day 1	2 ± 2	2 ± 2	
NRS day 2	2 ± 2	2 ± 2	
NRS day 3	2 ± 2	2 ± 2	
Pain, coughing			**0.018**
NRS day 0	2 ± 2	3 ± 3	**0.018**
NRS day 1	4 ± 2	4 ± 2	0.491
NRS day 2	4 ± 3	4 ± 2	0.435
NRS day 3	3 ± 3	3 ± 2	0.575
Pain, ambulating			0.189
NRS day 0	1 ± 2	2 ± 2	
NRS day 1	2 ± 2	2 ± 2	
NRS day 2	2 ± 2	2 ± 2	
NRS day 3	2 ± 2	2 ± 2	
Days with thoracic epidural analgesia, days	3 (2–3)	3 (2–3)	0.840
Systemic opioids,* mg			1.000
Total, in the first 3 days	10 (3–21)	12.4 (7–25)	*0.344*
Day 0	0 ± 0	0 ± 0	
Day 1	3 ± 7	1 ± 3	
Day 2	6 ± 7	9 ± 8	
Day 3	7 ± 9	7 ± 9	
Celebrex† with thoracic epidural analgesia, n (%)	9 (14)	10 (16)	1.000
Celebrex† after thoracic epidural analgesia, n (%)	48 (75)	51 (80)	0.673
No. patients receiving milk of magnesia, n (%)	52 (81)	45 (72)	0.297
Time spent out of bed, min			0.935
Day 0	26 ± 68	23 ± 54	
Day 1	167 ± 189	232 ± 220	
Day 2	185 ± 177	255 ± 387	
Day 3	163 ± 151	198 ± 136	

Data are presented as mean ± SD or as absolute numbers (percentage). Linear mixed model analysis: *P* values refer to the group main effect, and to the pairwise comparison; *P* values in italic: Wilcoxon–Mann–Whitney U test. *P* values in bold represent statistically significant results ($P < 0.05$).

Postoperative pain (NRS 0 to 10) could not be assessed 15 times because patients' refusal or because patients were discharged early on day 2 or day 3 (day 0: one patient in the control group; day 1: one patient in the control group; day 2: one patient in the goal-directed fluid therapy group; day 3: eight patients in the goal-directed fluid therapy group and four patients in the control group). Systemic opioids consumption could not be measured 14 times because missing data or patients were already discharged (day 1: one patient in the goal-directed fluid therapy group; day 2: one patient in the goal-directed fluid therapy group; day 3: eight patients in the goal-directed fluid therapy group and four patients in the control group). Time spent out of bed could not be assessed 12 times because patients were already discharged (eight patients in the goal-directed fluid therapy group and four patients in the control group).

*Intravenous morphine equivalents. †Celebrex 200 mg *per os* every 12 h.

NRS = Numeric Rating Scale.

lack of a universal definition characterizing a restrictive fluid management, and the absence of a standardized perioperative care,[44] it remains difficult to establish the real impact of fluid restriction on postoperative morbidity.[45–47]

Individualization of fluid therapy based on more objective measures of hypovolemia, commonly called goal-directed fluid therapy, has shown not only to accelerate the recovery of gastrointestinal function[19,22] but also reduce postoperative complications[22] and hospitalization,[21,22] especially in high-risk patients,[23,24] and mainly when compared with liberal fluid administration.[21] Because of these benefits, it has been recommended in patients undergoing major abdominal surgery.[36,48–50]

The results of the present study do not support the use of goal-directed fluid therapy to reduce the incidence of primary postoperative ileus 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 stroke volume and cardiac output in the goal-directed fluid therapy group during surgery.

Several reasons can explain these findings. First, patients were treated with several perioperative Enhanced Recovery After Surgery interventions that have been 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, which might have contributed to minimizing the occurrence of primary postoperative ileus in both groups.[2] This also has been demonstrated by two recent meta-analyses that have shown that when patients are treated with a more rational fluid management, and in the context of an Enhanced Recovery After Surgery program, the

Table 5. Incidence of PPOI and Recovery Gastrointestinal Function

	Goal-directed Fluid Therapy (n = 64)	Control (n = 64)	RR (95% CI)	*P* Values	$RR_{adjusted}$ (95% CI)	*P* Values
Primary postoperative ileus,* n (%)						
ITT analysis	14 (22)	14 (22)	1 (0.5–1.9)	1.000	1 (0.5–1.9)	0.094
Per protocol	12 (21)	12 (20)	1 (0.5–2.1)	*1.000*	1.1 (0.5–2.1)	0.225
No stoma, n (%)						
ITT analysis	9 (17)	7 (16)	1.2 (0.5–3.1)	0.615	1.3 (0.5–3.1)	0.316
Per protocol	7 (17)	7 (16)	1.1 (0.4–2.8)	0.882	1.1 (0.4–2.7)	0.272
Stoma, n (%)						
ITT analysis	5 (28)	(37)	0.7 (0.3–1.9)	0.556	0.8 (0.3–2)	0.226
Per protocol	5 (31)	5 (31)	1 (0.3–2.8)	1.000	1.1 (0.4–2.9)	0.477
Colonic surgery n (%)						
ITT analysis	9 (23)	6 (15)	1.5 (0.6–3.8)	0.389	1.4 (0.6–3.5)	0.370
Per protocol	7 (21)	6 (16)	1.3 (0.5–3.5)	0.597	1.2 (0.5–3.3)	0.385
Rectal surgery n (%)						
ITT analysis	5 (20)	8 (32)	0.6 (0.2–1.6)	0.333	0.7 (0.3–1.7)	0.147
Per protocol	5 (23)	6 (29)	0.8 (0.3–2.2)	0.661	0.9 (0.3–2.3)	0.298
Primary postoperative ileus						
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)	3 (2–3)	na	0.318	na	—
Per protocol	2 (1–4)	3 (2–4)	na	0.389	na	—
Time to first flatus, h						
ITT analysis	20 (12–26)	20 (12–24)	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 (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)	37 (58)	1.1 (0.8–1.5)	0.469	1.2 (0.9–1.6)	0.697
Per protocol	37 (66)	33 (56)	1.2 (0.9–1.6)	0.265	1.3 (0.9–1.7)	0.660
Vomiting,† n (%)						
ITT analysis	25 (39)	25 (39)	1 (0.6–1.5)	1.000	1.1 (0.7–1.6)	0.492
Per protocol	23 (41)	21 (36)	1.1 (0.7–1.8)	0.547	1.3 (0.8–2.1)	0.601
Abdominal distension, n (%)						
ITT analysis	49 (77)	55 (86)	0.9 (0.7–1)	*0.257*	0.9 (0.8–1.1)	0.938
Per protocol	43 (77)	51 (86)	0.9 (0.7–1.1)	*0.230*	0.9 (0.8–1.1)	0.856
Diet intolerance,‡ n (%)						
ITT analysis	15 (23)	17 (27)	0.9 (0.5–1.6)	*0.839*	0.9 (0.5–1.6)	0.582
Per protocol	14 (25)	14 (24)	1 (0.5–2)	*1.000*	1.1 (0.6–2.1)	0.967
Nasogastric tube insertion, n (%)						
ITT analysis	9 (14)	11 (17)	0.8 (0.4–1.8)	*0.808*	0.8 (0.4–1.8)	0.293
Per protocol	8 (14)	8 (14)	1 (0.4–2.6)	*1.000*	1.2 (0.5–2.9)	0.770
Number of skipped meals, n						
ITT analysis	1 (0–2)	1 (0–5)	na	0.551	na	-
Per protocol	1 (0–2)	1 (0–4)	na	0.770	na	-

Data are presented as median (interquartile range), as absolute numbers (percentage), or as RR (95% CI); *P* values in italic: Fisher exact test. 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. †Including patients who did not meet the criteria for primary postoperative ileus. ‡Diet intolerance: at the end of the day patients were asked to judge whether they tolerated 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; na = not applicable; PPOI = primary postoperative ileus; RR = relative risk.

benefits of goal-directed fluid therapy are offset by advancements in perioperative care.[28,29] 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 (less than 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 primary postoperative ileus or postoperative complications. Finally, approximately two thirds of patients in both groups were at

Table 6. QoR Score, LOS, 30-day Postoperative Complications, 30-day ED Visits, and 30-day Readmissions

	Goal-directed Fluid Therapy (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 (44)	25 (39)	1.1 (0.7–1.7)	0.590
In-hospital	22 (34)	20 (31)	1.1 (0.7–1.8)	0.707
Postdischarge	9 (14)	8 (12)	1.1 (0.5–2.7)	0.795
Patients with at least one 30-day medical complication, n (%)	18 (28)	14 (22)	1.3 (0.7–1.3)	0.414
Cardiovascular	3 (4.7)	2 (3.1)	1.2 (0.3–8.7)	*1.000*
Respiratory	3 (4.7)	0 (0)	na	*0.244*
Infectious	12 (19)	8 (12)	1.5 (0.7–3.4)	0.330
Other	9 (14)	9 (14)	1 (0.4–2.3)	1.000
Patients with at least one 30-day surgical complication, n (%)	20 (31)	18 (28)	1.1 (0.6–1.9)	0.699
Primary postoperative ileus	14 (22)	14 (22)	1 (0.5–1.9)	1.000
Anastomotic leakage	3 (4.7)	0 (0)	na	*0.244*
Bleeding	3 (4.7)	3 (4.7)	1 (0.2–4.8)	*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 (0.2–21.5)	*1.000*
Patients reoperated within 30 days, n (%)	1 (1.6)	3 (4.7)	0.3 (0–3.1)	*0.619*
30-day Clavien–Dindo classification, n (%)				
I	10 (16)	10 (16)	1 (0.4–2.3)	1.000
II	11 (17)	10 (16)	1.1 (0.5–2.4)	0.811
IIIa	5 (7.8)	2 (3.1)	2.5 (0.5–12.4)	*0.440*
IIIb-IVb	2 (3.1)	3 (4.7)	0.7 (0.1–3.9)	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)	9 (14)	1.4 (0.7–3.1)	0.349
Patients readmitted within 30 days, n (%)	8 (12)	6 (9.4)	1.3 (0.5–3.6)	0.571

Data are presented as median (interquartile range), as absolute numbers (percentages), or as RR (95% CI); *P* value in italic: Fisher exact test.

*ICU admission during primary LOS.

CCI = Comprehensive Complication Index; ED = emergency department; ICU = intensive care unit; LOS = length of hospital stay; na = not applicable; QoR = Quality of Recovery; RR = relative risk.

low risk for postoperative complications, and the benefits of goal-directed fluid therapy have been demonstrated mainly in high-risk patients.[23,24]

The main strength of this study is that it specifically evaluates the impact of goal-directed fluid therapy on the recovery of bowel function in the context of standardized and evidence-based perioperative care, limiting the risk of bias due to several perioperative confounding factors. However, it must be acknowledged that Enhanced Recovery After Surgery 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 goal-directed fluid therapy 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. Our institutional protocol is to use epidural analgesia for patients undergoing laparoscopic rectal surgery but not colonic surgery, based on results of a previous study showing better pain control with epidural analgesia in the first 48 h after laparoscopic rectal surgery compared with systemic opioids plus intravenous lidocaine.[37] In the current study, it was decided to standardize the analgesia technique to minimize the risk of bias, providing epidural analgesia to all patients. Although the use of epidural analgesia in laparoscopic colorectal surgery remains controversial, it is still used in established Enhanced Recovery After Surgery programs.[49]

Several limitations must be acknowledged. First, patients in the control group received a large volume of intravenous fluids, greater than what currently is recommended,[36] but similar to what is still infused in clinical practice.[51–54] Although the fluid regimen used is based on outdated perioperative fluid therapy principles,[45,48] it is consistent with what is recommended in

widely used anesthesia textbooks.[31] The two 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, colloid use alone has not been associated with postoperative gastrointestinal dysfunction, as also demonstrated by the results of our secondary analyses (data unsubmitted with the current manuscript). Similarly, the fluid regimen (volume and timing of fluid administration) was also significantly different between the two groups, further confounding the interpretation of these results.

Second, a more rational goal-directed fluid therapy protocol based on stroke volume optimization when clinically deemed, rather than on preemptive near-maximal stroke volume optimization, might have led to better results, as many patients in the control group were able to maintain adequate systemic perfusion (cardiac output), despite a submaximal stroke volume. Third, despite randomization, a higher proportion of patients in the goal-directed fluid therapy group received mechanical bowel preparation. However, after adjustment for the use of mechanical bowel preparation, the risk of developing primary postoperative ileus was unchanged ($RR_{adjusted}$, 1; 95% CI, 0.5 to 1.9.; $P = 0.094$), although the study was not powered to detect a significant difference is this subgroup of patients. Fourth, although we did not exclude obese patients, the average body mass index in the study population may be lower than in other populations, and these results may not be generalizable. Fifth, in the absence of a universal and validated definition of ileus, we used a definition based on an interdisciplinary consensus achieved among anesthesiologists and surgeons, based on literature review and focusing on clinically relevant symptoms. However, the incidence of primary postoperative ileus was similar to what has been reported previously in the context of an Enhanced Recovery After Surgery program.[15] Moreover, a secondary analysis including all patients of the study has shown that patients with primary postoperative ileus, but without any other complications, had a median increase in length of hospital stay of 4 days, and that primary postoperative ileus was an independent predictor of delayed readiness for discharge and prolonged hospital stay ($P < 0.001$ and $P = 0.001$, respectively; data unsubmitted with the current manuscript). Although the sample size is limited and these results need further validation, these findings suggest that this definition of primary postoperative ileus might accurately identify patients with a clinically meaningful gastrointestinal dysfunction in the context of an Enhanced Recovery After Surgery program. Finally, this study might have insufficient statistical power to determine whether goal-directed fluid therapy can reduce primary postoperative ileus, as its incidence was lower than expected. The expected incidence of primary postoperative ileus in the control group might have been overestimated, probably because some patients in the historical group used to calculate the sample size received intravenous morphine patient-controlled analgesia or had open surgery, factors known to delay the recovery of bowel function after colorectal surgery.[2] It also is possible that the volume of fluids received in the historical group might have been significantly higher or lower than what was infused in the control group, contributing to a higher incidence of primary postoperative ileus. 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 in clinical trials tend to have better outcomes regardless of the treatment they receive.[55]

In conclusion, within its limitations, this study shows that intraoperative goal-directed fluid therapy compared with fluid therapy based on traditional fluid management does not reduce the incidence of primary postoperative ileus in patients undergoing laparoscopic colorectal surgery in the context of an Enhanced Recovery After Surgery program. Its previously demonstrated benefits might have been offset by advancements in perioperative and surgical care. Nonetheless, fluid therapy always should be based on physiologic and scientific principles, to minimize the risk of complications associated with fluid overload and hypovolemia, especially in high-risk surgical patients.

Acknowledgments

The authors acknowledge Deltex Medical Ltd. (Chichester, United Kingdom) for loaning the esophageal Doppler monitor.

Research Support

Supported by the Gerard R. Douville Award, granted to Dr. Baldini, McGill University Health Center Research Institute, Montreal, Quebec, Canada.

Competing Interests

Dr. Baldini's academic research funding was used to purchase the esophageal Doppler probes. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: gabriele.baldini@mcgill.ca. Raw data available at: gabriele.baldini@mcgill.ca.

Correspondence

Address correspondence to Dr. Baldini: Department of Anesthesia, Montreal General Hospital, McGill University Health Centre, 1650 Cedar Ave, D10.145.2, Montreal, Quebec H3G 1A4, Canada. gabriele.baldini@mcgill.ca. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Augestad KM, Delaney CP: Postoperative ileus: Impact of pharmacological treatment, laparoscopic surgery and enhanced recovery pathways. World J Gastroenterol 2010; 16:2067–74

2. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN: Postoperative ileus: Recent developments in pathophysiology and management. Clin Nutr 2015; 34:367–76
3. Doorly MG, Senagore AJ: Pathogenesis and clinical and economic consequences of postoperative ileus. Surg Clin North Am 2012; 92:259–72, viii
4. Miller TE, Thacker JK, White WD, Mantyh C, Migaly J, Jin J, Roche AM, Eisenstein EL, Edwards R, Anstrom KJ, Moon RE, Gan TJ; Enhanced Recovery Study Group: Reduced length of hospital stay in colorectal surgery after implementation of an enhanced recovery protocol. Anesth Analg 2014; 118:1052–61
5. Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ: Postoperative ileus: It costs more than you expect. J Am Coll Surg 2010; 210:228–31
6. Iyer S, Saunders WB, Stemkowski S: Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm 2009; 15:485–94
7. Moore-Olufemi SD, Xue H, Attuwaybi BO, Fischer U, Harari Y, Oliver DH, Weisbrodt N, Allen SJ, Moore FA, Stewart R, Laine GA, Cox CS Jr: Resuscitation-induced gut edema and intestinal dysfunction. J Trauma 2005; 58:264–70
8. Uray KS, Laine GA, Xue H, Allen SJ, Cox CS Jr: Intestinal edema decreases intestinal contractile activity via decreased myosin light chain phosphorylation. Crit Care Med 2006; 34:2630–7
9. Uray KS, Laine GA, Xue H, Allen SJ, Cox CS Jr: Edema-induced intestinal dysfunction is mediated by STAT3 activation. Shock 2007; 28:239–44
10. Uray KS, Wright Z, Kislitsyna K, Xue H, Cox CS Jr: Nuclear factor-kappaB activation by edema inhibits intestinal contractile activity. Crit Care Med 2010; 38:861–70
11. Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F; Danish Study Group on Perioperative Fluid Therapy: Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative fluid regimens: A randomized assessor-blinded multicenter trial. Ann Surg 2003; 238:641–8
12. Chowdhury AH, Lobo DN: Fluids and gastrointestinal function. Curr Opin Clin Nutr Metab Care 2011; 14:469–76
13. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. Lancet 2002; 359:1812–8
14. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I: Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 2005; 103:25–32
15. Thacker JK, Mountford WK, Ernst FR, Krukas MR, Mythen MM: Perioperative fluid utilization variability and association with outcomes: Considerations for enhanced recovery efforts in sample US surgical populations. Ann Surg 2016; 263:502–10
16. Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR: Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med 1997; 23:276–81
17. Schnüriger B, Inaba K, Wu T, Eberle BM, Belzberg H, Demetriades D: Crystalloids after primary colon resection and anastomosis at initial trauma laparotomy: Excessive volumes are associated with anastomotic leakage. J Trauma 2011; 70:603–10
18. Volta CA, Alvisi V, Campi M, Marangoni E, Alvisi R, Castellazzi M, Fainardi E, Manfrinato MC, Dallocchio F, Bellini T: Influence of different strategies of volume replacement on the activity of matrix metalloproteinases: An *in vitro* and *in vivo* study. Anesthesiology 2007; 106:85–91
19. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS: Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97:820–6
20. Giglio MT, Marucci M, Testini M, Brienza N: Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: A meta-analysis of randomized controlled trials. Br J Anaesth 2009; 103:637–46
21. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM: Perioperative fluid management strategies in major surgery: A stratified meta-analysis. Anesth Analg 2012; 114:640–51
22. Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K; Optimisation Systematic Review Steering Group: Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: A Cochrane Systematic Review. Br J Anaesth 2013; 111:535–48
23. Hamilton MA, Cecconi M, Rhodes A: A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg 2011; 112:1392–402
24. Cecconi M, Corredor C, Arulkumaran N, Abuella G, Ball J, Grounds RM, Hamilton M, Rhodes A: Clinical review: Goal-directed therapy—what is the evidence in surgical patients? The effect on different risk groups. Crit Care 2013; 17:209
25. Brandstrup B, Svendsen PE, Rasmussen M, Belhage B, Rodt SÅ, Hansen B, Møller DR, Lundbech LB, Andersen N, Berg V, Thomassen N, Andersen ST, Simonsen L: Which goal for fluid therapy during colorectal surgery is followed by the best outcome: Near-maximal stroke volume or zero fluid balance? Br J Anaesth 2012; 109:191–9
26. Srinivasa S, Taylor MH, Singh PP, Yu TC, Soop M, Hill AG: Randomized clinical trial of goal-directed fluid therapy within an enhanced recovery protocol for elective colectomy. Br J Surg 2013; 100:66–74
27. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K; OPTIMISE Study Group: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA 2014; 311:2181–90
28. Gómez-Izquierdo JC, Feldman LS, Carli F, Baldini G: Meta-analysis of the effect of goal-directed therapy on bowel function after abdominal surgery. Br J Surg 2015; 102:577–89
29. Rollins KE, Lobo DN: Intraoperative goal-directed fluid therapy in elective major abdominal surgery: A meta-analysis of randomized controlled trials. Ann Surg 2016; 263:465–76
30. Challand C, Struthers R, Sneyd JR, Erasmus PD, Mellor N, Hosie KB, Minto G: Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. Br J Anaesth 2012; 108:53–62
31. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL: Intravascular fluids and electrolytes physiology, Miller's Anesthesia, 7th edition. Philadelphia, Elsevier Churchill Livingstone, 2010, pp 1705–30
32. Carli F, Charlebois P, Baldini G, Cachero O, Stein B: An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery. Can J Anaesth 2009; 56:837–42
33. Sanders G, Mercer SJ, Saeb-Parsey K, Akhavani MA, Hosie KB, Lambert AW: Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery. Br J Surg 2001; 88:1363–5
34. Jørgensen CC, Bundgaard-Nielsen M, Skovgaard LT, Secher NH, Kehlet H: Stroke volume averaging for individualized

goal-directed fluid therapy with oesophageal Doppler. Acta Anaesthesiol Scand 2009; 53:34–8

35. Levy BF, Fawcett WJ, Scott MJ, Rockall TA: Intra-operative oxygen delivery in infusion volume-optimized patients undergoing laparoscopic colorectal surgery within an enhanced recovery programme: The effect of different analgesic modalities. Colorectal Dis 2012; 14:887–92
36. Mythen MG, Swart M, Acheson N, Crawford R, Jones K, Kuper M, McGrath JS, Horgan A: Perioperative fluid management: Consensus statement from the enhanced recovery partnership. Perioper Med (Lond) 2012; 1:2
37. Wongyingsinn M, Baldini G, Charlebois P, Liberman S, Stein B, Carli F: Intravenous lidocaine *versus* thoracic epidural analgesia: a randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program. Reg Anesth Pain Med 2011; 36:241–8
38. Myles PS, Hunt JO, Nightingale CE, Fletcher H, Beh T, Tanil D, Nagy A, Rubinstein A, Ponsford JL: Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. Anesth Analg 1999; 88:83–90
39. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M: The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg 2009; 250:187–96
40. Slankamenac K, Nederlof N, Pessaux P, de Jonge J, Wijnhoven BP, Breitenstein S, Oberkofler CE, Graf R, Puhan MA, Clavien PA: The comprehensive complication index: A novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg 2014; 260:757–62; discussion 762–3
41. McGill University Health Centre Opioid Therapy Guidelines. Edited by McGill University Health Centre. Montreal, Quebec, Canada, McGill University Health Centre, 2008
42. Delaney CP, Kehlet H, Senagore A: Postoperative ileus: Profiles, risk factors and definitions—a framework for optimizing surgical outcomes in patients undergoing major abdominal and colorectal surgery. Clin Consensus Update Gen Surg 2006; 1
43. Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F; Danish Study Group on Perioperative Fluid Therapy: Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: A randomized assessor-blinded multicenter trial. Ann Surg 2003; 238:641–8
44. Bundgaard-Nielsen M, Secher NH, Kehlet H: 'Liberal' vs. 'restrictive' perioperative fluid therapy—a critical assessment of the evidence. Acta Anaesthesiol Scand 2009; 53:843–51
45. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. Anesthesiology 2008; 109:723–40
46. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J: Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br J Surg 2009; 96:331–41
47. Holte K, Sharrock NE, Kehlet H: Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth 2002; 89:622–32
48. Navarro LH, Bloomstone JA, Auler JO Jr, Cannesson M, Rocca GD, Gan TJ, Kinsky M, Magder S, Miller TE, Mythen M, Perel A, Reuter DA, Pinsky MR, Kramer GC: Perioperative fluid therapy: A statement from the International Fluid Optimization Group. Perioper Med (Lond) 2015; 4:3
49. Miller TE, Roche AM, Gan TJ: Poor adoption of hemodynamic optimization during major surgery: Are we practicing substandard care? Anesth Analg 2011; 112:1274–6
50. Soni N: British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP): Cassandra's view. Anaesthesia 2009; 64:235–8
51. Pestaña D, Espinosa E, Eden A, Nájera D, Collar L, Aldecoa C, Higuera E, Escribano S, Bystritski D, Pascual J, Fernández-Garijo P, de Prada B, Muriel A, Pizov R: Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). Anesth Analg 2014; 119:579–87
52. Ackland GL, Iqbal S, Paredes LG, Toner A, Lyness C, Jenkins N, Bodger P, Karmali S, Whittle J, Reyes A, Singer M, Hamilton M, Cecconi M, Pearse RM, Mallett SV, Omar RZ; POM-O (PostOperative Morbidity-Oxygen delivery) study group: Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: A multicentre, randomised, double-blind, controlled, mechanistic trial. Lancet Respir Med 2015; 3:33–41
53. Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J: Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: Retrospective two-centre analysis. Br J Anaesth 2015; 114:767–76
54. Lai CW, Starkie T, Creanor S, Struthers RA, Portch D, Erasmus PD, Mellor N, Hosie KB, Sneyd JR, Minto G: Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness. Br J Anaesth 2015; 115:578–89
55. Selby P, Autier P: The impact of the process of clinical research on health service outcomes. Ann Oncol 2011; 22 Suppl 7: vii5-vii9