

Goal-directed Intraoperative Fluid Administration Reduces Length of Hospital Stay after Major Surgery

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Background: Intraoperative hypovolemia is common and is a potential cause of organ dysfunction, increased postoperative morbidity, length of hospital stay, and death. The objective of this prospective, randomized study was to assess the effect of goal-directed intraoperative fluid administration on length of postoperative hospital stay.

Methods: One hundred patients who were to undergo major elective surgery with an anticipated blood loss greater than 500 ml were randomly assigned to a control group (n = 50) that received standard intraoperative care or to a protocol group (n = 50) that, in addition, received intraoperative plasma volume expansion guided by the esophageal Doppler monitor to maintain maximal stroke volume. Length of postoperative hospital stay and postoperative surgical morbidity were assessed.

Results: Groups were similar with respect to demographics, surgical procedures, and baseline hemodynamic variables. The protocol group had a significantly higher stroke volume and cardiac output at the end of surgery compared with the control group. Patients in the protocol group had a shorter duration of hospital stay compared with the control group: 5 ± 3 versus 7 ± 3 days (mean \pm SD), with a median of 6 versus 7 days, respectively ($P = 0.03$). These patients also tolerated oral intake of solid food earlier than the control group: 3 ± 0.5 versus 4.7 ± 0.5 days (mean \pm SD), with a median of 3 versus 5 days, respectively ($P = 0.01$).

Conclusions: Goal-directed intraoperative fluid administration results in earlier return to bowel function, lower incidence of postoperative nausea and vomiting, and decrease in length of postoperative hospital stay.

INTRAOPERATIVE hypovolemia is common and may be a potential cause of organ dysfunction, increased postoperative morbidity, and death.^{1,2} Goal-directed plasma volume expansion during the intraoperative period is associated with improved outcome and reduction in hospital stay in patients undergoing cardiac and major orthopedic surgery.³⁻⁵

The esophageal Doppler monitor (EDM) is an Food and Drug Administration–approved device that permits

rapid, minimally invasive, and continuous estimation of cardiac output.⁶ The cardiac output measurements obtained with the EDM have been shown to correlate well with the thermodilution method by different investigators.⁷⁻¹¹ Using the EDM to guide intraoperative plasma volume expansion, Sinclair *et al.*⁴ demonstrated significant improvement in postoperative recovery and shortened hospital stay in patients undergoing proximal femoral neck fracture repair. Mythen and Webb,³ in a study in cardiac patients, demonstrated a reduction in the incidence of gastrointestinal mucosal hypoperfusion and major complications in patients who received plasma volume optimization.

In this study, we investigated whether goal-directed intraoperative plasma volume expansion guided by the EDM would shorten the length of hospital stay and improve postoperative outcomes (gastrointestinal and renal dysfunction) in patients undergoing moderate-risk surgery.

Methods

After we obtained approval from the institutional review board, written informed patient consent was obtained from 100 patients with American Society of Anesthesiologists (ASA) physical status I, II, and III who were to undergo major elective general, urologic, or gynecologic surgery with an anticipated blood loss of greater than 500 ml. Exclusion criteria included patients with age less than 18 yr, emergency surgery, preoperative bowel obstruction, coagulopathy, significant renal and hepatic dysfunction (creatinine > 50% or liver enzymes > 50% upper limit of normal values), congestive heart failure, and esophageal pathology (avoid potential complications of the esophageal probe), and those undergoing gastric or esophageal surgery or who were on antiemetic medication within 3 days of surgery.

All patients were premedicated with midazolam and fentanyl. Before induction of anesthesia, an intravenous bolus of 5 ml/kg lactated Ringer's solution was administered, followed by an intravenous infusion of lactated Ringer's solution at a rate of $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, which was continued for the duration of surgery. Anesthesia was induced by an intravenous technique and maintained with a balanced inhalational technique incorporating isoflurane 0.5–1.5% and 50% nitrous oxide in oxygen. Tracheal intubation was facilitated with succinylcholine, and neuromuscular blockade was maintained using pan-

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curonium. All patients received 1.25 mg droperidol as a prophylactic antiemetic. Additional fentanyl up to $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was given as required. Ventilation was adjusted to maintain arterial carbon dioxide partial pressure at 35–40 mmHg, and temperature was maintained at greater than 35°C throughout surgery. If an epidural catheter was placed preoperatively for postoperative pain management, a 3-ml test dose consisting of lidocaine 1.5% with 1:200,000 epinephrine was administered, and no subsequent epidural local anesthetic drugs were administered intraoperatively. Postoperative analgesia was provided by either epidural (bupivacaine 0.125% and hydromorphone 0.001%) or patient-controlled analgesia with fentanyl. Anesthesia was maintained at a constant level as judged by standard clinical criteria.

Following induction of anesthesia, an esophageal Doppler probe (EDM™; Deltex Medical, Inc., Irving, TX) was greased with lubricating gel and inserted orally into the midesophagus in all patients. Blood flow signals were identified. Once achieved, satisfactory position was maintained by taping the probe cable to either the patient's face or the endotracheal tube. The EDM monitor displays a blood flow velocity waveform that represents the velocity of blood flow within the descending thoracic aorta. A nomogram incorporated in the monitor is used to estimate aortic cross-sectional area, enabling calculation of the left ventricular stroke volume from the area of the velocity–time waveform. This nomogram includes the patient's height, weight, and age.⁶ The total amount of time that blood is traveling in a forward direction within the aorta is the systolic flow time. This is corrected for heart rate to give the corrected flow time (FTc). The FTc has been shown to be a good index of systemic vascular resistance and is sensitive to changes in left ventricular preload.¹² Direct intraarterial pressure was monitored in addition to electrocardiography, non-invasive blood pressure, heart rate, end-tidal carbon dioxide tension, temperature, and pulse oximetry. When clinically indicated, a central venous catheter was placed following induction of anesthesia. All cardiovascular variables and urinary flow were monitored and recorded during general anesthesia. Types and volumes of all fluids administered intraoperatively (including but not limited to colloid and crystalloid solutions, blood, and blood products) were recorded, as were the volumes and doses of any drugs given during general anesthesia and an estimation made of blood loss.

Following insertion of the EDM probe, the patients were randomized into either the protocol or control group using a random number generator in sealed envelopes. In the protocol group, boluses of fluid were administered, guided by an algorithm depending on the Doppler estimations of stroke volume and FTc (fig. 1). This algorithm was similar to that used by Sinclair *et al.*⁴ A 200-ml aliquot of 6% hydroxyethyl starch in saline was

given when the FTc was less than 0.35 s. If the stroke volume was maintained or increased by the fluid challenge and the FTc remained below 0.35 s, the fluid challenge was repeated. If the stroke volume increased by more than 10% and the FTc exceeded 0.35 s, the fluid challenge was repeated until no further increase in stroke volume occurred. If the FTc increased above 0.40 s with no change in stroke volume, further fluid was not then administered until the stroke volume decreased by 10% of the last value. The procedure was started immediately after probe placement and continued every 15 min until maximum stroke volume and targeted FTc values had been reached. Further aliquots of fluid were given to keep the FTc at the targeted values. In addition, patients also received fluid equivalent to that judged to be lost as a result of surgical hemorrhage. When 20 ml/kg of 6% hydroxyethyl starch in saline had been given, lactated Ringer's solution was used for further fluid boluses as required. The designation of an upper limit of 20 ml/kg of 6% hydroxyethyl starch in saline represents the standard practice within our institution. Crystalloid was used in a 3:1 ratio for the replacement of surgical blood loss.

In the control group, the EDM monitor was turned away from the anesthesia care provider, and the screen was covered with an opaque card. The EDM variables were collected by an independent research personnel. Hemodynamic variables triggering fluid administration involved a urinary output less than $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, an increase in heart rate more than 20% above baseline or more than 110 beats/min, a decrease in mean systolic blood pressure less than 20% below baseline or less than 90 mmHg, or central venous pressure less than 20% of baseline. Boluses of 200 ml of fluid were administered until the above target was restored. The anesthesiologists would also administer additional fluid if deemed clinically indicated and were instructed to conduct anesthesia according to their customary practice.

For the treatment of anemia and hypocoagulation, the protocol called for the administration of blood products (erythrocytes, platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen) when clinically indicated and supported by the laboratory evidence of a hematocrit less than 23% or abnormal coagulation (platelet count $< 100,000/\text{l}$, prothrombin time > 1.5 times control, activated partial thromboplastin time > 1.5 times control, or fibrinogen $< 100 \text{ mg/dl}$). Patients were extubated, either in the operating room or postoperatively, when they fulfilled standard clinical criteria (adequate protective reflexes, adequate oxygenation, and stable hemodynamics). They were visited daily in the immediate postoperative period by independent research personnel unaware of the patient's randomization until hospital discharge or death. During the visit, the patients were asked specific questions on adverse events and presence of flatus. The information was recorded in a data collec-

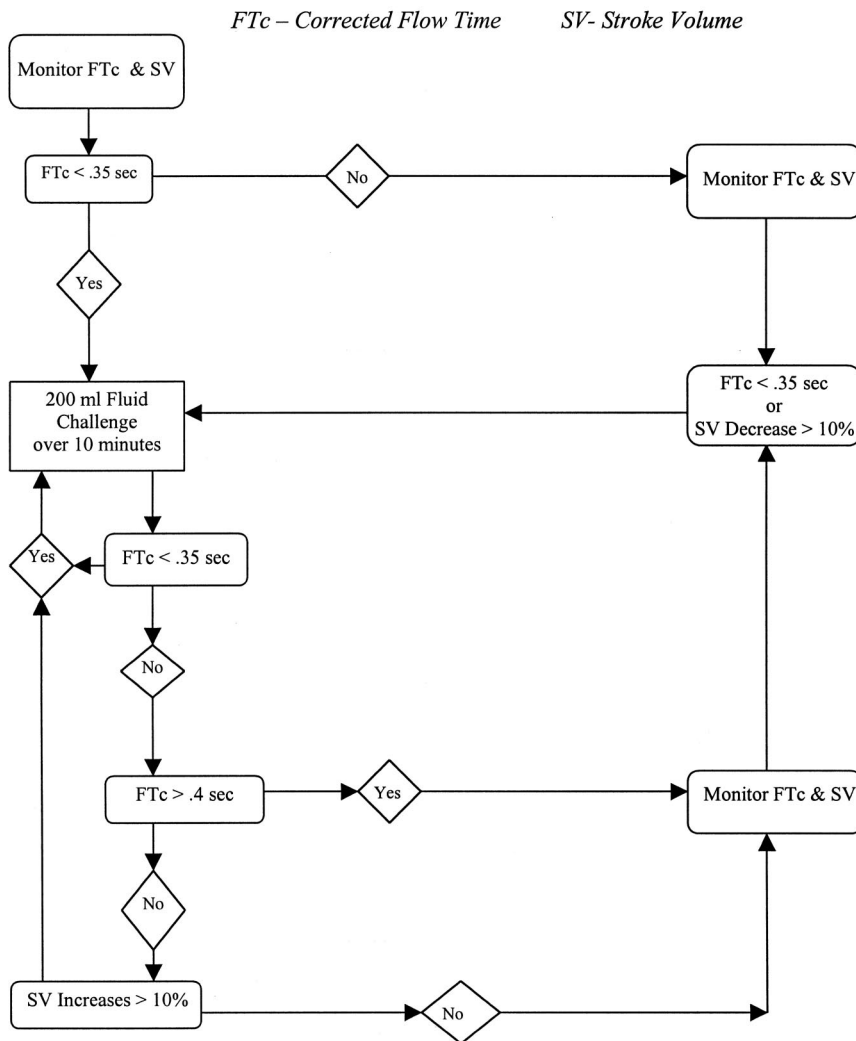


Fig. 1. Intraoperative fluid management algorithm. FTc = corrected flow time; SV = stroke volume.

tion form modified from a previous study in the same institution.¹⁵ Those who had flatus were started on oral fluids, which were followed by solid food if tolerated (without emetic symptoms within 4 h). The length of postoperative stay was recorded. Postoperative care and discharge criteria were predefined using the hospital care map and protocol. Rescue antiemetic treatment (4 mg intravenous ondansetron) was administered with two or more emetic episodes or on patient's request.

Data were analyzed comparing patients in the protocol group with those in the standard practice group on an intent-to-treat basis. The groups were compared using *t* test or Wilcoxon rank-sum tests as appropriate. The volumes of intravenous colloid and crystalloid administered to the two groups were compared using a one-way analysis of covariance adjusting for each patient's estimated blood loss. The incidence of adverse events was compared using the two-tailed Fisher exact test. A *P* value < 0.05 was considered statistically significant.

An earlier separate pilot study was conducted with 20 patients to familiarize researchers with the equipment and to determine the feasibility of the proposed

methodology. The results were used to estimate the necessary sample size for this prospective study. A sample of 50 patients in each group was calculated to have at least 90% power to detect a difference in mean of length of hospital stay of 2 days between the two groups, using a two-group *t* test with a 0.05 two-sided significance.

Results

One hundred patients were enrolled. Two patients were not included for analysis (one patient in each group) as neither had their scheduled surgery. The two groups were well matched with regard to demographics, ASA physical status, duration of anesthesia, intraoperative fentanyl use, and type of surgery (table 1).

The volume of colloid and crystalloid, erythrocyte, and blood product administration for the two groups is shown in table 2. Patients in the protocol group received more 6% hetastarch compared with the control group. Eleven patients in the protocol group received erythro-

Table 1. Demographic Data

	Protocol Group (n = 50)	Control Group (n = 50)
Age (yr)	56 ± 13	59 ± 12
Sex (M:F)	31:19	26:24
Race (%)		
White	84	84
Black	16	16
Weight (kg)	81 ± 14	81 ± 27
Height (cm)	170 ± 8	168 ± 10
ASA physical status		
I	3	8
II	36	32
III	11	10
Surgery type/epidural for postoperative analgesia		
General	16/3	15/4
Gynecologic	13/0	19/0
Urologic	21/3	16/4
Patients with central venous pressure monitoring	43	45
Use of vasoactive drugs	8	13
Hematocrit (%)		
At induction	40.1 ± 4.3	39.2 ± 5.1
End of surgery	32.2 ± 4.5	33.4 ± 4.3
Hemoglobin (g/dl)		
At induction	13.4 ± 1.9	12.9 ± 1.7
End of surgery	10.8 ± 1.5	10.9 ± 1.5
Intraoperative fentanyl (μg)	675 ± 355	610 ± 302
Duration of surgery (min)	250 ± 115	218 ± 90

Data are number of patients or mean ± SD. Vasoactive drugs were phenylephrine or esmolol administered in single doses.

ASA = American Society of Anesthesiologists.

cyte transfusion *versus* nine in the control group, and one patient each in the protocol group received fresh frozen plasma (351 ml) or platelets (538 ml), respectively. Baseline hemodynamic variables were similar between the two groups (table 3). There were no significant changes in heart rate and mean intraarterial blood pressure between the two periods in both groups. However, there was a significant increase in Doppler-derived variables (stroke volume, cardiac output, and FTc) from baseline to end of surgery in the protocol group compared with the control group (table 3).

The length of hospital stay was shorter for the protocol group compared with the control group: 5 ± 3 *versus*

Table 2. Intraoperative Fluid, Blood, and Blood Product Administration

	Protocol Group (n = 50)	Control Group (n = 50)
6% hetastarch in saline	847 ± 373*	282 ± 470
Lactated Ringer's solution	4405 ± 2650	4375 ± 2452
Erythrocytes	168 ± 386	118 ± 281
Estimated blood loss	703 ± 649	624 ± 632
Urinary output	544 ± 593	418 ± 380

Data are mean ± SD (volume in ml).

* $P < 0.01$.

7 ± 3 days (mean ± SD), 6 *versus* 7 days (median), respectively ($P = 0.03$). Patients in the protocol group also tolerated an oral solid regimen earlier than the control group: 3 ± 0.5 *versus* 4.7 ± 0.5 days (mean ± SD), 3 *versus* 5 days (median), respectively ($P = 0.01$). Fewer patients in the protocol group experienced severe postoperative nausea and vomiting requiring rescue antiemetic treatment ($P < 0.05$; table 4). There were no differences in the incidence of other complications (table 4).

Discussion

This prospective, randomized, controlled study demonstrates that goal-directed intraoperative fluid administration during major surgery results in earlier gastrointestinal function, a reduction in postoperative complications, and a shortened hospital stay.

Hypovolemia is common among patients scheduled for surgery. In addition to the inevitable losses in the perioperative period caused by surgical trauma, evaporation, and the use of dry anesthetic gases, the majority of patients are routinely required to fast for a minimum of 6 h preoperatively to reduce the risk of acid aspiration syndrome.¹⁴ Hypovolemia during the perioperative period has been associated with a significant increase in postoperative morbidity and mortality, ranging from postoperative nausea and vomiting¹⁵ to more serious complications such as organ dysfunction,³ as well as prolongation of hospital stay.⁴

Bennett-Guerrero *et al.*¹³ recently demonstrated that gastrointestinal dysfunction is the most common postoperative complication in patients undergoing moderate-risk surgery, especially those procedures involving laparotomy. Gastrointestinal dysfunction was the most frequent reason for a prolonged length of hospital stay. At postoperative day 5, 55% of the patients studied were unable to tolerate an enteral diet. More than 50% of patients who were still hospitalized on postoperative day 15 exhibited gastrointestinal dysfunction. Their findings echo the results of our study. The reduction in hospital stay observed was primarily the result of patients tolerating a solid regimen earlier. We also found the incidence of severe postoperative nausea and vomiting requiring rescue antiemetic therapy was higher in the control group compared with the protocol group. It is conceivable that improved perfusion of gastric mucosa as a result of additional fluid administration in the protocol group could have resulted in less postoperative nausea and vomiting, as was demonstrated by previous observation. In the same study, Bennett-Guerrero *et al.*¹³ found a significant correlation between intraoperative indices of tissue hypoperfusion (*e.g.*, gastric pHi, arterial base deficit) and gastrointestinal dysfunction. While we did not assess gastric mucosal perfusion, several studies

Table 3. Hemodynamic and Doppler-derived Variables at Baseline and at End of Surgery for Both Protocol and Control Groups

	Control		Protocol	
	Baseline	End of Surgery	Baseline	End of Surgery
Heart rate (beats/min)	74 ± 16	77 ± 13	75 ± 15	76 ± 14
Mean arterial pressure (mmHg)	81 ± 19	87 ± 17	82 ± 17	90 ± 19
Stroke volume (ml)	70 ± 17	67 ± 17	67 ± 24	76 ± 19*
Cardiac Output (l/min)	5.2 ± 1.7	5.1 ± 1.4	5.0 ± 1.7	5.8 ± 1.6*
Corrected flow time (s)	0.38 ± 0.04	0.37 ± 0.04	0.38 ± 0.04	0.40 ± 0.03*

* $P < 0.05$ comparing changes at end of surgery and baseline between the two groups.

Baseline = following induction of anesthesia and satisfactory placement of the esophageal Doppler probe as defined in the methods; End of Surgery = before reversal of neuromuscular blocking effects and emergence of anesthesia.

have shown a direct relation between hypovolemia and gut hypoperfusion.^{3,16} Hence, it is plausible that the protocol group that had optimal fluid administration during the intraoperative period may have had better gut perfusion, which resulted in a lower incidence of gastrointestinal dysfunction.

We use the EDM to guide intraoperative fluid administration. The EDM is a minimally invasive method for continuous monitoring of the circulation. There is good agreement between measures of cardiac output made simultaneously with the esophageal Doppler and a thermodilution pulmonary arterial catheter.^{9,10} Pulmonary arterial catheter insertion, however, requires technical skill and may be associated with life-threatening complications. Despite its widespread use, there is little or limited evidence that the use of a pulmonary arterial catheter benefits patients. Indeed, there is evidence that it may increase morbidity and mortality.^{17,18} There are

several limitations to the use of EDM. The monitor makes assumptions on the diameter of the aorta based on the weight and height of the patient. There is a learning curve to achieve proficient placement of the probe to capture maximal signal. Insertion of 12 EDM probes appears to be necessary to achieve adequate proficiency.¹⁹ There are other relatively noninvasive devices that measure stroke volume and cardiac output that may also be useful for goal-directed intraoperative fluid administration. These include noninvasive cardiac output using partial carbon dioxide rebreathing, transesophageal echocardiography, Fick indicator dilution technique using lithium, and thoracic impedance.

We used FTc to guide volume replacement as it has been shown to be a more sensitive indicator of cardiac filling than pulmonary arterial diastolic pressure and pulmonary arterial occlusion pressure.^{8,20} For pulmonary arterial diastolic pressure or pulmonary arterial occlusion pressure to increase, the left ventricle must be loaded sufficiently to increase left ventricular end-diastolic pressure. In a ventricle with normal diastolic compliance, major volume changes may not produce substantial pressure changes, thus limiting the usefulness of the pulmonary arterial diastolic pressure as a marker for filling. In contrast, the FTc value represents the amount of time required to eject the stroke volume, corrected for heart rate. As the ventricle is filled, it requires more time to eject the greater stroke volume, even in ventricles with normal compliance.

Other investigators have demonstrated that optimal fluid administration during the intraoperative period appears to reduce morbidity and length of hospital stay. Sinclair *et al.*⁴ demonstrated that plasma volume augmentation in patients undergoing open reduction of a femur fracture was associated with significantly faster recovery, with a reduction in the median time to being medically fit for discharge from 15 to 10 days, compared with a control group. In another study, Mythen and Webb³ demonstrated that esophageal Doppler-guided plasma volume augmentation significantly reduced the incidence of gastric mucosal hypoperfusion (56% to 7%) with significantly reduced complication rates and length

Table 4. Incidence of Postoperative Complications

	Protocol Group (n = 50)	Control Group (n = 50)
Acute renal dysfunction (urine output <500 ml)	2 (4)	4 (8)
Respiratory support for > 24 h	1 (2)	3 (6)
Cardiovascular (hypotension, pulmonary edema, arrhythmia)	1 (2)	2 (4)
Chest infection (clinical diagnosis)	2 (4)	2 (4)
Severe PONV requiring rescue antiemetic	7 (14)	18 (36)*
Coagulopathy	4 (8)	4 (8)
Wound infection	4 (8)	5 (10)

Data presented as number of patients (%). Postoperative complications definition based on Bennett-Gurrero *et al.*¹³

* $P < 0.05$ Fisher exact test.

Acute renal dysfunction = presence of oliguria (< 500 ml/day), increased serum creatinine (30% from preoperative value); Respiratory support = mechanical ventilation or continuous positive airway pressure; Cardiovascular = hypotension requiring pharmacologic therapy, arrhythmias requiring pharmacologic therapy or cardiogenic pulmonary edema; Chest infection = clinical diagnosis accompanied by an increase in leukocyte count above the normal range; PONV = postoperative nausea or vomiting; Coagulopathy = platelet count < 100,000/l, prothrombin time > 1.5 times control, activated partial thromboplastin time > 1.5 times control, and/or fibrinogen < 100 mg/dl; Wound infection = clinical diagnosis, positive wound culture results, or increase in leukocyte count.

of hospital stay following cardiac surgery. No patients in the treatment group developed major complications compared with six in the control group. The mean hospital stay was also shorter in the treatment group (6.4 vs. 10.1 days; $P = 0.01$). This improvement in outcome could potentially reduce healthcare costs. The results from these two studies are consistent with our findings and suggest that proactive intraoperative fluid administration can improve postoperative recovery in patients undergoing moderate- to high-risk surgery. However, this study does not address if optimal fluid administration without the EDM would result in similar benefits. This requires further investigation. Nevertheless, intraoperative fluid augmentation appears to confer significant benefits compared with customary practice.

In the current study, we have also demonstrated that routinely measured standard cardiovascular variables such as blood pressure, heart rate, and oxygen saturation were unreliable indicators of mild hypovolemia. This has been previously demonstrated.^{3,4} The immediate response to a reduction in circulating blood volume is redirection of blood flow from less vital organs, *e.g.*, splanchnic bed, in favor of organs that are more sensitive to ischemia.²¹ The measurement of normal central venous pressure or pulmonary arterial occlusion pressure will not exclude hypovolemia unless the response to a fluid challenge is considered.²² Baek *et al.*²³ found that more than half of a group of high-risk postoperative patients developed a decrease in central venous pressure and pulmonary arterial occlusion pressure in response to plasma volume expansion. While we only studied patients with no known history of congestive cardiac failure, it would not be possible to speculate if fluid administration guided by EDM would have a detrimental effect on patients with compromised myocardial function or perfusion.

There are limitations in this study. While the data were collected by independent dedicated research personnel not involved in the intraoperative management of patients, we were unable to blind the anesthesiologists as to the treatment group, and hence may have introduced bias. However, intraoperative fluid administration in both groups was guided by specific fluid administration protocols, which should minimize bias. It is conceivable that the use of certain medications intraoperatively as well as postoperatively may have influenced bowel function (*i.e.*, postoperative epidural analgesia, intraoperative nitrous oxide, and postoperative opioid). Nitrous oxide was used in all patients. There was no difference in the number of patients who received epidural or patient-controlled analgesia between the groups, and the pain scores and opioid use were similar. All patients were visited daily in the postoperative period, and all adverse events were systematically collected. Patients in the protocol group also received, on average, larger volumes of hetastarch compared with the control group,

as we wanted the control group to simulate as close as possible to receive "standard of care." Hence, the differences between the groups could be attributed to the differences in the type of fluids administered. While there were five more females in the control group compared with the protocol group, these differences were not statistically significant. The overall difference in hospital length of stay between the groups was admittedly small, a difference of 1 day (median) or 2 days (mean). These differences could be a result of unidentified group differences and factors other than goal-directed fluid administration.

In summary, for patients undergoing moderate- and high-risk surgery, goal-directed fluid administration with 6% hetastarch is associated with improved patient outcome and a slight reduction in the length of hospital stay.

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