Journal of Surgical Research 173, 68–74 (2012)
doi:10.1016/j.jss.2010.08.051

Impact of Restrictive Intravenous Fluid Replacement and Combined Epidural Analgesia on Perioperative Volume Balance and Renal Function Within a *Fast Track* Program[1]

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Originally submitted June 9, 2010; accepted for publication August 27, 2010

Background and Objective. **Key factors of *Fast Track* (FT) programs are fluid restriction and epidural analgesia (EDA). We aimed to challenge the preconception that the combination of fluid restriction and EDA might induce hypotension and renal dysfunction.**

Methods. **A recent randomized trial (NCT00556790) showed reduced complications after colectomy in FT patients compared with standard care (SC). Patients with an effective EDA were compared with regard to hemodynamics and renal function.**

Results. **61/76 FT patients and 59/75 patients in the SC group had an effective EDA. Both groups were comparable regarding demographics and surgery-related characteristics. FT patients received significantly less i.v. fluids intraoperatively (1900 mL [range 1100–4100] *versus* 2900 mL [1600–5900], $P < 0.0001$) and postoperatively (700 mL [400–1500] *versus* 2300 mL [1800–3800], $P < 0.0001$). Intraoperatively, 30 FT compared with 19 SC patients needed colloids or vasopressors, but this was statistically not significant ($P = 0.066$). Postoperative requirements were low in both groups (3 *versus* 5 patients; $P = 0.487$). Pre- and postoperative values for creatinine, hematocrit, sodium, and potassium were similar, and no patient developed renal dysfunction in either group. Only one of 82 patients having an EDA without a bladder catheter had urinary retention. Overall, FT patients had fewer postoperative complications (6 *versus* 20 patients; $P = 0.002$) and a shorter median hospital stay (5 [2–30] *versus* 9 d [6-30]; $P <$ 0.0001) compared with the SC group.**

Conclusions. **Fluid restriction and EDA in FT programs are not associated with clinically relevant hemodynamic instability or renal dysfunction.**

Key Words: **enhanced recovery; *fast track*; epidural analgesia; fluid restriction; hemodynamics; renal function.**

INTRODUCTION

Optimal fluid management represents a key issue of perioperative care of patients undergoing major abdominal surgery. The successful advent of *fast track* (FT) programs has provided new aspects to the ongoing debate of perioperative fluid management [1–6].

Traditional fluid management aims to maintain blood pressure and heart rate in order to prevent hypovolemia-induced chances of microcirculation that may be associated with organ dysfunction [6, 7]. As a consequence, patients generally have a postoperative fluid overload that is reflected by a significant weight gain [1, 6, 8].

So called FT concepts or enhanced recovery after surgery (ERAS) programs have been increasingly implemented into clinical practice during recent years. By limiting patients' perioperative stress response, postoperative complication rates and length of hospital stay can be reduced [2, 3, 5]. FT programs are primarily based on the use of epidural analgesia (EDA) to minimize opioid consumption, restrictive perioperative fluid management, early postoperative oral nutrition, and early ambulation [2, 3, 5, 9, 10].

[1] PODIUM presentation (S63) at the 2009 ASCRS Annual Meeting, May 2–6, 2009, Hollywood, Florida.
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0022-4804/$36.00

The beneficial effects of thoracic EDA on pain reduction, pulmonary complications, and postoperative intestinal motility have largely been demonstrated [11–19]; drawbacks are transient arterial hypotension in about 10%, pruritus and urinary complications [14, 18–21]. However, the impact of a restrictive fluid management on organ function is still under debate, and opponents are concerned for hypovolemia-induced organ dysfunction like renal insufficiency, myocardial ischemia, and impaired wound healing [6, 7]. On the other hand, excessive perioperative fluid administration may exert deleterious effects on cardiopulmonary function, and prolong postoperative bowel arrest [1, 6, 22–25]. In fact, there is increasing evidence in the literature that restrictive fluid regimens are favorable to reduce cardiopulmonary complications and enhance postoperative recovery without compromising wound healing [1, 3, 5, 6, 9, 22, 23, 25, 26].

We were recently able demonstrate that patients undergoing elective open colonic surgery have a significantly reduced complication rate, if they were included in a FT program [27]. The two independent predictors for low postoperative complications were an efficient EDA and perioperative fluid restriction [27]. As outlined before, restrictive fluid management and EDA may both lead individually to arterial hypotension, renal dysfunction, and electrolyte disturbance. Their combined impact has not yet been examined in detail. Since this multicentric prospective randomized trial provided precise data on different organ function, we performed for the present study a *post hoc* analysis in patients with an efficient EDA.

We aimed to assess whether additional fluid restriction had a negative impact on preservation of hemodynamics and renal function in patients having an effective EDA. Furthermore, electrolyte disturbances as well as clinical outcome were separately assessed.

METHODS

A prospective randomized trial (NCT00556790) assessing a FT regimen *versus* standard care (SC) was performed in 156 patients undergoing open elective colon resection at four surgical departments in Switzerland (Fig. 1) [27].

Patients in the SC group received a fixed restricted fluid regime according to institutional guidelines that were based on established recommendations [6, 28]. They received Ringer's lactate at 2 mL per kg bodyweight per h for preoperative loading, and 10 mL per kg bodyweight per h during the surgery, respectively. The actual bodyweight was measured usually the day before surgery. In the FT group, preoperative fasting (nil per mouth) time was 2–6 h for clear liquids. Loading volume to compensate external and internal loss caused by preoperative fasting, vasodilatation, and epidural analgesia (pre-block hydration) was performed by using Ringer's lactate solution at 1 mL per kg bodyweight per h. Intraoperatively, crystalloid fluid administration was limited to 5 mL per kg bodyweight per h. Preoperative fluid loading according to the reported formulas was initiated upon entry in the operation room area. The epidural catheter was habitually placed before induction of general anesthesia; therefore, fluid loading was administered approximately 30–45 min prior to use of the EDA and for a total time of about 45–60 min before skin incision. Intravenous fluid administration in the FT group was discontinued at postoperative d 1, unless there were medical indications to do otherwise. In the SC group, patients received 2000 mL Ringer's lactate per 24 h until postoperative d 3.

Additional colloid fluids or low-dose vasopressors were given, when mean arterial pressure dropped permanently (>1 h or three consecutive measurements) below 60 mm Hg or urine output was (3×) lower than 0.5 mL/kg/h. Vasopressors were privileged in order to avoid fluid overload. Low-dose vasopressors were norepinephrine up to 5 μg/min or ephedrine at a bolus dose of 10–25 mg intravenously (maximum 150 mg/24 h). Blood transfusion was limited to a hematocrit <25%. Patients in the FT group were allowed to drink immediately after surgery and to resume an oral diet on postoperative d 1, while the SC group started drinking and oral nutrition on postoperative d 2 and full oral nutrition on postoperative d 4. An epidural catheter with ropivacaine 0.33% or bupivacaine 0.25% was placed at thoracic level 6–9 preoperatively and removed on postoperative d 2. For additional analgesia, paracetamol was given intravenously at a fixed rate (4 × 1 g/d). A failure of EDA (inefficient EDA) was defined by the need for additional intravenous opioids. Perioperative fluid administration was recorded for the first 24 h after surgery. At postoperative d 1, the urinary catheter was removed according to the study protocol.

Outcome of primary interest in the present study was perioperative vasopressor requirements and/or need for additional fluid administration indicating clinically relevant hemodynamic instability. Of note, patient's outcome was assessed in this study by a *per protocol* analysis; as we were interested in the effect of EDA with and without additional fluid restriction, we included only patients with an efficient EDA in the present subgroup analysis. Secondary outcome parameters included plasma concentrations of sodium, potassium, creatinine, and hematocrit values pre- and postoperatively that served as surrogate parameters for perioperative fluid shifts. Furthermore, perioperative creatinine values were used to assess for risk of renal dysfunction according to the AKIN classification system (RIFLE criteria) [29]. Postoperative complications (30-d morbidity) were graded according to its severity, and a validated therapy-orientated complication score on a five-point scale described was used [30].

Statistical analysis was performed using standard software package SPSS 14.0 (SPSS, Inc., Chicago, IL). Descriptive statistics are expressed as mean [± standard deviation] or median [range] as appropriate. The Mann-Whitney U test was used to compare continuous variables, Chi-square and Fischer's exact tests were used for comparison of discrete variables. P-value < 0.05 was considered statistically significant.

RESULTS

Overall, 156 patients were included in the study and randomly assigned to either FT (n = 78) or SC (n = 78). There were two patients in the FT group and three patients in the SC group who were excluded due to withdrawal or other protocol violation. Another 31 patients (FT: 15, SC: 16) were excluded in the present study for EDA failure. Finally, 61 out of 76 FT patients (80%) and 59 out of 75 SC patients (79%) had an effective EDA and were included in the present per protocol analysis (Fig. 1).

Patients' Characteristics

The FT and SC groups matched well regarding gender, body mass index, American Society of Anesthetists

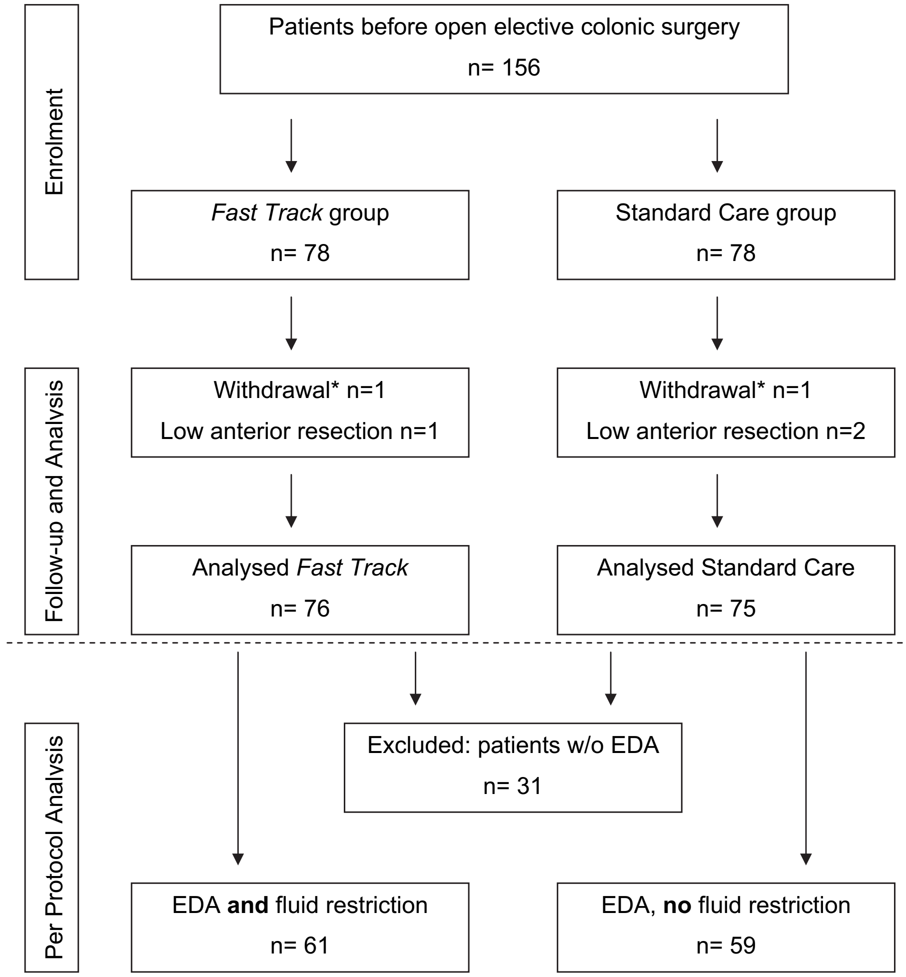

FIG. 1. Study flow chart. Patient flow of NCT00556790. For assessment of the combined effect of epidural analgesia (EDA) and fluid restriction on hemodynamics, a *per protocol* analysis was performed (below dotted line). The final analysis included 120 patients with a functional EDA; 61 of them had additionally a perioperative fluid restriction (*Fast Track*), while 59 had a traditional fluid management (Standard Care).

(ASA) class, indication for surgery, type and duration of the operation, as shown in Table 1. Patients in the FT group were slightly older (median of 62 y *versus* 59 in the SC group, $P = 0.037$). The vast majority of patients underwent colon resection for cancer (92% FT group, 85% SC group). Median operative times were 130 and 110 min for the FT group and SC group, whereby the difference was not statistically different. Median intraoperative blood loss was similar with 280 mL (0–1100 mL) in the FT group and 250 mL (0–1350 ml) in the SC group ($P = 0.544$).

Intraoperative and Postoperative Intravenous Fluid Replacement (Table 2, Fig. 2)

By adhering to the study protocol, FT patients received significantly less crystalloids intraoperatively compared to SC patients (median volume: FT group 1850 mL *versus* SC group 2900 mL; $P < 0.0001$). There were more FT patients who needed additional treatment by using colloids and/or vasopressors compared with the SC group to maintain intraoperative blood pressure and urinary output (FT group 30 of 61 patients, 49% *versus* SC group 19 of 59 patients, 32%; $P = 0.066$). Overall intraoperative fluid replacement was predominantly determined by crystalloid application.

During the postoperative course, the restrictive intravenous fluid regime was maintained in the FT group; hence, median fluid volume needed for FT patients was only 700 mL. SC patients received 2250 mL, and the difference was statistically significant ($P < 0.0001$). Overall, perioperative intravenous fluid replacement was 2600 and 4950 mL for FT patients and SC patients, respectively ($P < 0.0001$). Of note, FT patient were allowed to start drinking immediately after the operation. Only three of 61 FT patients and five of 59 SC patients ($P = 0.487$) needed a low dose vasopressor regimen to maintain mean arterial pressure and urine output, postoperatively. Two FT and two SC patients needed perioperative blood transfusions.

TABLE 1

Patient Demographics and Operation Characteristics

	FT	SC	*P*
No. of patients	61	59	
Gender (F/M)	41/20	49/10	0.472
Age (y)*	62 (27–91)	59 (39–89)	0.037
ASA 1+2/3+4	41/20	47/12	0.150
BMI (kg/m^2)	26 (18–33)	25 (19–35)	0.981
Indication: malignant/benign	56/5	50/9	0.266
Left/right-sided resection	40/21	39/20	1.000
Operating time (min)	130 (60–210)	110 (55–230)	0.112
Blood loss (mL)	280 (0–1100)	250 (0–1350)	0.544

Values are median (range) for age, BMI, operating time, and blood loss.

FT = *fast track*; SC = standard care; ASA score = American Society of Anesthetists; BMI = body mass index.

"Left" includes left hemicolectomy and rectosigmoid resection, "Right" includes right hemicolectomy and transverse resections.

*Statistical significance ($P < 0.050$).

Electrolyte Balance and Renal Function

Pre- and postoperative creatinine levels did not differ significantly and remained within the limits considered physiologic in both patient groups. No patient in either group had a creatinine increase of more than 10% postoperatively. Furthermore, no patient developed acute renal failure up to 30 d after surgery. Postoperative hematocrit values were slightly but significantly reduced in the SC group (median 38 *versus* 35%, $P < 0.0001$). Pre- and postoperative sodium levels were similar in FT patients (136.7 ± 3.6 mmol/L *versus* 136.4 ± 2.6mmol/L) compared with the SC group (138.0 ± 3.6 mmol/L *versus* 136.9 ± 2.8 mmol/L); potassium levels showed likewise only little variation (FT: 4.4 ± 0.5 mmol/L *versus* 4.3 ± 0.4 mmol/L; SC: 4.3 ± 0.7mmol/L *versus* 4.1 ± 0.5 mmol/L). Changes of creatinine and hematocrit expressed in median delta values (postoperative–preoperative value) showed significantly higher postoperative creatinine increase and hematocrit decrease in the FT group compared with SC group indicating relative intravascular hypovolemia (Fig. 3).

Complication Rates and Hospital Stay

Overall postoperative morbidity was 10% (6 of 61 patients) in the FT group compared with 34% (20 of 59 patients) in SC patients; and the difference was statistically significant ($P = 0.002$). Grades III and IV complications were two bleeding complications (FT: 1, SC: 1), two pulmonary embolisms (FT: 1, SC: 1), and one anastomotic leak (SC). Median hospital stay was significantly reduced in the FT group compared with the SC group with 5 d [2–30] *versus* 9 d [6–30] ($P < 0.0001$), respectively (Fig. 4).

According to the study protocol, urinary catheters were removed the morning of postoperative d 1 in 82 patients of both groups with a functioning EDA with only two complications: one urinary retention needing reinsertion of a catheter and one urinary tract infection. Comparatively, there was one urinary infection in the remaining 38 patients having their bladder catheter disconnected only after removal of the EDA.

DISCUSSION

Fluid overload negatively affects outcome after major abdominal surgery and has to be considered *versus* the risk of hypovolemic hypotension induced by overly restrictive fluid regimens [3, 6, 28]. Since enhanced recovery program recommend additional use of thoracic EDA, its sympathetic block might trouble hemodynamics even further [14, 18–21]. To assess the combined effect of these two measures, patients undergoing open colon resection within an enhanced recovery program have been analyzed in this present post hoc subgroup analysis [27].

We found that 30% and 10% of all patients had an intraoperative and postoperative arterial hypotension or reduced urinary output, respectively. A stringent fluid management had no additional significant adverse effect in patients with an EDA. Our findings confirm the analysis of Marret *et al.* that postoperative arterial hypotension is observed in approximately 10% of patients with EDA undergoing colorectal surgery [20].

TABLE 2

Intra- and Postoperative Intravenous Fluid Administration

	FT	SC	*P*
No. of patients	61	59	
Intra-OP crystalloids (mL)*	1850 (1100–3800)	2900 (1600–4900)	<0.0001
Post-OP crystalloids (mL)*	700 (400–1500)	2250 (1800–3800)	<0.0001
24 h fluids (mL)*	2600 (1800–4900)	4950 (3900–9700)	<0.0001

Values are median and range in brackets for intravenous fluids (mL).

FT = *fast track*; SC = standard care.

Intra-OP = intraoperative; Post-OP = postoperative.

*Statistical significance ($P < 0.050$).

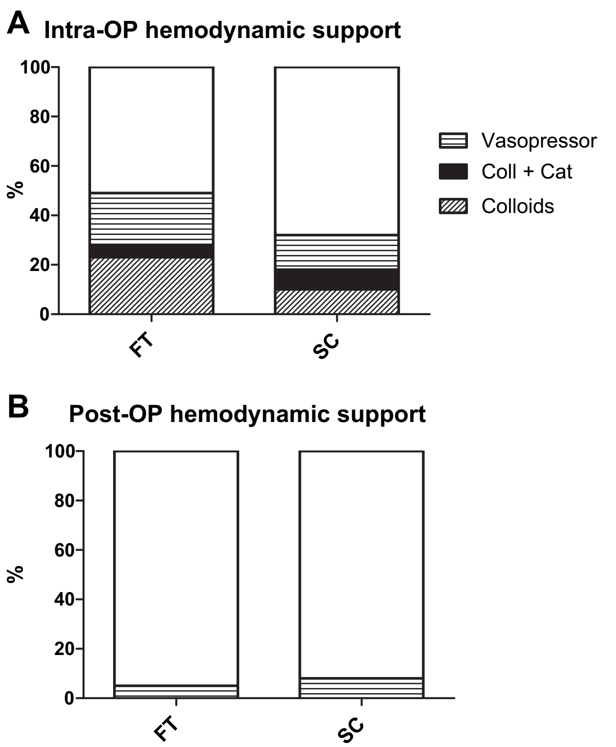

FIG. 2. Intra- and postoperative hemodynamic support. (A) Percentage of patients with intraoperative (intra-OP) need for colloids (shaded slope), vasopressors (shaded horizontally) or both (black). (B) Percentage of patients with postoperative (post-OP) need for vasopressors (shaded horizontally). FT = *fast track*; SC = standard care.

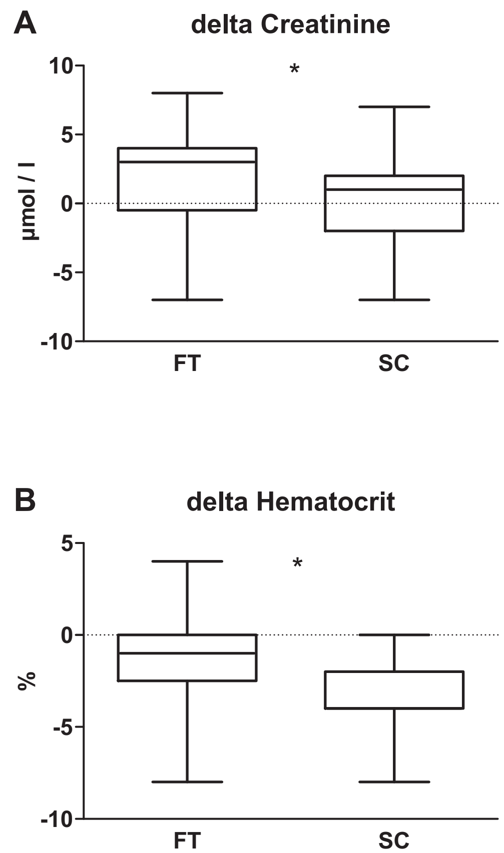

FIG. 3. Delta values for creatinine and hematocrit. Box plots with minimal and maximal differences (postoperative–preoperative) for creatinine (A) and hematocrit (B). FT = *fast track*; SC = standard care. *Statistical significance ($P < 0.050$).

Arterial hypotension was countered in all patients preferentially with vasopressors rather than crystalloid infusions in order to avoid further postoperative fluid overload, which has been shown to affect outcome after major abdominal surgery adversely [6, 31]. Indeed, patients with additional fluid restriction in the FT group had significantly reduced complications and shorter hospital stay. Several prospective clinical trials, including this study, have shown that avoidance of fluid overload in combination or without a FT program primarily decreases nonsurgical complications and disturbance of wound healing [1, 6, 8, 26, 27, 32]. It was found that crystalloid fluids had negatively affected cardiopulmonary function in healthy volunteers [33]. Measures to minimize a preoperative hypovolemic state by reducing preoperative fasting to a minimum for example, or avoiding perioperative hypovolemia seem necessary in FT programs [3, 5, 10, 23].

Alternatively to a stringent fluid regime, some groups propagate a goal directed plasma volume expanding fluid administration controlled by esophagus Doppler or pulse contour analyzed cardiac index [6, 7, 34, 35]. However, its clinical applicability is demanding and the benefit of these work-intensive algorithms and invasive tools compared with simple dogmatic restrictive crystalloid based fluid regimes in colonic surgery has not been shown yet.

FT patients showed a significantly higher increase in their postoperative creatinine level compared with the SC group. However, no patient in either group appeared to be at risk of renal dysfunction according to the AKIN classification system (RIFLE criteria), as none showed a creatinine increase of more than 10% postoperatively in either group [29]. Furthermore, the absolute difference of only 2.0 μmol/L may not be clinically relevant, but may rather reflect a dilution effect of the liberal compared with the restrictive fluid management. This assumption is supported by a slightly more pronounced decrease of the postoperative hematocrit value in the SC group despite similar blood loss. Finally, no postoperative renal failure occurred up to 30 d after surgery.

Since an EDA at the thoracic level 6–9 without a urinary catheter was not associated with higher urinary retention rate, our results suggest that prolonged urinary catheterization is not necessary. These findings are confirmed by a prospective study by Basse *et al.* [36].

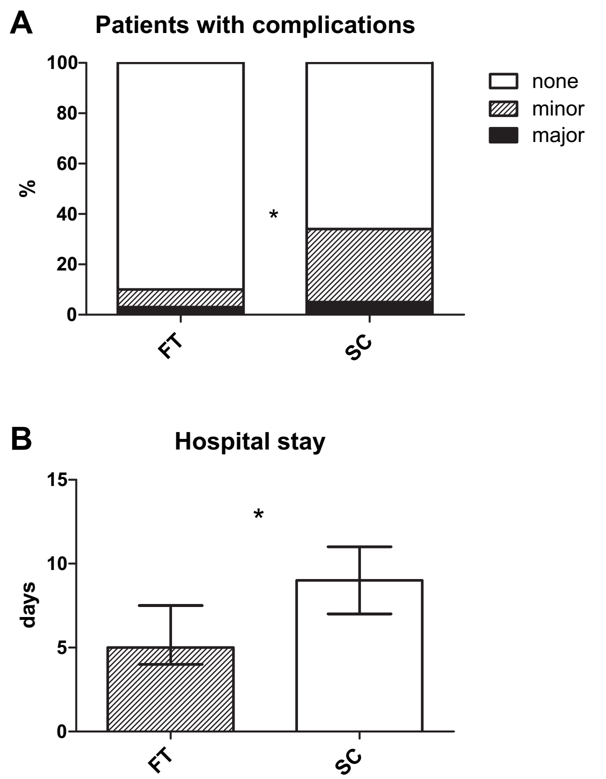

FIG. 4. Clinical outcome measures. (A) Percentage of patients with minor (shaded) and major (black) complications. Major complication is defined as ≥3b according to [30]. (B) Median hospital stay with interquartile range (error bars). FT = *fast track*; SC: standard care. *Indicates statistical significance ($P < 0.050$).

Several issues of the present study need to be discussed. First, randomized data should usually be analyzed according to the intention-to-treat principle to obtain results that are realistic and generalizable. Therefore, intention-to-treat analysis was performed to compare complications and hospital stay between FT and SC patients [27]. However, a per protocol analysis gives a more accurate estimate of perioperative hemodynamic instability in patients with an effective EDA with different fluid replacement regimens; therefore, the present analysis was performed per protocol. Further, the sample size was calculated for an assumed reduction of postoperative complications [27], and might be insufficient to control type II error regarding the outcome measures addressed in this study. However, 120 patients constitute a fair number in a field, where randomized data are still pretty scarce.

In conclusion, avoiding perioperative fluid overload and an effective EDA are key factors in decreasing postoperative complications within an enhanced recovery program. Adding a stringent fluid regimen to a functional EDA appears to have only marginal impact on hemodynamic stability and renal function being of little clinical relevance.

ACKNOWLEDGMENTS

MH, SM, PAC, and ND have received research support and/or lecture fees from Fresenius-Kabi, Switzerland.

Contributors for the Zurich Fast Track Trial Group are as follows: Sven Müller, Martin Hübner, Nicolas Demartines, Department of Visceral Surgery, CHUV, Lausanne and formerly Visceral and Transplant Surgery, University Hospital Zurich; Pierre A. Clavien, Visceral and Transplant Surgery, University Hospital Zurich; Marco P. Zalunardo, Konrad Maurer, Baulig Werner, Institute of Anesthesiology, University Hospital Zurich; Marco Decurtins, Department of Surgery, Kantonsspital Winterthur; Lukas Eisner, Department of Surgery, Kantonsspital Olten; Italo Castelli, Department of Anesthesiology, Kantonsspital Olten; Hans P. Keller, Department of Anesthesiology, Kantonsspital Winterthur; Igor Langer, Department of Visceral Surgery, CHUV, Lausanne; Hans Gelpke, Felix Grieder, Department of Surgery, Kantonsspital Winterthur; Thorsten Carstensen, Andreas Gehrz, Department of Surgery, Kantonsspital Olten; Thierry Spahr, Institute of Anesthesiology, University Hospital Zurich; Reto Paganoni, Department of Anesthesiology, Kantonsspital Olten.

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