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ORIGINAL ARTICLE

The impact of different infusion solutions on postoperative recovery following colorectal cancer surgery

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Summary

Purpose: *The purpose of this study was to compare two groups in postoperative recovery, whether there were any complications and whether the length of their hospital stay differed. One group received intraoperatively a combination of crystalloids and a small colloid dose, while the other group received only the crystalloids intraoperatively.*

Methods: *This randomized prospective study included 80 patients with colorectal cancer prepared for major elective colorectal surgery. The patients were randomly assigned to either the control group (CG) which received only crystalloid solutions intraoperatively or to the research group (RG) which received a combination of colloid and crystalloid solutions. Regional and general endotracheal anesthesia techniques were combined in all patients. Goal-directed fluid therapy was administered to patients in both groups. After extubation, patients were transferred in the Intensive Care Unit (ICU). We measured the administered fluids, fluid balance, the volume of received red packed cells (RPC) and fresh frozen plasma (FFP). Recorded were the first bowel movement, the first flatus, the tolerance on oral food, complications by Clavian-Dindo classification, days of patient's recovery delay in the ICU, Surgery Department (SD) and the total length of hospital stay (LOS).*

Results: *Statistically significant differences were present in all parameters of postoperative recovery. RG patients showed better results relative to the CG patients. RG patients were faster in restoring bowel movement and peristalsis, get the first postoperative stool and re-acquire oral food tolerance. According to the Clavian-Dindo classification of complications, no significant difference between these two groups was noted.*

Conclusions: *Goal-directed colloid-crystalloid therapy significantly improved postoperative recovery.*

Key words: *colorectal surgery, goal-directed fluid therapy, infusion solutions, LOS, peristalsis, postoperative recovery*

Introduction

Perioperative fluid therapy and its impact on postoperative recovery has been studied extensively, but the optimal type and volume of infusion solutions remains controversial and uncertain.

Colorectal surgery and bowel resection secondary to colorectal cancer is followed by a notable loss of fluids. Intravenous fluid therapy is integral and a lifesaving part of the treatment. The primary goal of intraoperative fluid administration is to ensure adequate circulating volume, which will in turn ensure adequate blood circulation, tissue perfusion and oxygenation. Improved tissue perfusion and

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oxygenation may prevent the progression of tissue oxygen deficit and hence reduce the frequency of complications and organ dysfunction [1].

The cause of insufficient blood circulation and perfusion is an inadequate type and volume of fluid administration. It is clinically recognized as either hypovolemia or fluid overload.

Hypovolemia is common among patients scheduled for surgery. In addition to the inevitable fluid loss 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 at the very least 6 hrs preoperatively so as to reduce the risk of acid aspiration syndrome. Hypovolemia during perioperative period leads to insufficient circulation, decreased oxygen delivery to organs and peripheral tissues, causing organ dysfunction and shock, and prolongation of hospital stay. Apart from the damage to other tissues, hypovolemia also results in an intra-mucosal acidosis of the gut [2], leading to impairment of postoperative gastrointestinal function and causing complications [3]. Gastrointestinal dysfunction is the most frequent cause of a prolonged hospital stay [4].

Fluid overload, on the other hand, leads to interstitial edema and local inflammation and it impairs the regeneration of collagen, thereby weakening the tissue healing which increases the risk of postoperative wound infections, wound ruptures, and anastomotic leakage [5]. Apart from these reasons for impaired wound healing, there are other causes such as malnutrition (lower prognostic nutritional index) [6], age, body mass index (BMI) and surgical technique.

In a study conducted by Kulemann et al., it was shown that the excessive intraoperative intravenous administration of crystalloids promoted inflammation and accelerated collagenolysis in rats. These findings suggest that unrestrained administration of intravenous crystalloids induces adverse inflammatory responses and compromises wound healing [7]. Both crystalloids and colloids increase intestinal blood flow and systemic arterial pressure, but colloids may have longer duration effect. The duration of plasma volume expansion produced by each colloid is governed by the rate of loss of colloid molecules from the patient's circulation and metabolism. Indicators of magnitude and duration of plasma volume expansion (PVE) are the intravascular half-life and the fraction of administered volume retained within the circulation after a specific time. Ninety minutes after the administration of one liter of Hydroxyethyl Starch (HES) solution produces a PVE of 0.7-0.8 liters [8]. The predominant effect of colloid solutions is based on the change in blood rheology. Colloids reduce blood viscosity by simple hemodilution, and thus, improve blood flow characteristics [9]. The magnitude of this effect is proportional to the degree of plasma volume expansion and is therefore initially greater for the lower molecular weight (130,000–150,000 Dalton) of HES which produces a large initial increment in intravascular volume and, therefore, a larger hemodilution effect. Thus, the volume expansion effect of colloids is based on their constitution, not on their volume.

The use of colloids also results in a net movement of fluids from the intestinal lumen to the blood, whereas crystalloids can exacerbate transmucosal fluid movement into the intestinal lumen. According to some authors, there is a theoretical advantage of using colloids in the perioperative period as lower volumes are needed to achieve similar haemodynamic endpoints, resulting in reduced tissue edema and greater anastomotic integrity [10].

Intraoperative fluid resuscitation with predominantly colloids appears to improve the quality of postoperative recovery compared to crystalloids. Recent evidence suggests that colloid resuscitation may result in less edema and a better quality of recovery in the postoperative period. Specifically, these patients had a lower frequency of nausea, vomiting and severe pain, which could be explained by the lower degree of tissue edema [11].

The lack of agreement on how to define and grade postoperative complications has generated a new classification of complications. Based on the type of therapy needed to correct the complication, Clavian and Dindo established a simple and applicable new classification principle [12,13].

Previous studies usually compared postoperative outcomes between crystalloid and colloid use in cases where patients were critically ill. Our idea was to evaluate whether a difference in appearance of postoperative complications in surgical population exists after attaching a small dose of colloid solution and crystalloids during surgery. The recommended dose of 6% HES 130/0.4 ranges from a maximum of 33 ml/kg per day to a maximum of 50 ml/kg per day [14].

In our study we used the dose of 10 ml per kg of body mass.

Correction of anemia in case of patients with resectable gastrointestinal malignancy is mandatory, because it improves surgical stress response, wound healing process and quality of life. The hemoglobin (Hgb) and hematocrit (Hct) values, the patient's age and performance status, cardiovascular and pulmonary reserves should be taken into account prior to any attempt of perioperative correction of anemia [15].

For proper tissue oxygenation, especially for the surgical patient, it is crucial to keep the baseline Hgb level. In every day clinical practice, correction of anemia is usually based on Hgb values. It can be seen from previous experience that the majority of healthy persons could tolerate surgical stress with Hgb value higher than 10 g/dL, whereas in case of younger patients preoperative Hgb values of 6-7 g/dL are sufficient. In instances of coexisting conditions, such as impaired cardiopulmonary function, renal, liver or vascular diseases, it is of utmost importance to keep the Hgb level above 10 g/dL [16,17].

The aim of this study was to compare two groups in postoperative recovery, whether there were any complications and whether the length of their stay in hospital differed. One group received intraoperatively a combination of crystalloids and a small colloid dose, while the other group received only the crystalloids intraoperatively. The main hypothesis is that combined solutions are superior to those containing only crystalloids in achieving better postoperative outcomes and shorter postoperative hospital stay.

Many clinical experts use the combination of these fluid types in everyday practice. However, no studies provide evidence on benefits or complications regarding this kind of fluid therapy.

According to suggestions for fluid replacement, we used a hemodynamic algorithm for the Goal-Directed fluid therapy based on the optimization of stroke volume (SV) [18,19], intraoperatively and then 24 hrs after the operation. Goal-Directed fluid therapy is based on the use of esophageal Doppler monitor for perioperative fluid replacement. Esophageal Doppler monitor is a Food and Drug Administration–approved device that permits rapid, minimally invasive, continuous estimation of cardiac output and continuous monitoring of blood circulation [20].

Several meta-analyses suggest that individualized Goal-Directed fluid therapy can reduce organ-specific complications in cases where patients undergo major surgery [21-23].

Methods

Study design

This prospective randomised study included 80 patients with colorectal cancer. They underwent surgical treatment at the Oncology Clinic of the Institute for Oncology and Radiology of Serbia, situated in Belgrade.

After this project was approved by the ethics committee of the School of Medicine, University of Belgrade, written consents were collected from 80 patients with American Society of Anesthesiologists (ASA) physical status I, II, or III who were to undergo major elective colorectal surgery with an anticipated blood loss of 500 ml or higher.

The criteria for the study inclusion were the following: patients with colon cancer, elective surgery, consent to participate in the study, ASA class 1, 2 or 3, over 18 years of age.

Patients who were not eligible for the study inclusion: younger than 18, in need of an urgent operation, coagulopathies, significant cardiac, hepatic and/or renal impairment, patients with esophageal pathology (to avoid potential complications of the esophageal probe), ASA score over 3, and patients who wanted to withdraw from the study or refused to participate.

Patients

The patients were randomly assigned to either the control group (CG) or the research group (RG). This process was carried out by a computer generated program package. Subjects in the CG received only crystalloid solutions (Solutio Hartman, B Braun, Germany) intraoperatively. Patients in the RG first received colloid (6% Hydroxyethyl Starch 130/0.4 6g in 100mL, Fresenius Kabi, Norway) at a dose of 10mg/kg of body mass and then they were given the crystalloid solution (Solutio Hartman) until the end of the operation.

The patients were pre-medicated 30 min before the administration of anesthesia, then warmed for 15 min and received 500 ml of the crystalloid solution.

In all patients, the anesthesia technique was combined (regional and general endotracheal).

Anesthesia

Propofol was administered for anesthesia induction, while we used rocuroniumin so as to facilitate tracheal intubation and keep the muscles relaxed. Anesthesia was maintained with sevofluran, analgesia was maintained by continuous application of 0.25% chirocaine through epidural catheter and low doses of remifentanyl intravenously. The patients were mechanically ventilated and warmed during surgery in order to maintain physiological central body temperature. A nasogastric probe, esophageal Doppler probe, temperature probe, central venous catheter and arterial line were used in all patients.

Having used the hemodynamic algorithm for fluid resuscitation, the CG patients were given only the crystalloid solution (Solutio Hartman). On the other hand, we started with the colloid boluses in the RG (6% Hydroxyethyl Starch). The assigned dose of colloids was 10ml/kg, and when it was spent, the fluid infusion continued with Hartman solution until the end of the operation.

RPC and FFP were used according to indications for them.

Patients were extubated, either in the operating room or postoperatively in the ICU, after they had fulfilled standard clinical criteria (adequate protective reflexes, adequate oxygenation, and stable hemodynamics). In the immediate postoperative period, they were visited daily by independent research personnel which was unaware of the patients' group (assigned at random)

up until the patients were discharged from hospital. During the visit, the patients were asked specific questions and inspected on different occurrences and presence of bowel movement. Those who have had bowel movement were put on oral fluids, followed by solid food (if tolerated without emetic symptoms within 4 hrs).

We kept track of fluids administered intraoperatively, fluid balance 24 and 48 hrs after surgery, the number of patients who received RPC, FFP, and measured the volume of RPC and FFP in those patients needed intraoperatively and postoperatively. Complications using the Clavian-Dindo classification, which is based on the type of therapy needed to correct complications were recorded.

Also, the number of days patients stayed in ICU, SD and total LOS were recorded.

Table 1. Patient characteristics and comorbidity at baseline

Characteristics	*Descriptive data*			*p value*
	Whole group n (%)	*Control group n (%)*	*Research group n (%)*	
Gender				ns[2]
Male	43 (53.8)	26 (61.9)	17 (44.7)	
Female	37 (46.3)	16 (38.1)	21 (55.3)	
Age (years)				ns[1]
Mean (SD)	63.2 (12.4)	63.2 (13.4)	63.18 (11.3)	
Median (range)	64 (23-86)	64.5 (24-81)	63.5 (23-86)	
BMI (kg/m^2)				ns[1]
Mean (SD)	25.9 (3.9)	25.6 (3.9)	26.2 (3.9)	
Median (range)	26.2 (18.3-37)	26.2 (18.3-33.7)	26.1 (19.8-37.0)	
ASA status				ns[3]
I	13 (16.3)	10 (23.8)	3 (7.9)	
II	40 (50)	17 (40.5)	23 (60.5)	
III	27 (33.8)	15 (35.7)	12 (31.6)	
Comorbidity (presence of types)	55 (68.8)	29 (69.1)	26 (68.4)	ns[2]
Cardiac comorbidity	48 (60)	25 (59.5)	23 (60.5)	ns[2]
Hypertension	44 (55)	23 (54.8)	21 (55.3)	ns[2]
Angina pectoris	6 (7.5)	2 (4.8)	4 (10.5)	ns[3]
Myocardial infarction	4 (5)	2 (4.8)	2 (5.3)	ns[3]
Percutaneous coronary intervention	2 (2.5)	1 (2.4)	1 (2.6)	ns[3]
Atrial arrhythmias	4 (5)	1 (2.4)	3 (7.9)	ns[3]
Ventricular arrhythmias	5 (6.3)	3 (7.1)	2 (5.3)	ns[3]
Compensated heart insufficiency	7 (8.8)	2 (4.8)	5 (13.2)	ns[3]
Cerebrovascular insult	2 (2.5)	1 (2.4)	1 (2.6)	ns[3]
Chronic obstructive pulmonary disease	11 (13.4)	4 (9.5)	7 (18.4)	ns[3]
Restrictive pulmonary disease	-	-	-	-
Endocrine and metabolic disease	18 (22.5)	11 (26.2)	7 (18.4)	ns[3]
Diabetes mellitus				
Insulin dependent	12 (15)	7 (16.7)	5 (13.2)	ns[2]
Insulin independent	3 (3.8)	1 (2.4)	2 (5.3)	ns[3]
Hypothyroidism	6 (7.5)	4 (9.5)	1 (2.6)	ns[3]
Hematological disease	2 (2.5)	1 (2.4)	1 (4)	ns[3]
Psychiatric disease	6 (7.5)	3 (7.1)	3 (7.9)	ns[3]
Lee's revised cardiac risk index				ns[3]
II	61 (76.3)	33 (78.6)	28 (73.7)	
III	14 (17.5)	7 (16.7)	7 (18.4)	
IV	5 (6.3)	2 (4.8)	3 (7.9)	
Total patients	80	42 (100)	38 (100)	-

BMI: body mass index, ASA: American Society of Anesthesiologists, ns: not statistically significant, [1]Wilcoxon rank sum test, [2]Pearson's chi-square test, [3]Fisher's exact test

Statistics

Summary statistics (frequencies, percents, mean, median, standard deviation, and range) were used for data description. Statistical tests were used for normality data testing (Kolmogorov–Smirnov;Shapiro-Wilk) and for comparison between control and research group (Wilcoxon rank sum, Pearson's chi-square and Fisher's exact test). The statistical level of significance was set at $p<0.05$ and the Bonferroni correction was used for multiple testing at the same set of data. Methods of survival analysis were used for ICU stay, Surgery Departament stay and LOS evaluation: Kaplan-Meier product-limit method; median of survival analysis with corresponding 95% CI; log-rank test.

The statistical analyses were done with the program R (version 3.3.2 (2016-10-31) -- "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit); downloaded: January 21, 2017).

Results

Out of all 80 participants who took part in the study 53.8% were men and 46.2% women. The average age of all participants was 63.2 years, the average BMI was 25.9 kg/m^2 and the most common ASA status was II (50% of all the patients).

68.8% of patients had no comorbidity, whereas 60% were with cardiac comorbidity, and 55% with arterial hypertension.

Assumed surgical risk assessment for major cardiac event, according to Revised Lee risk Score was low (class 2, 0.9%) for 76.3% of the patients (Table 1).

The CG with 42 and the RG with 38 patients were homogeneous at all baseline characteristics and concomitant diseases (Table 1).

The average duration of anesthesia in the whole group was 136.2 min, and the average duration of surgery was 117 min. Out of all patients, 27.5% had previous surgery, 36.3% received neoadjuvant chemotherapy and 11.3% were subjected to preoperative radiation.

There was no statistically significant difference in the duration of anesthesia and surgery between the two groups.

The groups did not differ significantly in terms of number of patients who had previously had gynecological or liver surgery apart from colorectal surgery. We did not find any difference between groups when it came to the frequency of patients who had neoadjuvant chemotherapy, preoperative radiation or previous surgery (Table 2).

The average volume parameter of crystalloids in the whole group was 2796 ml, fluid balance for 24 hrs was 1169 ml and 4014ml for 48 hrs. Out of all patients, RPC was administered to 12.5% intraoperatively, to 18.8% 6 hrs postoperatively, and FFP to 10% of patients 24 hrs after the operation (Table 3).

The volume of crystalloids spent intraoperatively was significantly lower in the RG in contrast to the CG (Table 3).

Fluid balance was also significantly lower in the RG compared to the CG 24 hrs following surgery, and 48 hrs after surgery this difference disappeared (Table 3).

We did not find any notable difference in the frequency of patients who received RPC (intraoperatively, 6 hrs, 24 hrs postoperatively), or in volume of RPC (intraoperatively, 6 hrs, 24 hrs postoperatively; Table 3), though it should be noted that the difference in transfused RPC volume 24

Table 2. Earlier operation, preoperative and surgery characteristics

Characteristics	*Descriptive data*			*p value*
	Whole group n (%)	*Control group n (%)*	*Research group n (%)*	
Earlier operation	22 (27.5)	8 (19.1)	14 (36.8)	ns[2]
Preoperative treatment				
With neoadjuvant chemotherapy	29 (36.3)	15 (35.7)	14 (36.8)	ns[2]
With preoperative radiation	9 (11.3)	4 (9.5)	5 (13.2)	ns[3]
Anesthesia duration (min)				ns[1]
Mean (SD)	136.2 (52.8)	140.1 (54.26)	131.8 (50.1)	
Median (range)	120 (60-340)	120 (60-340)	120 (60-300)	
Surgery duration (min)				ns[1]
Mean (SD)	117 (52.2)	119.5 (51.6)	114.2 (53.5)	
Median (range)	107.5 (20-320)	110 (30-320)	102.5 (20-280)	
Colorectal and gynecological surgery	8 (10)	5 (11.9)	3 (7.9)	ns[3]
Colorectal and liver surgery	15 (18.8)	7 (16.7)	8 (21.1)	ns[2]

ns: not statistically significant, [1]Wilcoxon rank sum test, [2]Pearson's chi-square test, [3]Fisher's exact test

Table 3. Use of red packed cells and fresh frozen plasma during and after surgery

Fluid balance, blood and derivatives	*Descriptive data*			*p value*
	Whole group	*Control group*	*Research group*	
Intraoperative volume of crystalloids				<0.01[1]
Mean (SD)	2796 (1386.1)	3433 (1195.5)	2091 (1243.69)	
Median (range)	2925 (100-8400)	3500 (800-8400)	1650 (100-5800)	
Fluid balance after surgery				
24 hours after surgery (ml)				<0.01[1]
Mean (SD)	1169 (1360.5)	1541 (1220.42)	758.5 (1404.08)	
Median (range)	1062 (-1100-6055)	1292 (-1000-4800)	410 (-1100-6055)	
48 hours after surgery (ml)				ns[1]
Mean (SD)	4014 (7616.04)	-62.74 (1447.81)	-538.2 (1040.96)	
Median (range)	3000 (1000-7700)	-415 (-2350-5370)	-490 (-4200-1500)	
Red packed cells (RPC) transfusion				
With intraoperatively RPC, n (%)				ns[2]
Volume of transfused RPC	10 (12.5)	5 (11.9)	5 (13.16)	ns[1]
Mean (SD)	389.5 (249.4)	234 (22.75)	545 (281)	
Median (range)	252.5 (200-1000)	240 (200-260)	525 (235-1000)	
With RPC 6h after surgery, n (%)				ns[2]
Volume of transfused RPC	15 (18.8)	10 (23.81)	5 (13.16)	ns[1]
Mean (SD)	414.7 (177.9)	385 (137.51)	464 (236.05)	
Median (range)	505 (22-660)	420 (200-530)	550 (220-660)	
With RPC 24h after surgery, n (%)				0.051[3]
Volume of transfused RPC	11 (13.8)	9 (21.43)	2 (5.26)	ns[1]
Mean (SD)	337 (240.6)	358.1 (268.06)	252.5 (17.68)	
Median (range)	252.5 (220-1000)	247.5 (220-1000)	252.5 (240-265)	
With fresh frozen plasma use , n (%)				
Intraoperatively	3 (3.8)	-	3 (7.89)	ns[3]
Use after 6 hrs	6 (7.5)	3 (7.14)	3 (7.89)	ns[3]
Use after 24 hrs	8 (10)	6 (14.29)	2 (5.26)	ns[3]

ns: not statistically significant, RPC: red packed cells, ns: not statistically significant, [1]Wilcoxon rank sum test, [2]Pearson's chi-square test, [3]Fisher's exact test

Table 4. Postoperative recovery

Postoperative recovery characteristics in days	*Whole group*	*Control group*	*Research group*	*p value (Wilcoxon test)*
First flatus				<0.01
Mean (SD)	3.4 (1.3)	3.5 (1.3)	2.4 (1.0)	
Median (range)	3 (2-8)	3 (2-7)	2 (1-6)	
Peristaltic restoration				<0.01
Mean (SD)	3 (1.3)	3.7 (1.4)	3 (1.1)	
Median (range)	3 (1-7)	3 (2-8)	3 (2-7)	
First stool				<0.01
Mean (SD)	3.7 (1.5)	4.1 (1.6)	3.3 (1.3)	
Median (range)	3 (1-8)	4 (2-8)	3 (1-7)	
POF tolerance				<0.01
Mean (SD)	3.7 (1.3)	4.1 (1.4)	3.2 (1.0)	
Median (range)	3 (2-8)	4 (3-8)	3 (2-7)	

SD: standard deviation

hrs after operation was near statistical significance (p=0.051; Table 3).

No significant difference between the groups in the frequency of patients who received FFP was found (Table 3).

A statistically significant difference in all parameters of postoperative recovery was noted (Table 4). In the whole group, first flatus appeared on the 3.4th day, peristaltic restoration was achieved on the third day on average, oral feeding tolerance on average on the 3.7th day. The RG patients were faster to restore bowel movement and peristalsis, get the first postoperative stool and re-acquire oral food tolerance in comparison to the CG patients (Table 4).

Table 5. Complications

Characteristics	*Whole group n (%)*	*Control group n (%)*	*Research group n (%)*	*p value*
Clavien-Dindo classification				<0.05[2]
Grade 1	29 (36.3)	9 (21.4)	20 (52.6)	
Grade 2	40 (50)	24 (57.1)	16 (42.1)	
Grade 3	-	-	-	
Grade 4	10 (12.5)	8 (19.1)	2 (5.3)	
Grade 5	1 (1.3)	1 (2.4)	0 (0)	
Clavien-Dindo -categories				0.051[2]
Grades 1-2	69 (86.3)	33(78.6)	36(94.7)	
Grades 3-5	11 (13.8)	9 (21.4)	2 (5.3)	
Complications				
All types of complications	29 (36.3)	19 (45.2)	10 (26.3)	ns[1]
Cardiovascular	9 (11.3)	6 (14.3)	3	ns[1]
Hypertension	4 (5)	2 (4.8)	2	ns[1]
Arrhythmia	3 (3.8)	2 (4.8)	1	ns[1]
Cardiac failure	4 (5)	2 (4.8)	2 (5.3)	ns[1]
Acute myocardial infarction	-	-	-	-
Cardiac arrest	1 (2.4)	1 (2.4)	0 (0)	ns[1]
Respiratory	3 (3.8)	2 (4.8)	2 (5.3)	ns[1]
Pulmonary embolism	4 (5)	2 (4.8)	2 (5.3)	ns[1]
ARDS	-	-	-	-
Mechanical ventilation	-	-	-	-
Renal	2 (2.5)	2 (4.8)	0 (0)	ns[1]
ARF without dialysis	2 (2.5)	2 (4.8)	0 (0)	ns[1]
ARF with dialysis	-	-	-	-
Cerebrovascular (CVI/TIA)	-	-	-	-
Cognitive	11 (13.8)	7 (16.7)	4 (10.5)	ns[1]
Delirium postoperative	5 (6.3)	4 (9.5)	1 (2.6)	ns[1]
COPD	6 (7.5)	3 (7.1)	3 (7.9)	ns[1]
Gastrointestinal	26 (32.5)	13 (31)	13 (34.2)	ns[1]
Nausea	26 (32.5)	13 (31)	13 (34.2)	ns[1]
Vomiting	15 (18.8)	10 (23.8)	5 (13.2)	ns[1]
Surgical	12 (15)	9 (21.4)	3 (7.9)	ns[1]
Acute bleeding	8 (10)	7 (16.7)	1 (2.6)	0.059[2]
Anastomosis dehiscence	-	-	-	-
Reoperation	8 (10)	7 (16.7)	1 (2.6)	0.059[2]
Ileus	2 (4.8)	2 (4.8)	0 (0)	ns[1]
Surgical wound infections	3 (3.8)	1 (2.4)	2 (5.3)	ns[1]
Intra-hospital mortality	-	-	-	-

ns: not statistically significant, ARDS: acute respiratory distress syndrome, ARF: acute renal failure, CVI: cerebrovascular insult, TIA: transitory ischemic attack, COPD: cognitive postoperative disorder, [1]Pearson's chi-square test, [2]Fisher's exact test

Table 6. Length of stay in ICU, SD and total stay in hospital

Hospital stay	*Whole group*	*Control group*	*Research group*	*p value (Wilcoxon test)*
ICU stay				<0.01
Mean (SD)	4.3 (2.2)	4.8 (2.1)	3.7 (2.2)	
Median (range)	4 (1-15)	4.5 (2-15)	3 (1-13)	
SD stay				<0.01
Mean (SD)	6.4 (1.5)	6.8 (1.2)	5.8 (1.6)	
Median (range)	7 (2-10)	7 (3-10)	6 (2-10)	
LOS				<0.01
Mean (SD)	10.6 (2.4)	11.6 (1.9)	9.6 (2.5)	
Median (range)	10 (4-18)	11 (9-18)	9 (4-18)	

ICU: intensive care unit, SD: surgery department, LOS: length of hospital stay

Table 7. Survival analysis results for ICU, SD stay and LOS in days

Time	*Median (0.95% CI) in days*			*Log-rank, p*
	Whole group	*Control group*	*Research group*	
ICU stay	4 (3-4)	4.5 (4-5)	3.0 (3-4)	0.006
SD stay	7 (6-7)	7 (7-7)	6 (5-7)	0.0059
LOS	10 (10-11)	11 (11-12)	9 (9-10)	0.0002

ICU: intensive care unit, SD: surgery department, LOS: length of hospital stay

According to Clavian-Dindo classification of complications, 50% of all patients had grade 2, while grade 3 was not recorded, and 12.5 % had grade 4 and only 1.3 % had grade 5. In fact, 86.3% had minor and 13.8% of patients had major complications (grades 4 and 5; Table 5).

In total, 36.3 % of all patients had some kind of complication. The most common ones were gastrointestinal (32.5%), surgical (15%) and cognitive (13.8%) (Table 5).

We found that there was a statistically significant difference in the frequency of level (grade) of complications according to Clavian-Dindo classification system.

In the RG, grade 1 complications (52.63% vs 21.43%) were significantly more frequent, while the instances of more severe complications (grade 4) were significantly lower in the RG (Table 5).

Major complications (grade 3-5) were less probable to occur in the RG. This difference in probability was close to the limit of statistical significance (Table 5). Average ICU discharge delay for the whole group was 4.3 days and LOS for the whole group was 10.6 days (Table 6).

The average ICU stay, SD stay and LOS were lower in the RG compared to the CG (Table 6).

Survival analysis methods were used to analyze the ICU stay, SD stay and LOS in hospital and the results are presented in Table 7 and Figures 1, 2 and 3.

It was observed that the ICU and SD stay and LOS for the RG patients were shorter in comparison to patients in the CG.

Discussion

The main finding of this study was that colloid-crystalloid based Goal-Directed fluid therapy group (the RG) was associated with faster recovery, less complications according to the Clavian–Dindo classification, reduced patients' stay in ICU, SD and total stay in hospital (LOS). These beneficial effects might come second to lesser intraoperative crystalloids requirement, lesser fluid balance after 24 hrs and less collected autologous blood.

Restrictive fluid therapy is safer and a more beneficial way of fluid replacement in abdominal surgery [24,25]. Increased postoperative complications are common after perioperative fluid overload [24]. Fluid overload causes interstitial edema and pulmonary and cardiac dysfunction [25,26]. It is well known that the use of lower volume of colloid solutions is associated with better intraoperative circulatory flow and, at the same time, it prevents potential fluid overload [27]. In this study, the group, chosen at random and set to receive combined solutions (RG), required less crystalloids and had a smaller fluid balance after 24 hrs passed. Fluid balance represents the difference

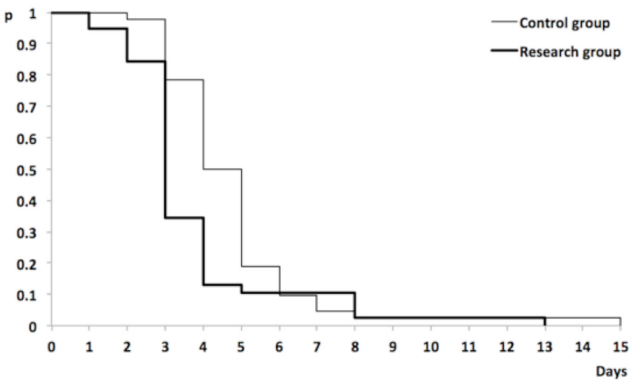

Figure 1. Intensive Care Unit stay (p=0.006).

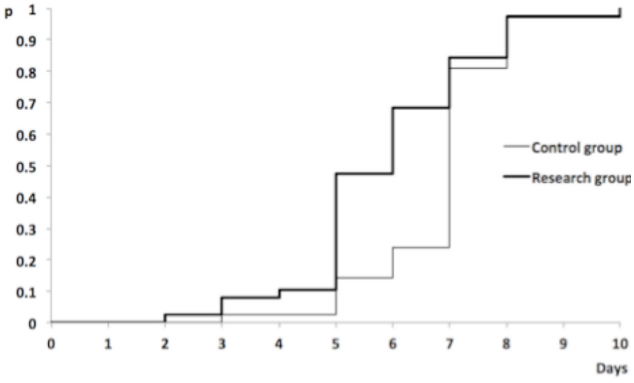

Figure 2. Surgery Department stay (p=0.0059).

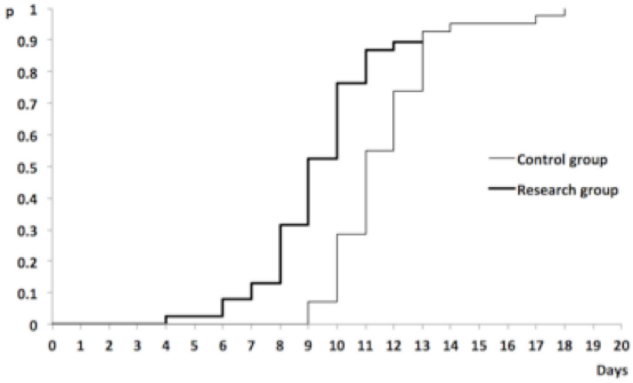

Figure 3. Length of hospital stay (p=0.0002).

between given and lost fluids 24 hrs after surgery, including the period of surgery. This means that even after 24 hrs after surgery, the RG had a better hemodynamics and required less infusion of fluids. A significant difference in postoperative recovery among groups can be noted, however, there were no differences in postoperative complications. In a larger study, 202 patients were randomly picked to receive Goal-Directed crystalloid or Goal-Directed colloid solution. The authors found that more fluid was required intraoperatively in the crystalloid group and it had a higher fluid balance within the following 24 hrs. Despite this, no major differences were observed between the groups in postoperative complications, recuperation of gastrointestinal function or the duration of hospital stay [28].

Colloids have proven to have an effect on hemostasis, which partly occurs as the result of simple hemodilution of clotting factors and partly due to colloid specific effects on components of the hemostatic mechanism. Despite that fact, the study of Yates et al. demonstrated an increase in clot formation time and the MA (a measure of platelet function) in crystalloid group that was not apparent in the HES group [28].

Medium and low molecular weight of HES solutions (6% Hydroxyethyl Starch 130/0.4) have been shown to produce similar, but lesser effects compared to the higher molecular weight products and it is believed that the risk of increased blood loss is minimal with these products [29,30].

In our study, the small dose of 6% HES could not affect the hemostatic mechanism, but it reduced crystalloid volume and possibly their capability of hemodilution. Although there was no difference in the number of patients and volume of transfused RPC perioperatively, 24 hrs after surgery more patients in the CG received RPC. All patients in the study, in both groups, had normal preoperative hemostatic and platelet function. This fact indicates, as well, that hemodilution could happen during surgery and that it is the reason why blood loss was greater after surgery.

Our major finding is that patients in the RG, those who received the combined type of solutions, needed less infusion, were faster to restore bowel movement and peristalsis, needed less time to develop food tolerance and were able to eat liquid and solid food in a shorter period of time. In a study with colon cancer patients who underwent elective resections, Lobo et al. underlined the importance of fluid restriction. Patients were picked at random according to standard (3 L water and 154 mmol sodium per day) and restrictive fluid regimens (2 L water and 77 mmol sodium per day). In both groups, crystalloid solutions were used. Gastric emptying was measured using a technetium labeled-meal on the fourth postoperative day. They found that the restrictive group had significantly improved liquid and solid gastric emptying, that their bowel functions restored earlier and that they needed to stay in hospital for a shorter period of time [31]. A recent meta-analysis examining liberal in contrast to restrictive regimes, showed that there was a significant increase in the frequency of pneumonia and pulmonary edema in the liberal group. This analysis showed a great reduction in time needed for bowel movement to be restored, for the passage of flatus and length of hospital stay in

the restrictive group [32]. We used Clavian-Dindo classification, which appeared as a reliable and a compelling tool for quality assessment in surgery [12,13].

In our study, the frequency of the complications in the RG was low in almost all grades, except for grade 1, which presents usual deviations from the standard postoperative course that do not require any treatment. More frequent complications were in the CG, in grades 2 and 4 (in comparison to the RG), which was of great importance for us. So as to rank a complication in an objective and reproducible manner, the therapy used to solve a specific complication is the basis of this classification. Therefore, in regards to the CG, the RG exhibited less serious complications in accordance to the required therapy and the intervention in our study.

A recent meta-analysis suggests that currently there are insufficient data to identify a difference in outcomes associated with crystalloids and HES in scheduled or elective noncardiac surgery [33].

We did not find any significant difference in groups regarding individual complications.

In general, postoperative bleeding after surgical colorectal procedures is a rare complication. The risk depends on the performed surgical procedures, patient comorbidities and on impaired clotting system [34]. Postoperative bleeding in our study was less apparent in the RG, and although it was not statistically significant, this group of patients was more prone to bleeding due to coagulopathies provoked by higher volume of infused crystalloids. Although there are more factors which can cause postoperative bleeding, the type and volume of solutions also play an important role.

Postoperative gastrointestinal morbidity is expressed as inability to tolerate oral or enteral tube feeding, nausea, vomiting and abdominal distension. These are usually reasons of delayed discharge [35]. We demonstrated that our patients in the RG had a better postoperative recovery and were discharged faster from hospital.

Conclusion

Goal-directed colloid-crystalloid therapy significantly improved postoperative recovery, especially restoration of gastrointestinal function and it shortened the hospital stay. We did not find any differences concerning postoperative complications when comparing these two ways of therapies.

If the fact that the duration of hospital discharge delay was significantly shorter is taken into consideration, this way of beneficial therapy could probably contribute to lower costs of treatment.

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Conflict of interests

The authors declare no conflict of interests.

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