

## ANESTHESIOLOGY

# Effect of Intraoperative Goal-directed Balanced Crystalloid *versus* Colloid Administration on Major Postoperative Morbidity

## A Randomized Trial

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*Anesthesiology* 2019; 130:728–44

A key role for anesthesiologists is to maintain intraoperative hemodynamic stability, a task that is complicated by large fluid losses consequent to major surgery. Volume replacement is the major compensation for fluid loss. Crystalloid salt solutions are the most commonly used perioperative fluids because they are inexpensive, readily available, and relatively nontoxic.<sup>1</sup> However, crystalloid solutions start to leave the intravascular space within minutes, thereafter providing little hemodynamic support. Crystalloids also accumulate in tissues including lungs and incision sites, thus promoting edema, weight gain, and prolonged recovery.<sup>2–4</sup>

In contrast, colloids remain in the circulation for hours, thus promoting hemodynamic stability.<sup>5,6</sup> Albumin was the original colloid volume replacement fluid and has been used since the 1940s.<sup>7</sup> However, being a human product, albumin is expensive, and the supply is sometimes limited. Consequently, starch preparations are now by far the most commonly used colloid volume expander.<sup>8</sup>

In septic and critically ill patients, starch preparations cause renal injury and death,<sup>9–12</sup> which has alarmed the European Medicines Agency<sup>13</sup> and the U.S. Food and Drug Administration.<sup>14</sup> Short-term use of starches has not been associated with renal toxicity,<sup>15</sup> but their effectiveness and safety has yet to be evaluated in a robust perioperative trial.<sup>16</sup> Furthermore, despite limited evidence worldwide, the issuing of IV fluid solutions to hospital departments has

## ABSTRACT

**Background:** Crystalloid solutions leave the circulation quickly, whereas colloids remain for hours, thus promoting hemodynamic stability. However, colloids are expensive and promote renal toxicity in critical care patients. This study tested the hypothesis that goal-directed colloid administration during elective abdominal surgery decreases 30-day major complications more than goal-directed crystalloid administration.

**Methods:** In this parallel-arm double-blinded multicenter randomized trial, adults having moderate- to high-risk open and laparoscopically assisted abdominal surgery with general anesthesia were randomly assigned to Doppler-guided intraoperative volume replacement with 6% hydroxyethyl starch 130/0.4 (n = 523) or lactated Ringer's solution (n = 534). The primary outcome was a composite of serious postoperative cardiac, pulmonary, infectious, gastrointestinal, renal, and coagulation complications that were assessed with a generalized estimating equation multivariate model. The primary safety outcome was a change in serum creatinine concentration up to 6 months postoperatively, compared to baseline concentrations.

**Results:** A total of 1,057 patients were included in the analysis. Patients assigned to crystalloid received a median [quartile 1, quartile 3] amount of 3.2 l [2.3, 4.4] of crystalloid, and patients assigned to colloid received 1.0 l [0.5, 1.5] of colloid and 1.8 l [1.2, 2.4] of crystalloid. The estimated intention-to-treat common effect relative risk for the primary composite was 0.90 for colloids *versus* crystalloids (95% CI: 0.65 to 1.23, *P* = 0.51), and 18% (91 of 523) of colloid patients and 20% (103 of 534) of crystalloid patients incurred at least one component of the primary outcome composite. There was no evidence of renal toxicity at any time.

**Conclusions:** Doppler-guided intraoperative hydroxyethyl starch administration did not significantly reduce a composite of serious complications. However, there was also no indication of renal or other toxicity.

(ANESTHESIOLOGY 2019; 130:728–44)

## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Crystalloid solutions leave the circulation quickly, whereas colloids remain for hours, thus promoting hemodynamic stability. However, colloids are expensive and promote renal toxicity in critical care patients. Whether goal-directed intraoperative tetrastarch colloid administration reduces complications or promotes renal injury remains unknown.

### What This Article Tells Us That Is New

- In a large randomized trial comparing intraoperative goal-directed 6% hydroxyethyl starch with goal-directed lactated Ringer's solution in patients having major abdominal surgery, 6% hydroxyethyl starch reduced neither a composite of serious complications nor the duration of hospitalization. However, 6% hydroxyethyl starch did not cause acute or long-term renal toxicity.

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 677. This article has a visual abstract available in the online version.

Submitted for publication February 8, 2018. Accepted for publication November 30, 2018. From the Department of Anesthesia and Intensive Care Medicine, Medical University of Vienna, Vienna, Austria (B.K.); and the Departments of Outcomes Research (D.I.S., A.K.) and General Anesthesiology (A.K.), Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio.

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changed in recent years to less colloids, particularly synthetic solutions, and relatively more crystalloids, particularly buffered solutions.<sup>17,18</sup>

We therefore tested the primary hypothesis that a 30-day composite of serious complications is reduced by intraoperative administration of colloid (Voluven, Fresenius Kabi, Germany) *versus* crystalloid (lactated Ringer's solution) in patients having moderate to high-risk open and laparoscopically assisted abdominal surgery with general anesthesia. Our secondary hypothesis was that colloid administration reduces the primary composite outcome augmented by 30-day all-cause mortality and hospital readmission and that colloid administration reduces a composite of minor complications. A tertiary hypothesis was that colloid administration reduces hospital length of stay. Our primary safety outcome was the change in serum creatinine concentration at various postoperative times.

A difficulty with comparing crystalloids and colloids is that volume requirements with each fluid differ. Because colloids remain intravascular longer than crystalloids, less fluid is required; but how much less depends on the specific colloid used and patient status, both of which vary over time. There is thus little justification in comparing specific volume ratios of crystalloids and colloids.<sup>19,20</sup> We therefore used guided fluid management—based on optimizing cardiovascular performance—to provide physiologically similar quantities of each fluid type throughout surgery.<sup>21–23</sup>

## Materials and Methods

This trial was conducted with institutional review board approvals at three participating institutions and was registered at ClinicalTrials.gov (the trial was initially registered at NCT00517127 when it started at the Medical University of Vienna [Vienna, Austria] and was reregistered at NCT01195883 when the Cleveland Clinic [Cleveland, Ohio] joined the study). The trial was originally initiated at the Medical University of Vienna and registered in 2007. After 259 patients were enrolled in Vienna, in 2010, the Cleveland Clinic and thereafter thereafter the Ohio State University (Columbus, Ohio) joined, the trial was reregistered by the Cleveland Clinic. With the reregistration in 2010, we also improved our study protocol. Especially individual parts of the major and minor complications were outlined in more detail. Thus, the second trial registration was more detailed than the first. Nevertheless, the same outcome data were prospectively evaluated in all patients. Treatment was also consistent throughout the entire trial. Several sub-studies, which were performed at the Medical University of Vienna only, were in the initial trial registration and are not part of this manuscript.

Written consent was obtained from all patients. We evaluated patients scheduled for open or laparoscopic-assisted abdominal surgery expected to last at least 2 h who were age 18 to 80 yr, were American Society of Anesthesiologists (ASA) physical status I–III, and had a body mass index of less than 35 kg/m<sup>2</sup>. We excluded patients who had

compromised kidney function (estimated creatinine clearance less than 30 ml/min), estimated cardiac ejection fraction less than 35%, severe chronic obstructive pulmonary disease, coagulopathies, or known esophageal or aortic abnormalities. Patients were given 5 to 7 ml/kg of lactated Ringer's solution during anesthetic induction, followed by 3 to 5 ml · kg<sup>-1</sup> · h<sup>-1</sup> of the solution for maintenance, normalized to ideal body weight, throughout surgery.

## Randomization and Masking

Shortly before induction of anesthesia, patients were randomized 1:1, stratified by study site, to either goal-directed crystalloid administration (lactated Ringer's solution) or goal-directed colloid administration (hydroxyethyl starch 6% 130/0.4, Voluven, Fresenius Kabi, Germany). The maximum dose of the colloid was 1,500 ml. We chose hydroxyethyl starch 130/0.4 because it was the newest starch and associated with least renal or coagulation side effects. Furthermore, it was the most commonly used starch in Europe at the time. The randomization sequence was generated by the study statistician (E.J.M.) using the PLAN procedure in SAS statistical software (SAS Institute, USA) using randomly sized blocks and stratified by clinical site. Allocation was initially concealed with sequentially numbered sealed envelopes and then later in the study with a web-based system. A trained study coordinator at each site evaluated eligibility, obtained informed consent, and then on the day of surgery enrolled the participants by either opening the concealed envelope or accessing the web-based system. Intraoperative investigators and clinicians were not blinded to treatment. However, an observer strictly blinded to group assignment evaluated complications during hospitalization. Subsequently, a blinded investigator called patients 30 days after surgery to assess postdischarge complications (primary outcome) and hospital readmission and vital status (secondary outcomes) described in this section below.

Intraoperative investigators administered the study fluids strictly following our fluid algorithm. Intraoperative fluid administration was guided by esophageal Doppler (CardioQ, Deltex Medical Group PLC, United Kingdom) using a previously published algorithm.<sup>22</sup> Based on stroke volume and corrected aortic flow time, boluses of 250 ml of the designated fluid were given over 5 min. Specifically, one fluid bolus was given preoperatively, and baseline fluid was started during induction of anesthesia. Fluid bolus as by randomization started after insertion of the esophageal Doppler probe.

Anesthesia management was standardized. We used balanced anesthesia with inhalational agents. Epidural catheters were allowed. However, dosing had to be initiated at the end of the study for postoperative analgesia.

Target intraoperative hematocrit was maintained at 30% in patients having both cardiovascular disease and an age more than 65 yr and 28% in patients with one or the other, and 26% in those with neither. Significant cardiovascular disease

was defined by previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, hypertension requiring treatment (or having a diastolic blood pressure exceeding 90 mmHg), or peripheral vascular disease. In the postoperative recovery unit we administered fluid at  $2\text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , with additional fluid given as deemed clinically necessary. Postoperative analgesia was provided per institutional routine.

The primary outcome was postoperative morbidity, defined by a composite of major complications, similar to those used in many fluid management studies.<sup>24,25</sup> It included cardiac, pulmonary, infectious, gastrointestinal, renal, and coagulation complication.

Preplanned secondary outcomes included: (1) a composite of minor complications including superficial incisional infection as per Centers for Disease Control and Prevention (Atlanta, Georgia) criteria, postoperative fever, urinary tract infection, ST-segment change, nonventricular arrhythmias, hemodynamic disturbances requiring vasoactive drugs, unplanned intensive care unit admission, small peritoneal pleural effusions, gastrointestinal paralysis, deep venous thrombosis, acute kidney injury, and transient neurologic complications; and (2) the primary composite augmented by readmission and mortality. We also evaluated the duration of hospitalization as a tertiary outcome. Our safety outcome was in-hospital serum creatinine concentrations and, as available, serum creatinine concentration up to 6 months postoperatively. (See appendix 2).

## Statistical Analyses

The colloid and crystalloid groups were compared for balance on demographic and baseline characteristics using standard summary statistics and absolute standardized difference, defined as the difference in means or proportions divided by the pooled SD. Any variable with an absolute standardized difference greater than 0.20 was considered imbalanced and would be adjusted for in all analyses.

### Primary Outcome

The primary analysis was intention to treat so that all randomized patients were included in all analyses. For the primary outcome of major complications, we assigned outcome values for missing outcome data (*i.e.*, postrandomization through 30 days) using last observation carried forward ( $n = 14$  cases) when the outcome for a component of the composite was known at hospital discharge but not between discharge and 30 days. Five patients had a single major outcome component missing with all other components being negative; for analysis, we assumed that they did not have had any complications.

We assessed the treatment effect on the major complications *via* a common effect “global” relative risk estimated across six outcomes of interest. In this multivariate analysis, each patient was represented once for each outcome event. The within-subject correlation among the outcomes was accounted for using a generalized estimating equation

model with an unstructured working correlation matrix. Treatment-by-site interaction was assessed in a separated generalized estimating equations model.

As a sensitivity analysis we assessed the treatment effect on the collapsed composite of the six major complications (*i.e.*, any *vs.* none) using a chi-square test. The Breslow–Day test was used to assess whether the treatment effect on the collapsed composite outcome differed across the three hospitals. Due to the protocol change after 259 patients were enrolled, we also conducted a sensitivity analysis to assess whether there was an interaction effect between treatment group and the protocol change.

### Secondary and Tertiary Outcomes

We assessed the treatment effect on the collapsed composite of any minor complication and on a collapsed composite of any major complications plus 30-day mortality and 30-day readmission, each with a chi-square test. The minor complication analysis was a per-protocol analysis because more than 10% of patients ( $n = 145$ ) had at least one minor component missing, making an intention-to-treat analysis with conservative assignment unrealistic.

Duration of hospitalization and readmission were analyzed as time to discharge alive and time to readmission, and the treatment effects were assessed using Cox proportional hazards models. To avoid bias from considering early deaths as short hospitalizations and thus favorable lengths of stay, patients who died in the hospital were assigned the longest observed hospital stay of any patient and censored at that time (*i.e.*, not discharged alive). Patients who died within 30 days after surgery were censored at the date of death for the time to readmission analysis. Because only 1% of patients died within 30 days, a competing risks analysis was unnecessary.

### Safety Outcomes

Because harm was reported in septic critical care patients during the course of our study,<sup>9–12</sup> the Data Safety and Monitoring Board (Cleveland, Ohio) added renal toxicity as a safety outcome. We compared colloids and crystalloids groups on the maximum postoperative serum creatinine concentration during hospitalization and within 6 months thereafter with analysis of covariance adjusted for the preoperative serum creatinine. Because serum creatinine concentrations were not normally distributed, we analyzed them on a log scale, with treatment effect reported as the ratio of geometric means. We also assessed between-group differences in creatinine changes over time using linear mixed models to adjust for within-patient correlation: (1) over postoperative days 1 to 14 and (2) over postoperative months 1 to 6.

### Interim Analyses

We used a group-sequential design in which four interim analyses were planned with a maximum enrollment of 1,112 patients, using the  $\gamma$  spending values of  $-4$  for efficacy and  $-1$  for futility. At the final analysis, primary outcome CI used the interim-adjusted  $\alpha$  of 0.04.

The significance criterion for each secondary outcome was  $P < 0.017$  (i.e.,  $0.05/3$ , Bonferroni correction for two secondary outcomes and one tertiary outcome). For simplicity of presentation, we refer to these adjusted intervals as 95% CI throughout. SAS software version 9.4 for Windows (SAS Institute, USA) was used for analyses.

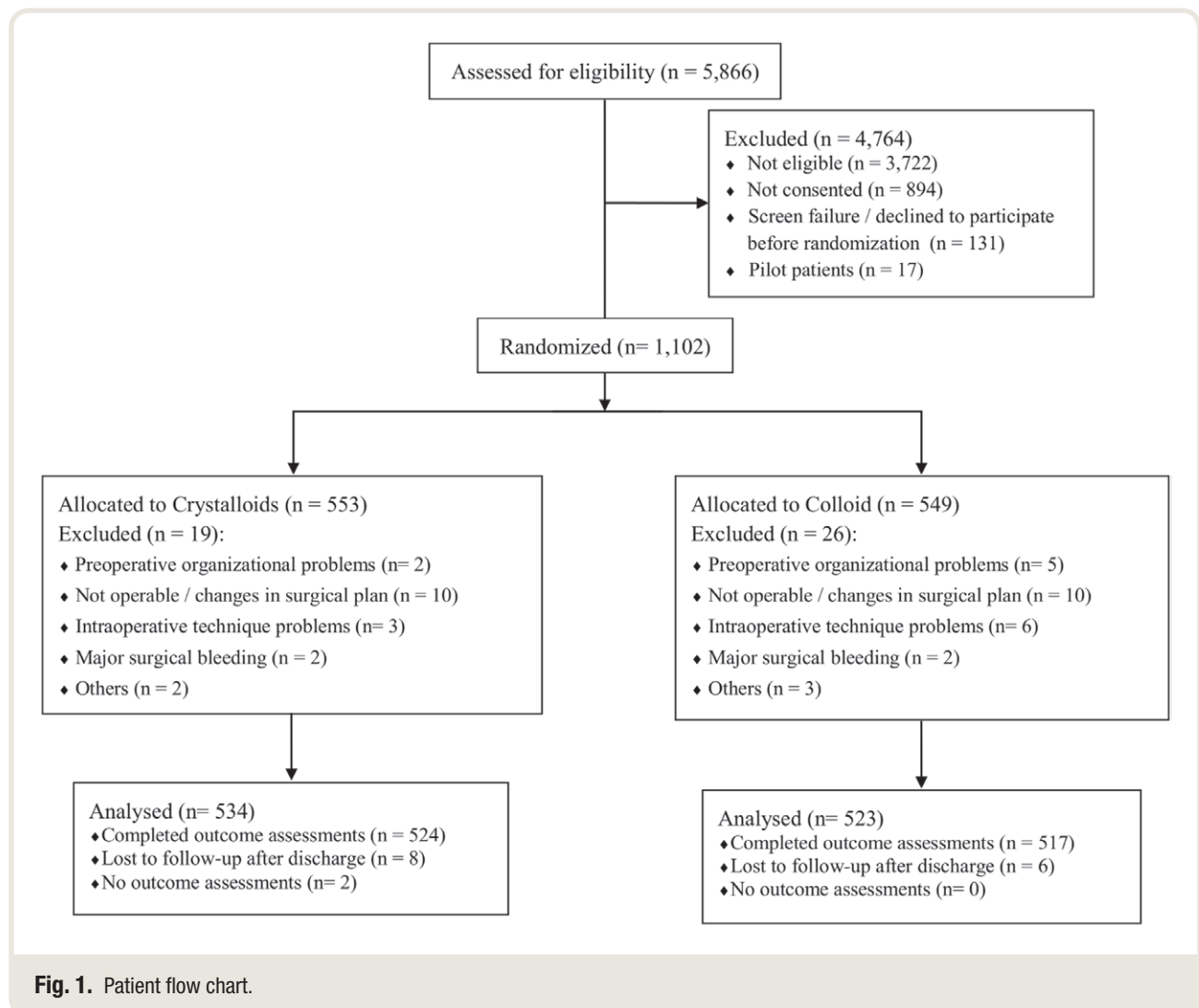
### Power Analysis

Our maximum sample size of 1,112 (including interim and final analyses) was based on being able to detect a risk reduction of 30 to 40% across the outcomes in our multivariate generalized estimating equation model with 80% power at the 0.05 significance level. Based on our own pilot data of 259 patients (enrolled under the initial study registration) and evaluated in blinded fashion, we assumed individual incidences for the outcomes of interest of the combined treatment groups ranging from 2 to 10% and within-subject correlations ranging from about 0.05 to 0.30 across the outcomes. Detectable risk reduction for the planned sample size is expressed as a range because it depends on the degree of correlation among

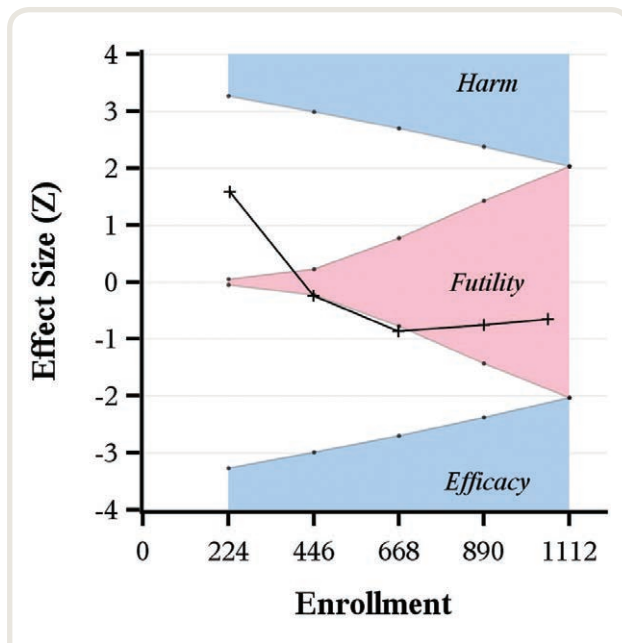
components of the composite, which was unknown in the trial design phase.

### Results

Patients were enrolled between November 2006 and October 2016, mostly at the Cleveland Clinic and Medical University of Vienna. At the fourth interim analysis ( $n = 890$ , 80% of planned enrollment), there was no difference between crystalloid and colloid groups across the six major complications (intention-to-treat analysis,  $P = 0.40$ ). The futility boundary was crossed so the study was stopped per protocol. While outcomes data on the initial 890 patients were being collected and analyzed, 219 additional patients were randomized. We thus report results from 1,102 randomized patients. After 52 patients withdrew, 1,057 patients remained for analysis, including 507 from the Medical University of Vienna, 498 from Cleveland Clinic, and 45 from Ohio State University (figs. 1 and 2).







**Fig. 2.** Interim monitoring results for the primary analysis: common effect generalized estimating equation relative risk of colloid *versus* crystalloid across six postoperative major complications. Group sequential futility boundary (pink region) was crossed at the fourth interim analysis (N = 890); the trial was therefore stopped for futility. While outcomes data on the initial 890 patients were being collected and analyzed, 219 additional patients were randomized. We thus report results from 1,102 randomized patients. After 52 patients withdrew, 1,057 patients remained for analysis. The vertical axis is the Z statistic corresponding to the standardized treatment effect estimated at each interim analysis; negative values indicate efficacy of colloid (significant if reaching lower blue region), whereas positive values indicate harm (significant if reaching upper blue region).

Of 1,102 patients in total, 259 patients were enrolled under the initial protocol. Sixteen patients were lost to follow-up after discharge, including 14 patients who had outcomes evaluated at discharge: we carried forward their last observations for the primary analysis. Two others without discharge values (both in the crystalloid group) were assigned 30-day outcomes under a conservative scenario. Only 10 patients had laparoscopically assisted surgery, whereas the remainder of the patients had open abdominal surgery.

Patients given colloid and crystalloid were well balanced on baseline characteristics, so no covariable adjustment was needed in the analyses (table 1; appendices 3 and 9). The median [quartile 1, quartile 3] amount of crystalloid given to patients assigned to crystalloid was 3.2 l [2.3, 4.4]. Patients assigned to colloid were given 1.0 l [0.5, 1.5] of colloid and 1.8 l [1.2, 2.4] of crystalloid.

Appendix 4 lists the components of the primary and secondary composites, the incidence of each component, and the incidence of each composite. Figure 3 is a forest plot showing the primary outcome relative risks and individual

group risks overall, by study site, and by component. In total, 18% (91 of 523) of colloid patients and 20% (103 of 534) of crystalloid patients incurred at least one component of the primary outcome composite.

No difference was found between colloid and crystalloids on the primary outcome composite, with an estimated common effect relative risk across the six major complications for colloid *versus* crystalloid patients of 0.90 (95% CI, 0.65 to 1.23),  $P = 0.51$  (table 2; fig. 3). We also assessed the treatment effect on the collapsed composite of the major complications (any *vs.* none), with estimated relative risk of having any major complication of 0.90 (95% CI, 0.69 to 1.18),  $P = 0.43$  (table 2). No interactions were detected across the complication components or among sites, so that the treatment effect was not found to differ across components of the composite of major complications or to vary by clinical site. Further, the treatment effect on the primary outcome composite did not vary by ASA group (III *vs.* II or lower),  $P = 0.99$ .

There was no interaction between before and after the protocol change on primary outcome ( $P = 0.37$ ). For patients who were enrolled before the protocol change, the relative risk of the primary outcome for the colloid group compared with crystalloid was 1.13 (95% CI, 0.11 to 2.09),  $P \geq 0.9$ ; after the protocol change the estimated relative risk was 1.08 (95% CI, 0.86 to 1.36),  $P \geq 0.9$ .

No treatment effect was found on the secondary outcome of any minor complication, with relative risk (98.3% CI) of 0.95 (0.81 to 1.23; table 3),  $P = 0.42$ , in colloid *versus* crystalloid: incidence of any minor complication was 48% for the colloid patients and 51% (appendix 5) for the crystalloid patients. Neither was there an effect of colloid *versus* crystalloid on the secondary composite outcome of any major complications (primary composite) plus 30-day mortality or 30-day readmission, with relative risk (98.3% CI) of 0.89 (0.69 to 1.14),  $P = 0.26$ .

Thirty-day mortality was 1.0% for colloid patients and 0.8% for crystalloid patients, with estimated relative risk of 1.28 (98.3% CI, 0.26 to 6.29) for colloid *versus* crystalloid,  $P = 0.71$ . The 30-day readmission rate was 11.9% in the colloid group and 12% in the crystalloid group. Finally, no difference was found between the randomized groups on length of hospital stay, with median [quartiles] length of hospital stay of 7 [5, 11] days for both groups (hazard ratio [98.3% CI] of 1.05 [0.90 to 1.21]),  $P = 0.45$ .

After adjusting for baseline serum creatinine, the ratio of geometric means for maximum creatinine during the hospital stay was 0.97 (95% CI, 0.93 to 1.01) for colloid *versus* crystalloid,  $P = 0.19$ . There was also no difference up to 6 months after discharge, with an estimated ratio of geometric means of 0.97 (95% CI, 0.93 to 1.02; fig. 4),  $P = 0.23$ . There were no creatinine differences between the groups over the initial 14 postoperative days ( $P = 0.84$ ; appendices 5 and 6) or initial 6 months ( $P = 0.54$ , appendices 7 and 8).

**Table 1.** Baseline and Intraoperative Characteristics (N = 1,057)

Variables	Colloids (n = 523)	Crystalloids (n = 534)	ASD*
Age, yr	52 ± 16	52 ± 16	0.03
Body mass index, kg/m <sup>2</sup>	25.5 [22.3, 29.1]	25.5 [22.4, 28.6]	0.01
Female, no. (%)	242 (46)	268 (50)	0.08
ASA physical status, no. (%)			0.06
I	54 (11) <sup>7</sup>	46 (9) <sup>1</sup>	
II	300 (58)	316 (59)	
III	162 (32)	171 (32)	
Race (white), no. (%)	495 (95)	508 (95)	0.02
Medical history, no. (%)			
Pulmonary disease	41 (8) <sup>9</sup>	38 (7) <sup>13</sup>	0.03
Cardiovascular disease	142 (27) <sup>3</sup>	161 (30) <sup>2</sup>	0.07
Neurologic disease	25 (5) <sup>20</sup>	23 (5) <sup>17</sup>	0.02
Diabetes	40 (8) <sup>21</sup>	38 (7) <sup>16</sup>	0.02
Insulin use	11 (2) <sup>21</sup>	7 (1) <sup>19</sup>	0.06
History of PONV	43 (8) <sup>1</sup>	48 (9) <sup>1</sup>	0.03
Alcohol (more than 25 drinks per week)	24 (5) <sup>49</sup>	29 (6) <sup>43</sup>	0.04
Smoking status			0.12
No	271 (59) <sup>82</sup>	299 (63) <sup>98</sup>	
Yes, currently	95 (21)	100 (21)	
Yes, quit	95 (21)	77 (16)	
Preoperative bowel preparation			0.03
Home	53 (10) <sup>3</sup>	56 (11) <sup>1</sup>	
Hospital	115 (22)	112 (21)	
None	351 (68)	365 (68)	
Preoperative lab			
Creatinine, mg/dl	0.8 [0.7, 1.0] <sup>3</sup>	0.8 [0.7, 0.9] <sup>7</sup>	0.06
Albumin, g/dl	4.4 [4.0, 5.0] <sup>99</sup>	4.4 [4.0, 5.1] <sup>113</sup>	0.05
Hemoglobin, mg/dl	13.6 ± 5.4 <sup>3</sup>	13.2 ± 1.9 <sup>1</sup>	0.09
Hematocrit, %	39.4 ± 5.1 <sup>3</sup>	39.4 ± 5.1 <sup>1</sup>	0.01
Normotest/PT, s	103.0 [77.0, 121.0] <sup>230</sup>	100 [81, 121] <sup>246</sup>	0.03
APTT STA, s	34.0 [30.6, 36.9] <sup>229</sup>	33.1 [30.7, 36.1] <sup>239</sup>	0.10
Preoperative IV fluid per weight, ml/kg	6.0 [0, 7.7] <sup>26</sup>	6.2 [0, 7.8] <sup>28</sup>	0.02
Intraoperative variables			
Duration of anesthesia, h	4.4 [3.4, 5.7]	4.5 [3.6, 5.7]	0.07
Duration of surgery, h	3.4 [2.4, 4.5]	3.4 [2.5, 4.7]	0.08
Crystalloid, l	1.8 [1.2, 2.4]	3.2 [2.3, 4.4]	0.70
Colloid, l	1.0 [0.5, 1.5] <sup>2</sup>	0 [0, 0] <sup>10</sup>	2.62
Number of boluses	4 [2, 6]	5 [3, 8]	0.44
Blood given, ml	0 [0, 0] <sup>9</sup>	0 [0, 0] <sup>10</sup>	0.13
Estimated blood lost, ml	250 [100, 500] <sup>1</sup>	250 [100, 500] <sup>1</sup>	0.05
Estimated urine output, ml	320 [195, 500] <sup>4</sup>	340 [200, 500] <sup>6</sup>	0.04
Other fluids, ml	100 [0, 400] <sup>36</sup>	100 [0, 450] <sup>40</sup>	0.05
Net fluids, l	2.67 [1.85, 3.45] <sup>3</sup>	3.07 [2.15, 4.21] <sup>6</sup>	0.34
TWA MAP, mmHg	80 ± 9 <sup>34</sup>	80 ± 9 <sup>34</sup>	0.01
End-tidal Pco <sub>2</sub> , mmHg	34.6 ± 2.4 <sup>35</sup>	34.3 ± 2.3 <sup>35</sup>	0.16
Final intraoperative core temperature, °C	36.8 ± 3.0 <sup>35</sup>	36.6 ± 2.8 <sup>36</sup>	0.04
TWA FiO <sub>2</sub> , %	68 ± 15 <sup>34</sup>	69 ± 20 <sup>35</sup>	0.03
MAC, %	2.2 ± 2.6 <sup>37</sup>	2.1 ± 1.9 <sup>36</sup>	0.03
Phenylephrine, mg†	0.10 [0, 0.40]	0.10 [0, 0.50]	0.15

Summary statistics are presented as percentages of patients, means ± SD, or median [quartile 1, quartile 3], respectively. Superscript numbers represent number of missing values. Net fluids: sum of colloids, crystalloids, and other fluids minus estimated urine output.

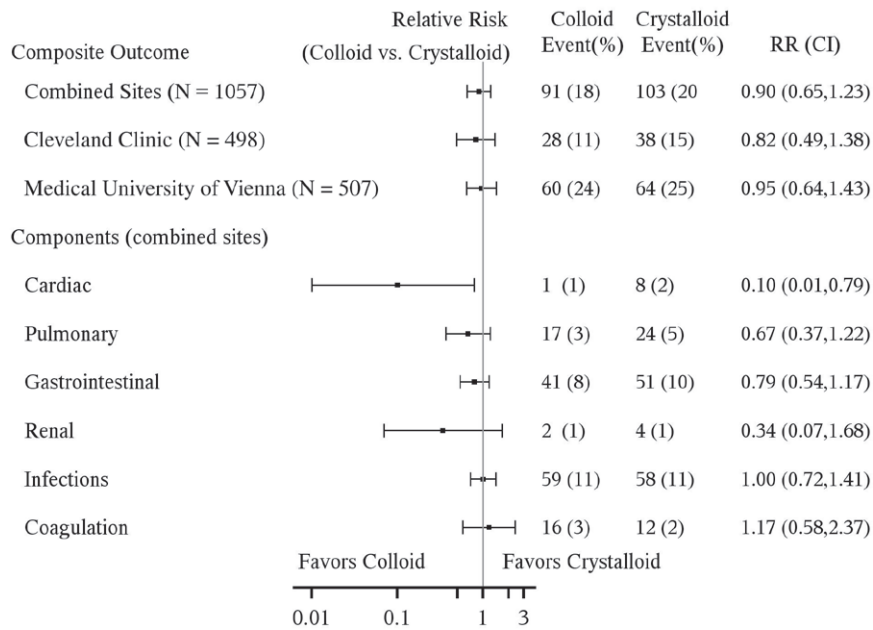
\*Absolute standardized difference (ASD): absolute difference in means or proportions divided by the pooled SD; ASD values of 0.2, 0.5, and 0.8 represent small, median, and large differences.

†Only three patients at Cleveland Clinic and one patient at the Medical University of Vienna were given epinephrine; one patient at Cleveland Clinic was given vasopressin; no patients at Cleveland Clinic were given norepinephrine.

APTT, partial thromboplastin time; ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; FiO<sub>2</sub>, fraction inspired oxygen concentration; MAC, minimum alveolar concentration, a measure of anesthetic dose; MAP, mean arterial pressure; Pco<sub>2</sub>, end-tidal partial pressure of carbon dioxide; PONV, postoperative nausea and vomiting; PT, prothrombin time; TWA, time weighted average.

Stage 1 acute kidney injury was observed in 20 (3.9%) colloid patients and 12 (2.3%) crystalloid patients; stage 2 injury was observed in 1 (0.2%) colloid patient and 4 (0.8%) crystalloid patients; and there

was no stage 3 acute kidney injury. Acute kidney injury did not differ significantly, with an estimated odds ratio of 1.33 (95% CI, 0.69 to 2.58, colloids *vs.* crystalloids, *P* = 0.40).



**Fig. 3.** Forest plot with estimated relative risks for primary analysis: overall (common effect generalized estimating equation multivariate model) and by component. Estimated treatment effect of colloids *versus* crystalloids on the composite outcome of any major complications and individual components of the composite outcome. Relative risk (RR) was not estimated for Ohio State University patients by themselves due to low incidence, but Ohio State University was included in the “all patients” analyses.

**Table 2.** Primary Outcome: Effect of Colloids *versus* Crystalloids on Composite Endpoint Vector of Six Types of Major Postoperative Complications (N = 1,057)

Analysis	Primary Analysis Common Effect GEE Model*		Sensitivity Analysis Collapsed Composite (Any vs. None)†	
	Relative Risk (95% CI) Colloid/Crystalloid	P Value	Relative Risk (95% CI) Colloid/Crystalloid	P Value
All patients (N = 1,057)	0.90 (0.65 to 1.23)	0.51	0.90 (0.69 to 1.18)	0.43
Cleveland Clinic only (n = 498)	0.82 (0.49 to 1.38)	0.45	0.74 (0.46 to 1.20)	0.20
Medical University of Vienna only (n = 507)	0.95 (0.64 to 1.43)	0.82	0.96 (0.69 to 1.32)	0.77
Ohio State University only (n = 52)	‡	‡	‡	‡

For two crystalloid patients from the Medical University of Vienna with completely missing data, all components were assigned “no event.” Treatment-by-site interaction was 0.49 (nonsignificant) for Cleveland Clinic and Medical University of Vienna. Sensitivity analysis: primary analysis when adjusting for clinical site gives relative risk of 0.89 (0.65 to 1.22), *P* = 0.46. CI adjusts for interim monitoring on the primary outcome.

\*Common effect “global” relative risk across the six major complications was estimated using a generalized estimating equation model with six records/patient (one/component) and unstructured working correlation matrix. Within-site analysis for the Medical University of Vienna used a compound symmetry correlation structure to avoid convergence issues.

†Collapsed composite (any *versus* none) of having any major complications was assessed using a chi-square test.

‡Relative risk was not estimated for Ohio State University by itself due to low incidence, but Ohio State University was included in the “all patients” analyses. GEE, generalized estimating equations.

**Discussion**

The incidence of a composite of serious complications did not differ significantly for goal-directed crystalloids and colloids; results were similar when the primary composite was augmented by hospital readmission and death. There was also no difference in a composite of minor complications.

Our results thus do not support superiority of hydroxyethyl starch colloids over less-expensive crystalloids in terms of major and minor complications.

A recent consensus statement by the European Society of Intensive Care Medicine recommended using colloids in critically ill patients only in the context of clinical trials.<sup>26</sup> Regulatory authorities in both Europe<sup>13</sup> and the United

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**Table 3.** Secondary Outcomes: Comparison between Colloid and Crystalloid Patients on Secondary Outcomes

Secondary outcome	Treatment Effect (98.3% CI; Colloid vs. Crystalloid)*	P Value
Primary composite plus 30-day readmission and death (n = 1,043)	0.89 (0.69 to 1.14)†	0.26
Readmission within 30 days (n = 1,057)‡	1.0 (0.65 to 1.52)§	0.99
30-day mortality (n = 1,057)	1.28 (0.26 to 6.29)†	0.71
Any minor complication		
All patients (n = 912)	0.95 (0.81 to 1.23)†	0.42
CCF only (n = 480)	1.04 (0.80 to 1.35)†	0.74
Vienna only (n = 389)	0.87 (0.71 to 1.06)†	0.09
OSU only (n = 43)	1.18 (0.48 to 2.91)†	0.66
Tertiary outcome		
Hospital length of stay (n = 1,057)	1.05 (0.90 to 1.21)§	0.45

\*CI values are actually 98.3% in this table: Bonferroni correction for three outcomes (primary composite plus 30-day readmission and death, any minor complication and hospital length of stay).

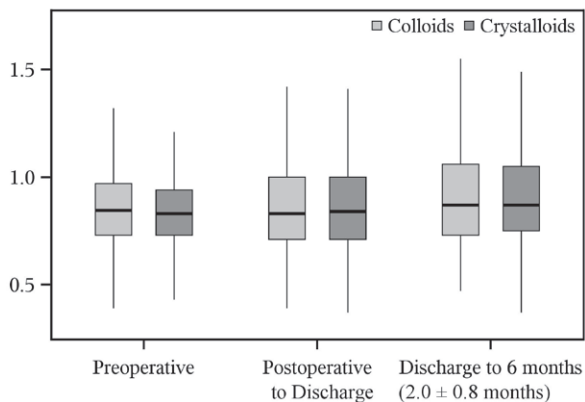
†Relative risk.

‡The outcome was time to readmission and 10 dead patients were treated as censored at postoperative 30 days.

§Hazard ratio.

||The outcome was time to discharge alive (hospital stay) and six dead patients in hospital were assigned to the longest observed hospital stay.

CCF, Cleveland Clinic Foundation; OSU, Ohio State University.

**Fig. 4.** Box plots of preoperative serum creatinine concentration and maximum postoperative serum creatinine before hospital discharge and within 6 months. Postdischarge length of follow-up across patients is presented as means  $\pm$  SDs. No differences were found.

States<sup>14</sup> have issued cautions about the use of hydroxyethyl starch solutions in patients with sepsis, burn injuries, or critical illness. However, the perioperative period differs in that even patients having major surgery are generally less fragile than critical care patients and are rarely septic. Furthermore,

low doses of colloids are usually given over relatively short periods. Perhaps consequently, we saw no evidence that colloid administration provoked renal injury during hospitalization, at least as estimated by serum creatinine concentration. There were also no evidence of renal injury up to 6 months postoperatively, although late creatinine measurements were not required by protocol and thus available in only a small fraction of patients. Use of hydroxyethyl starch 130/0.4 thus appears to be safe from a renal perspective in noncardiac surgery patients.

Our results are consistent with previous small perioperative studies<sup>27</sup> and with meta-analyses of previous studies.<sup>28,29</sup> As in our study, Yates *et al.*<sup>30</sup> concluded that there is no benefit in using hydroxyethyl starch over using crystalloids. In 202 patients undergoing colorectal surgery, no difference was seen in the number of patients who suffered gastrointestinal morbidity on postoperative day 5 (30% in the hydroxyethyl starch group *vs.* 32% in the crystalloid group; adjusted odds ratio 0.96 [0.52 to 1.77]). No difference in the incidence of postoperative complications was seen between the groups. However, crystalloid patients received significantly larger amounts of fluid.<sup>30</sup>

However, a recent trial of 160 noncardiac surgical patients who were randomized to goal-directed crystalloid or colloid reports lower postoperative morbidity scores in patients assigned to colloids, along with fewer major and minor complications.<sup>31</sup> Ours as well as their study used similar baseline infusion rates, and even the total amount study fluid administered as per protocol was comparable in the two studies. However, Joosten *et al.*<sup>31</sup> used large amounts of rescue colloids for hemodynamic stability, especially in the crystalloid group. This might have affected the overall administered fluid amount, which resulted in a greater difference of fluid given between the two groups. Despite the fact that both trials enrolled open abdominal surgical patients, our patients were probably slightly healthier and had less severe and somewhat shorter surgery. Our study patients had general anesthesia while Joosten *et al.*<sup>31</sup> allowed general and regional anesthesia. Although there are these methodologic differences, it is unclear why their results should differ from those in our 1,057 patients. The most likely assumption is that a study with just 160 patients and variability in patient population and anesthesia management was underpowered.

Feldheiser *et al.*<sup>32</sup> showed that goal-directed colloidal administration is associated with better hemodynamic stability. Interestingly, stroke volume and cardiac output were improved, but not mean arterial pressure which might be an important predictor for myocardial injury after noncardiac surgery.

Of note, in our study we saw a smaller number of cardiac events in patients receiving colloids. We had one colloid and eight crystalloid patients with cardiac events, which is too small a number to draw any conclusions. However, it



has been shown recently that perioperative hypotension is associated with myocardial injury after noncardiac surgery.<sup>33</sup> Thus, better hemodynamic stability with colloids might result in improved cardiac outcome.

There remains considerable controversy over the ideal amount of fluid to be given during various types of surgery, and there is considerable variation from site to site. Nonetheless, there is some consensus that goal-directed management is most likely to target the best dose in individual patients,<sup>34</sup> although results are not entirely consistent.<sup>30,35</sup> An important feature of our trial is thus that goal-directed fluid management was used in all patients. Titrating fluid replacement to stroke volume not only provided comparable physiologic amounts of each fluid throughout surgery, but also provided the right amounts of each presumably at the correct times.<sup>32,36–38</sup>

We used a baseline infusion rate of approximately 4 ml kg<sup>-1</sup> h<sup>-1</sup> lactated Ringer's solution. Crystalloid patients received on average five fluid boluses, and colloid patients received four fluid boluses. Thus, the total amount of fluids was similar in our two study groups. The amount of vasopressors was slightly but not significantly higher in patients receiving crystalloids.

Independent of Doppler guidance, the modest amount of fluid given—about 3 l over 4.5 h—is consistent with the current approach to fluid restriction. We used lactated Ringer's as our crystalloid as it is perhaps the most commonly used intraoperative balanced salt solution and, unlike normal saline, does not promote hyperchloremic acidosis.<sup>39,40</sup>

We selected hydroxyethyl starch 130/0.4, which is a third-generation colloid that is thought to cause less renal injury and coagulopathy than older starch preparations.<sup>41–43</sup> We avoided albumin because it is expensive and sometimes in short supply, although recent research suggests that human albumin protects the endothelial surface layer and might thus reduce interstitial edema.<sup>44</sup>

Colloid solutions are usually given to patients having large operations in which there is substantial volume loss. We thus restricted enrollment to patients having moderate to major open or laparoscopically assisted abdominal surgery, those most likely to require substantial volume replacement. In fact, only a minimal number of our patients (10 patients) had laparoscopically assisted surgery. Our results thus apply to general surgical patients likely to be given colloids. Our patient population was relatively healthy, with the majority of patients having an ASA physical status of II, a mean age of around 50 yr, and a body mass index near 25 kg/m<sup>2</sup>. It remains possible that starch solutions are more effective and/or more toxic in patients having significant cardiac or renal comorbidities, in older patients, or in obese patients. All of our patients had major surgery, but it remains possible that patients having the most invasive operations respond differently, including those having cardiac, major trauma, or transplant surgery with significant blood loss. The dose of colloid

was approximately 1 l over 3 h, which is moderate considering that the maximum recommended dose is 33 ml/kg per 24 h. During the study, results of a major trial became available and showed that large volumes of colloid given over a period of days in critical care patients promoted renal toxicity.<sup>10</sup> Consequent concerns slowed enrollment in Europe for several years. A resulting limitation of our trial is that enrollment lasted for an 11-yr period—a slow recruitment rate at a time of major changes in the understanding and practices of fluid resuscitation along with improvements in surgical practice. Because the trial was randomized, background changes in practice do not constitute bias. However, to the extent that practice changes, results may be less relevant to current patients than the ones who enrolled in our trial earlier. For example, stroke volume is now more often used to guide fluid administration than correct flow time. However, it seems unlikely that practice changes account for our results or that a new trial would identify substantial benefit or toxicity in similar patients. Despite the long enrollment period, there were no substantive changes to the protocol or outcomes. Our study demonstrates the difficulties of large randomized trials and the fact that not only funding or lack thereof but also the regulatory environment can effect enrollment. The colloid we studied is but one of several; it remains approved by both the U.S. Food and Drug Administration and the European Medicines Agency. Naturally, results might differ with alternative colloids.

Another limitation is that clinicians knew which fluid the patients were getting, which could have led to ascertainment bias influencing additional fluid management by clinicians. However, fluids were given by research fellows and was based on strict criteria. Outcomes were evaluated by a separate team of investigators who were blinded to fluid allocation and intraoperative management.

In summary, Doppler-guided intraoperative hydroxyethyl starch administration did not reduce composites of serious complications. Nor did hydroxyethyl starch reduce the duration of hospitalization, but there was also no indication of renal or other toxicity. Because starch colloids are more expensive than crystalloids and apparently do not reduce perioperative complications, they should be used sparingly in surgical patients.

## Research Support

Supported in part by Fresenius Kabi (Bad Homburg, Germany). Deltex Medical (Chichester, United Kingdom) provided the esophageal Doppler monitors and disposables. The sponsors were not involved in protocol development, data acquisition, or data analysis.

## Competing Interests

The authors declare no competing interests.



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## Appendix 2. Definition of Major Complications

Organ Systems	Complications
Cardiac	Acute heart failure, myocardial infarction, ventricular arrhythmia
Pulmonary	Pulmonary embolism, pulmonary edema, respiratory failure, pneumonia
Gastrointestinal	Bowel and surgical anastomosis stricture/obstruction or anastomotic leak, internal or external fistulas, peritoneal effusions
Renal	Dialysis
Infections	Deep or organ/space surgical site infection, sepsis
Coagulation	Bleeding

### Requirements for Major Complications

Major Complications	Requirements for Acceptance
Deep or organ/space surgical site infection	CDC criteria (see below)
Sepsis	Positive blood culture and at least two of the following: hypo- or hyperthermia, tachycardia, tachypnea, leukopenia/leukocytosis ± DIC or multiorgan dysfunction
Bowel and surgical anastomosis stricture/obstruction or anastomotic leak	Requiring surgical intervention
Ileus	Requiring surgical intervention
Bleeding	Requiring transfusion of more than four units and/or surgical intervention during the postoperative follow-up period
Large peritoneal/pleural effusion	Diagnosed by x-ray, ultrasound, and/or aspiration and requiring chest tube, surgery, or ICU admission
Internal or external fistula formation	Requiring intervention
Pulmonary emboli	Sudden death or confirmation by V–Q scan showing high probability for pulmonary emboli, spiral CT scan or pulmonary arteriogram
Pulmonary edema and congestive heart failure	Shortness of breath, crepitation, peripheral edema, third heart sound, and radiologic signs (cardiomegaly, interstitial edema, alveolar edema) requiring medical treatment with diuretics
Acute heart failure	Requiring inotropic therapy within 72 h of surgery
Myocardial infarction	ECG changes and/or elevated myocardial enzymes (cTn-T ≥ 0.03 and/or CK ≥ 170IU and MB ≥ 5%)
Ventricular arrhythmias	ECG changes requiring medical treatment and/or electroconversion
Renal failure	Requiring dialysis
Respiratory failure	Requiring intubation for more than 3 days
Pneumonia	New infiltrate on CXR combined with two of the following: temperature > 38°C, leukocytosis, and positive sputum or bronchial culture

CDC, Centers for Disease Control and Prevention; CK, creatine kinase; CT, computed tomography; cTn-T, cardiac troponin; CXR, chest X-ray; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; ICU, intensive care unit; MB, muscle/brain; V–Q, ventilation perfusion.

**Appendix 3.** Preoperative Medications, Primary Diagnosis, and Type of Surgery (N = 1,057)

Variables	Colloids (N = 523)	Crystalloids (N = 534)	ASD*
Preoperative medication, no. (%)			
α-Blocker	11 (2) <sup>27</sup>	17 (3) <sup>23</sup>	0.07
Central α-agonists	2 (0) <sup>27</sup>	1 (0) <sup>22</sup>	0.04
β-Blocker	57 (11) <sup>26</sup>	68 (13) <sup>22</sup>	0.05
β-Agonist	11 (2) <sup>26</sup>	8 (2) <sup>22</sup>	0.05
Peripheral α-agonists	2 (0) <sup>26</sup>	1 (0) <sup>22</sup>	0.04
Nitrates	4 (1) <sup>26</sup>	4 (1) <sup>23</sup>	0.00
Opioids	80 (16) <sup>26</sup>	74 (14) <sup>23</sup>	0.05
Ace inhibitor	86 (17) <sup>27</sup>	80 (16) <sup>22</sup>	0.05
Calcium antagonist	30 (6) <sup>26</sup>	36 (7) <sup>22</sup>	0.04
Corticosteroids	38 (8) <sup>26</sup>	36 (7) <sup>22</sup>	0.02
Antidiabetics	25 (5) <sup>26</sup>	29 (6) <sup>22</sup>	0.03
Insulin	12 (2) <sup>26</sup>	8 (2) <sup>23</sup>	0.06
Primary diagnosis, no. (%)			
Cancer	161 (52)	146 (48)	
Ulcerative colitis/proctitis	82 (54)	70 (46)	
Liver metastases	59 (53)	52 (47)	
Crohn's disease	39 (45)	47 (55)	
Other intestinal diseases	40 (49)	41 (51)	
Tumor	42 (53)	38 (48)	
Diverticulitis	24 (62)	15 (38)	
Fistula	13 (39)	20 (61)	
Other liver diseases	9 (27)	24 (73)	
Enteritis/enterocolitis	14 (50)	14 (50)	
Pancreatitis	16 (64)	9 (36)	
Other pancreas diseases	8 (73)	3 (27)	
Gynecology diseases	4 (40)	6 (60)	
Hernia	4 (50)	4 (50)	
Gallbladder diseases	2 (29)	5 (71)	
Bowel obstruction	1 (17)	5 (83)	
Others	16 (40)	24 (60)	
Type of surgery (NOT mutually exclusive), no. (%)			
Liver resection	125 (24)	113 (21)	0.07
Ileostomy	113 (22)	129 (24)	0.06
Colectomy	108 (21)	123 (23)	0.06
Pancreatectomy	56 (11)	70 (13)	0.07
Panoduodenectomy	37 (7)	43 (8)	0.04
Proctectomy	37 (7)	35 (7)	0.02
Hysterectomy	14 (3)	17 (3)	0.03
Cholecystectomy	13 (2)	10 (2)	0.04
Lymphadenectomy	4 (1)	4 (1)	0.00
Nephrectomy	3 (1)	2 (0)	0.03
Splenectomy	11 (2)	8 (2)	0.05
Other resection	80 (15)	70 (13)	0.06
Lap exploratory	72 (14)	73 (14)	0.00
Rectal surgery	8 (2)	14 (3)	0.08
Anastomosis	51 (10)	62 (12)	0.06
Closure colostomy	18 (3)	17 (3)	0.01
Bowel resection	16 (3)	9 (2)	0.09
Sigma resection	11 (2)	10 (2)	0.02
Hernia repair	10 (2)	5 (1)	0.08

Summary statistics are presented as percentages of patients. Superscript number represents number of missing values.

\*Absolute standardized difference (ASD): absolute difference in means or proportions divided by the pooled SD; ASDs of 0.2, 0.5, and 0.8 represent small, median, and large differences.

**Appendix 4.** Incidence of Components of Postoperative Complications (N = 1,057)

Outcome	Before Discharge		Discharge to POD 30		Overall (30-day)	
	Colloid (n = 523)	Crystalloid (n = 534)	Colloid (n = 508)*	Crystalloid (n = 517)*	Colloid (n = 523)	Crystalloid (n = 534)
Major complications						
Cardiac	0 (0)	8 (2) <sup>2</sup>	1 (< 1) <sup>6</sup>	1 (< 1) <sup>9</sup>	1 (< 1) <sup>6</sup>	8 (2) <sup>10</sup>
Acute heart failure						
Myocardial infarction						
Ventricular arrhythmia						
Pulmonary	16 (3)	17 (3) <sup>2</sup>	1 (< 1) <sup>6</sup>	7 (1) <sup>9</sup>	17 (3) <sup>6</sup>	24 (5) <sup>10</sup>
Pulmonary embolism						
Pulmonary edema						
Respiratory failure						
Pneumonia						
Pulmonary pleural effusion						
Gastrointestinal	35 (7)	41 (8) <sup>2</sup>	6 (1) <sup>6</sup>	11 (2) <sup>9</sup>	41 (8) <sup>6</sup>	51 (10) <sup>10</sup>
Bowel and surgical anastomosis, stricture/obstruction or anastomotic leak						
Internal or external fistulas						
Peritoneal effusions						
Renal (requiring dialysis)	2 (< 1)	2 (< 1) <sup>2</sup>	0 (0) <sup>6</sup>	2 (< 1) <sup>9</sup>	2 (< 1) <sup>6</sup>	4 (1) <sup>10</sup>
Infections	40 (8)	40 (8) <sup>2</sup>	22 (4) <sup>6</sup>	20 (4) <sup>9</sup>	59 (11) <sup>6</sup>	58 (11) <sup>10</sup>
Deep or organ/space surgical site infection						
Sepsis						
Coagulation (bleeding)	14 (3)	10 (2) <sup>2</sup>	2 (< 1) <sup>6</sup>	2 (< 1) <sup>9</sup>	16 (3) <sup>6</sup>	12 (2) <sup>10</sup>
Minor complications						
Unplanned ICU admission	20 (4)	33 (6) <sup>2</sup>	3 (1) <sup>6</sup>	3 (1) <sup>9</sup>	22 (4) <sup>6</sup>	36 (7) <sup>10</sup>
Minor unplanned operation	24 (5) <sup>16</sup>	18 (3) <sup>12</sup>	5 (1) <sup>21</sup>	5 (1) <sup>23</sup>	29 (6) <sup>28</sup>	23 (5) <sup>29</sup>
Cardiac	32 (6)	45 (8) <sup>2</sup>	4 (1) <sup>100</sup>	2 (< 1) <sup>101</sup>	35 (8) <sup>95</sup>	46 (10) <sup>94</sup>
Ischemia						
Nonventricular Arrhythmia						
Hemodynamic disturbances						
Pulmonary effusion	35 (7) <sup>11</sup>	44 (8) <sup>9</sup>	4 (1) <sup>6</sup>	4 (1) <sup>9</sup>	38 (8) <sup>17</sup>	46 (9) <sup>17</sup>
Deep venous thrombosis	2 (< 1)	2 (< 1) <sup>2</sup>	0 (0) <sup>6</sup>	6 (1) <sup>10</sup>	2 (< 1) <sup>6</sup>	7 (1) <sup>11</sup>
Gastrointestinal	65 (12)	94 (18) <sup>2</sup>	12 (2) <sup>6</sup>	11 (2) <sup>9</sup>	75 (15) <sup>6</sup>	103 (20) <sup>10</sup>
Effusion						
Gut paralysis						
Progressive renal insufficiency	2 (< 1)	4 (1) <sup>2</sup>	2 (< 1) <sup>6</sup>	3 (1) <sup>9</sup>	4 (1) <sup>6</sup>	7 (1) <sup>10</sup>
Infection	100 (19) <sup>1</sup>	122 (23) <sup>2</sup>	46 (9) <sup>6</sup>	40 (8) <sup>9</sup>	139 (27) <sup>6</sup>	151 (29) <sup>10</sup>
Superficial						
Fever						
Cystitis or urinary tract infection						
Transient neurologic	3 (1)	7 (1) <sup>2</sup>	0 (0) <sup>6</sup>	1 (< 1) <sup>9</sup>	3 (1) <sup>6</sup>	8 (2) <sup>10</sup>
Any major morbidity	70 (13)	76 (14) <sup>2</sup>	28 (6) <sup>6</sup>	33 (7) <sup>9</sup>	91 (18) <sup>6</sup>	103 (20) <sup>10</sup>
Any minor morbidity	173(34) <sup>11</sup>	202 (38) <sup>6</sup>	59 (15) <sup>102</sup>	58 (14) <sup>103</sup>	214 (48) <sup>76</sup>	234 (51) <sup>71</sup>

Superscript numbers represent the number of missing values. Pulmonary pleural effusion was not asked on the old version of the case report form for 22 and 23 patients at discharge and 30-day follow-up, respectively. We assumed that those patients did not have pulmonary pleural effusion given the evidence that they did not have other pulmonary complications. Unplanned operation was not asked on the old version of the case report form for 22 and 17 patients at discharge and 30-day follow-up, respectively. Those were reported as missing in the above table.

\*In total, 15 patients in crystalloid group and 17 patients in the colloid group died during hospital stays < 30 days or stayed in hospital for > 30 days; therefore, the 30-day follow-up was not done.

ICU, intensive care unit; POD, postoperative day.

**Appendix 5.** Summary of Preoperative and Serum Creatinine Concentrations from Postoperative Days 1 to 14

Creatinine (mg/dl)	N	Colloids (n = 523)	N	Crystalloids (n = 534)
Preoperative	520	0.85 [0.73, 0.97]	527	0.83 [0.73, 0.94]
Maximum postoperative before discharge	521	0.83 [0.71, 1.00]	527	0.85 [0.71, 1.00]
POD 1	476	0.79 [0.67, 0.94]	493	0.77 [0.66, 0.92]
POD 2	437	0.74 [0.62, 0.90]	431	0.75 [0.63, 0.87]
POD 3	341	0.75 [0.61, 0.88]	373	0.73 [0.60, 0.85]
POD 4	316	0.73 [0.61, 0.88]	341	0.74 [0.60, 0.86]
POD 5	259	0.72 [0.61, 0.86]	263	0.74 [0.62, 0.87]
POD 6	195	0.75 [0.61, 0.88]	204	0.76 [0.64, 0.91]
POD 7	170	0.74 [0.59, 0.88]	175	0.75 [0.62, 0.88]
POD 8	115	0.76 [0.65, 0.92]	110	0.75 [0.62, 0.92]
POD 9	101	0.78 [0.64, 0.92]	95	0.77 [0.66, 0.96]
POD 10	89	0.76 [0.61, 0.97]	99	0.75 [0.63, 1.00]
POD 11	64	0.76 [0.62, 0.92]	76	0.74 [0.62, 0.88]
POD 12	65	0.75 [0.62, 0.93]	52	0.77 [0.65, 0.94]
POD 13	43	0.82 [0.56, 0.96]	59	0.71 [0.59, 0.82]
POD 14	45	0.82 [0.66, 0.96]	45	0.72 [0.63, 0.92]

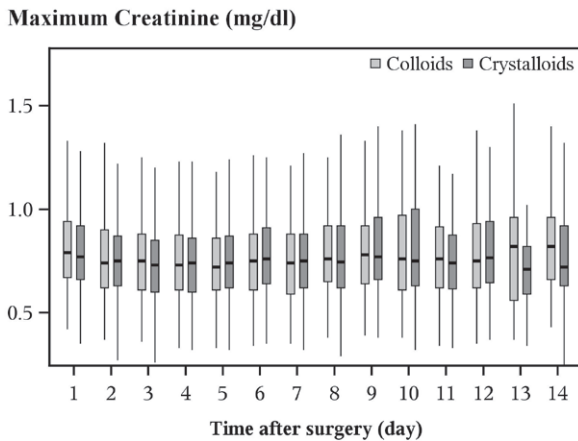
Numbers in brackets indicate range. POD, postoperative day.

**Appendix 7.** Summary of Preoperative and Maximum Serum Creatinine Concentrations within Each Month after Surgery

Creatinine (mg/dl)	N	Colloids (n = 523)	N	Crystalloids (n = 534)
Preoperative	520	0.85 [0.73, 0.97]	527	0.83 [0.73, 0.94]
Maximum postoperative within 6 months	521	0.87 [0.73, 1.06]	529	0.87 [0.75, 1.05]
Within 1 month	521	0.85 [0.72, 1.01]	529	0.85 [0.72, 1.02]
1 to 2 months	152	0.84 [0.72, 1.04]	177	0.84 [0.73, 0.96]
2 to 3 months	71	0.78 [0.70, 1.04]	87	0.80 [0.70, 0.93]
3 to 4 months	34	0.83 [0.75, 0.98]	44	0.78 [0.72, 0.93]
4 to 5 months	21	0.83 [0.72, 0.94]	18	0.71 [0.63, 0.79]
5 to 6 months	12	0.84 [0.73, 1.00]	3	0.62 [0.54, 0.73]

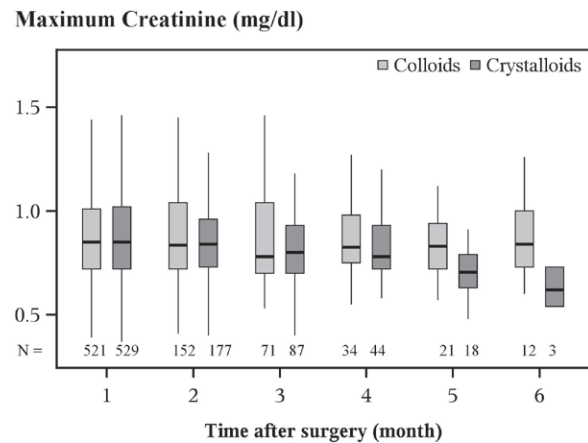
The data are number of patients (n) and median [quartile 1, quartile 3].

**Appendix 6. Box Plots of Maximum Postoperative Serum Creatinine Concentrations from Postoperative Days 1 to 14**



Bottoms and tops of the boxes are 25th and 75th percentiles, the middle line is the median, and the whiskers extend to the smaller of the end of the data (minimum or maximum) or 1.5 interquartile ranges beyond the top or bottom of box. Creatinine values between 0.5 and 1.4 mg/dl are generally considered to be in the normal range.

**Appendix 8. Box Plots of Maximum Postoperative Serum Creatinine Concentrations from Postoperative Months 1 to 6**



Bottoms and tops of boxes are 25th and 75th percentiles, the middle line is the median, and the whiskers extend to the smaller of the end of the data (minimum or maximum) or 1.5 interquartile ranges beyond the top or bottom of box. Creatinine values between 0.5 and 1.4 mg/dl are generally considered to be in the normal range. Sample size for each period for colloids and crystalloids is as follows (see appendix 7): surgery to 1 month (521, 529), 1 to 2 months (152, 177), 2 to 3 months (71, 87), 3 to 4 months (34, 44), 4 to 5 months (21, 18), and 5 to 6 months (12, 3).



**Appendix 9-1.** Baseline and Intraoperative Characteristics before the Protocol Was Changed on March 2, 2011 (N = 259)

Variables	Colloids (n = 128)	Crystalloids (n = 131)	ASD*
Age, yr	55.1 ± 14.1	56.2 ± 12.8	0.08
Body mass index, kg/m <sup>2</sup>	25.7 ± 4.8	29.6 ± 45.6	0.12
Female, no. (%)	57 (45)	70 (53)	0.18
ASA physical status, no. (%)			0.21
I	30 (23)	25 (19)	
II	80 (63)	94 (72)	
III	18 (14)	12 (9)	
Race (white), no. (%)	126 (98)	130 (99)	0.08
Medical history, no. (%)			
Pulmonary disease	7 (6) <sup>4</sup>	7 (6) <sup>6</sup>	0.002
Cardiovascular disease	44 (35) <sup>2</sup>	47 (36) <sup>2</sup>	0.03
Neurologic disease	7 (6) <sup>20</sup>	4 (4) <sup>17</sup>	0.14
Diabetes	11 (10) <sup>20</sup>	14 (12) <sup>16</sup>	
Insulin use	2 (2) <sup>21</sup>	0 (0) <sup>19</sup>	0.20
History of PONV	14 (11)	13 (10)	0.03
Alcohol (more than 25 drinks per week)	0 (0) <sup>48</sup>	2 (2) <sup>42</sup>	0.21
Smoking status			0.02
No	43 (64) <sup>51</sup>	47 (64) <sup>57</sup>	
Yes, currently	18 (27)	20 (27)	
Yes, quit	6 (9)	7 (9)	
Preoperative bowel preparation			0.13
Home	1 (1)	0 (0)	
Hospital	37 (29)	36 (27)	
None	90 (70)	95 (73)	
Preoperative lab			
Creatinine, mg/dl	0.9 [0.8, 1.0]	0.9 [0.8, 0.9]	0.27
Albumin, g/dl	4.6 [4.0, 43.1] <sup>7</sup>	4.5 [3.9, 42.5] <sup>10</sup>	0.05
Hemoglobin, gm/dl	13.4 ± 2.8	13.3 ± 2.2	0.05
Hematocrit, %	39.1 ± 4.2	39.2 ± 4.0	0.03
Normotest/PT, s	114.5 [98, 130]	113 [97, 131] <sup>1</sup>	0.01
APTT STA, s	35.2 [32.7, 37.9]	35.0 [32.1, 37.6] <sup>2</sup>	0.12
Preoperative IV fluid per weight, ml/kg	6.7 [5.8, 7.9]	6.8 [6.1, 7.9]	0.11
Intraoperative variables			
Duration of anesthesia, h	4.6 [3.5, 5.7]	4.8 [4.0, 5.9]	0.17
Duration of surgery, h	3.7 [2.7, 4.7]	3.8 [3.0, 5.0]	0.16
Crystalloid, l	1.5 [1, 2]	3.1 [2.2, 4.4]	1.26
Colloid, l	1 [0.5, 1.5]	0.0 [0.0, 0.0]	4.78
Number of boluses	4.0 [2.0, 5.5]	6.0 [3.0, 10.0]	0.61
Blood given, ml	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.30
Estimated blood lost, ml	300 [200, 625]	300 [200, 500] <sup>1</sup>	0.11
Estimated urine output, ml	300 [200, 445]	300 [170, 500]	0.08
Other fluids, ml	350 [200, 450]	400 [300, 500]	0.26
Net fluids, l	2.46 [1.85, 3.3]	3.2 [2.1, 4.3]	0.51
TWA MAP, mmHg	76.4 ± 8.3 <sup>34</sup>	74.6 ± 9.0 <sup>34</sup>	0.21
End-tidal Pco <sub>2</sub> , %	34.2 ± 3.3 <sup>34</sup>	33.5 ± 3.2 <sup>34</sup>	0.20
Final intraoperative core temperature, °C	37.0 ± 4.3 <sup>35</sup>	36.6 ± 0.6 <sup>35</sup>	0.13
TWA Fio <sub>2</sub> , %	79.4 ± 1.8 <sup>34</sup>	79.4 ± 3.4 <sup>34</sup>	0.01
MAC Hours	0.7 ± 0.5 <sup>34</sup>	0.7 ± 0.4 <sup>34</sup>	0.07
Phenylephrine, mg	0.0 [0.0, 0.4]	0.1 [0.0, 0.6]	0.27

Summary statistics are presented as percentages of patients, means ± SD, or medians [quartile 1, quartile 3], respectively. Superscript numbers represent number of missing values.

\*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD; ASD of 0.2, 0.5, and 0.8 represent small, median, and large differences.

APTT, partial thromboplastin time; ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; Fio<sub>2</sub>, fraction inspired oxygen concentration; MAC, minimum alveolar concentration, a measure of anesthetic dose; MAP, mean arterial pressure; Pco<sub>2</sub>, end-tidal partial pressure of carbon dioxide; PONV, postoperative nausea and vomiting; PT, prothrombin time; ST, ST-segment; TWA, time weighted average.

**Appendix 9-2.** Baseline and Intraoperative Characteristics after the Protocol Was Changed on March 2, 2011 (N = 798)

Variables	Colloids (n = 395)	Crystalloids (n = 403)	ASD*
Age, yr	50.3 ± 15.8	50.5 ± 16.2	0.01
Body mass index, kg/m <sup>2</sup>	25.8 [22.3, 29.4]	25.6 [22.4, 29.0]	0.01
Female, no. (%)	185 (47)	198 (49)	0.04
ASA physical status, no. (%)			0.06
I	24 (6) <sup>7</sup>	21 (5) <sup>1</sup>	
II	220 (57)	222 (55)	
III	144 (37)	159 (40)	
Race (white), no. (%)	369 (93)	378 (94)	0.02
Medical history, no. (%)			
Pulmonary disease	34 (9) <sup>5</sup>	31 (8) <sup>7</sup>	0.03
Cardiovascular disease	98 (25) <sup>1</sup>	114 (28)	0.08
Neurologic disease	18 (5)	19 (5)	0.01
Diabetes	29 (7) <sup>1</sup>	24 (6)	0.06
Insulin use	9 (2)	7 (2) <sup>1</sup>	0.04
History of PONV	29 (7) <sup>1</sup>	35 (9) <sup>1</sup>	0.05
Alcohol (more than 25 drinks per week)	24 (6) <sup>1</sup>	27 (7) <sup>1</sup>	0.03
Smoking status			0.13
No	228 (58) <sup>1</sup>	252 (63)	
Yes, currently	77 (20)	80 (20)	
Yes, quit	89 (23)	70 (17)	
Preoperative bowel preparation			0.03
Home	52 (13) <sup>4</sup>	56 (14) <sup>1</sup>	
Hospital	78 (20)	76 (19)	
None	261 (67)	270 (67)	
Preoperative lab			
Creatinine, mg/dl	0.8 [0.7, 1.0] <sup>3</sup>	0.8 [0.7, 0.9] <sup>7</sup>	0.00
Albumin, g/dl	4.3 [4.0, 4.7] <sup>92</sup>	4.3 [4.0, 4.7] <sup>103</sup>	0.03
Hemoglobin, gm/dl	39.5 ± 5.4 <sup>3</sup>	39.4 ± 5.4 <sup>1</sup>	0.02
Hematocrit, %	40.1 [37.5, 42.7] <sup>3</sup>	39.7 [36.8, 42.9] <sup>1</sup>	0.05
Normotest/PT, s	89.1 [12.9, 110] <sup>230</sup>	88.5 [15.3, 105] <sup>245</sup>	0.04
APTT STA, s	32.6 [29.0, 35.7] <sup>230</sup>	32.3 [29.8, 34.7] <sup>237</sup>	0.09
Preoperative IV fluid per weight, ml/kg	5.7 [0.0, 7.5] <sup>26</sup>	5.6 [0.0, 7.8] <sup>28</sup>	0.01
Intraoperative variables			
Duration of anesthesia, h	4.4 [3.3, 5.7]	4.4 [3.4, 5.6]	0.04
Duration of surgery, h	3.2 [2.3, 4.4]	3.2 [2.3, 4.6]	0.06
Crystalloid, l	1.85 [1.25, 2.4]	3.3 [2.33, 4.39]	0.61
Colloid, l	1.0 [0.5, 1.5] <sup>2</sup>	0.0 [0.0, 0.0] <sup>10</sup>	2.01
Number of boluses	4.0 [2.0, 6.0]	5.0 [2.0, 8.0]	0.38
Blood given, ml	0 [0, 0] <sup>9</sup>	0 [0, 0] <sup>10</sup>	0.00
Estimated blood lost, ml	237 [100, 500] <sup>1</sup>	200.0 [100, 450]	0.03
Estimated urine output, ml	340 [190, 550] <sup>4</sup>	350 [200, 500] <sup>6</sup>	0.03
Other fluids, ml	0 [0, 350] <sup>36</sup>	0 [0, 450] <sup>40</sup>	0.03
Net fluids, l	2.68 [1.87, 3.55]	3.2 [2.28, 4.38]	0.37
TWA MAP, mmHg	80.7 ± 8.5	81.3 ± 8.5	0.07
End-tidal Pco <sub>2</sub> , %	34.7 ± 2.1 <sup>1</sup>	34.4 ± 2.0 <sup>1</sup>	0.16
Final intraoperative core temperature, °C	36.7 ± 3.1	36.7 ± 3.1 <sup>11</sup>	0.03
TWA Fio <sub>2</sub> , %	65.4 ± 1	65.9 ± 21.7 <sup>1</sup>	0.02
MAC, h	2.6 ± 2.8 <sup>3</sup>	2.5 ± 2.0 <sup>2</sup>	0.03
Phenylephrine, mg	0.1 [0.0, 0.4]	0.1 [0.0, 0.6]	0.12

Summary statistics are presented as percentages of patients, means ± SD, or medians [quartile 1, quartile 3], respectively. Superscript numbers represents number of missing values.

\*Absolute standardized difference: absolute difference in means or proportions divided by the pooled SD; ASD of 0.2, 0.5, and 0.8 represent small, median, and large differences.

APTT, partial thromboplastin time; ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; Fio<sub>2</sub>, fraction inspired oxygen concentration; MAC, minimum alveolar concentration, a measure of anesthetic dose; MAP, mean arterial pressure; Pco<sub>2</sub>, end-tidal partial pressure of carbon dioxide; PONV, postoperative nausea and vomiting; PT, prothrombin time; ST, ST-segment; TWA, time weighted average.

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