Crystalloid *versus* Colloid for Intraoperative Goal-directed Fluid Therapy Using a Closed-loop System

A Randomized, Double-blinded, Controlled Trial in Major Abdominal Surgery

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ABSTRACT

Background: The type of fluid and volume regimen given intraoperatively both can impact patient outcome after major surgery. This two-arm, parallel, randomized controlled, double-blind, bi-center superiority study tested the hypothesis that when using closed-loop assisted goal-directed fluid therapy, balanced colloids are associated with fewer postoperative complications compared to balanced crystalloids in patients having major elective abdominal surgery.

Methods: One hundred and sixty patients were enrolled in the protocol. All patients had maintenance-balanced crystalloid administration of 3 ml · kg^{-1} · h^{-1}. A closed-loop system delivered additional 100-ml fluid boluses (patients were randomized to receive either a balanced-crystalloid or colloid solution) according to a predefined goal-directed strategy, using a stroke volume and stroke volume variation monitor. All patients were included in the analysis. The primary outcome was the Post-Operative Morbidity Survey score, a nine-domain scale, at day 2 postsurgery. Secondary outcomes included all postoperative complications.

Results: Patients randomized in the colloid group had a lower Post-Operative Morbidity Survey score (median [interquartile range] of 2 [1 to 3] *vs.* 3 [1 to 4], difference –1 [95% CI, –1 to 0]; $P < 0.001$) and a lower incidence of postoperative complications. Total volume of fluid administered intraoperatively and net fluid balance were significantly lower in the colloid group.

Conclusions: Under our study conditions, a colloid-based goal-directed fluid therapy was associated with fewer postoperative complications than a crystalloid one. This beneficial effect may be related to a lower intraoperative fluid balance when a balanced colloid was used. However, given the study design, the mechanism for the difference cannot be determined with certainty. **(Anesthesiology 2018; 128:55-66)**

THERE is increasing evidence that intraoperative fluid administration may affect patient outcomes after major surgery.[1] Two main factors have been implicated in the literature. On one hand, the quantity of fluid administered has been shown to significantly influence the incidence of postoperative complications.[2,3] As expected, this can be difficult to evaluate as there are large variations in every practitioner's approach to fluid management, which has resulted in a wide variation of patient care.[4,5] Combating this variation, goal-directed fluid therapy based on the optimization of flow-related variables has been shown to represent the best approach for fluid administration in high-risk surgical patients.[6,7] Unfortunately, the adoption of these strategies has tended to be low among providers and institutions.[8,9] One of the challenges in implementation is that goal-directed fluid therapy strategies require substantial training and vigilance in application. Compliance with treatment protocols has been shown to be suboptimal even in study conditions.[10,11] To address this problem, our team has

What We Already Know about This Topic

- Quantity of fluid and choice of crystalloid or colloid for intraoperative fluid therapy may have an impact on outcome after major surgery. Goal-directed fluid therapy can be used to guide the quantity of fluid given but may be difficult to use in clinical settings. A closed-loop system increases the clinical feasibility of goal-directed therapy.

What This Article Tells Us That Is New

- In a randomized controlled trial, closed-loop goal-directed colloid therapy had better postoperative outcomes compared to closed-loop goal-directed crystalloid therapy.

This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast. A.J. and A.D. are co-first authors.

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developed a closed-loop fluid administration system in order to assist providers in consistently applying goal-directed fluid therapy strategies in the operating room. This system has demonstrated feasibility and efficacy across a variety of clinical scenarios.[12–17] The system delivers fluid boluses using a standardized protocol and thus can maintain nearly 100% compliance and remove the provider as one of the main sources of variation for patient care.

In addition to how and how much fluid is delivered, the type of fluid administered can also play a role.[18] In intensive care, large randomized controlled trials have suggested that hydroxyethyl starches (HES) are associated with a higher incidence of complications.[19,20] Alternatively, the use of perioperative HES is still considered to be safe by many authors.[21–24] The debate over the optimal intravenous fluid is therefore still unresolved for patients undergoing major surgery. Theoretically, colloids have the advantage of maintaining intravascular osmotic pressure for an increased amount of time when using lower volumes to achieve the same hemodynamic endpoints compared to crystalloids.[25] As such, using HES as opposed to crystalloids within an automated closed-loop to guide goal-directed fluid therapy in patients undergoing major surgery may be associated with less fluid accumulation and fewer postoperative complications. Using a closed-loop system would thus allow us to specifically study the impact of the fluid administered since the system would be free from both variations in practice and in compliance with the goal-directed fluid therapy protocol.

We tested this hypothesis in a two-arm, parallel, randomized controlled, double-blind, bi-center superiority study, where patients scheduled for nonurgent major open abdominal surgery were randomized to receive either a balanced crystalloid solution (Plasmalyte; Baxter, Belgium) or a balanced colloid solution (Volulyte; Fresenius Kabi GmbH, Germany; see appendix 1 for precise composition) delivered by our automated closed-loop system.

Materials and Methods

Ethics

This trial was approved by the Ethics Committee of Brugmann and Erasme Hospitals (Brussels, Belgium) and registered on December 5, 2014 at clinicaltrials.gov (NCT02312999). The study was conducted in two centers in Brussels (Brugmann and Erasme Hospitals) from April 2015 through November 2016. All patients provided written informed consent before surgery.

Inclusion and Exclusion

Inclusion criteria were adult patients scheduled to undergo general anesthesia for elective open abdominal surgery expected to last at least 3 h. Exclusion criteria were patients less than 18 yr old, an American Society of Anesthesiologists physical status score greater than 3, a preoperative left ventricular ejection fraction less than 30%, significant cardiac arrhythmias or aortic regurgitation, coagulation disorders (activated partial thromboplastin time greater than 1.5 times normal value), preoperative renal insufficiency (serum creatinine greater than 2 mg/dl, oliguria, anuria, or hemodialysis), impaired hepatic function (phosphatase alkaline, aspartate aminotransferase, alanine aminotransferase greater than 2 times normal value), emergency surgery, preoperative infection, current pregnancy or lactation period, known allergy to HES, and participation in another trial. Additionally, patients who were found to have metastatic dissemination upon first surgical look and had their procedures cancelled (surgical time less than 3 h) were excluded. Finally, any patient that required an unexpected supra renal aortic clamping during their aortic surgery was also excluded.

Randomization, Blinding, and Data Collection

The randomization of the study (1:1) was created by the hospital pharmacist in blocks of 10, using internet-based randomization software (http://www.randomization.com; randomization plan created March 20, 2015, 15:50:08). The morning of surgery, blinded fluid solutions (visually identical plastic bags of 500 ml) were delivered to the anesthesiologist in charge of the patient. Study fluids were only identified by the assigned patient number. The preparation, storage, and dispensing of the study fluids was done independently by the hospital pharmacy of each institution. Importantly, all investigators remained blinded to the treatment allocation until the end of the study and the finalization of the statistical analysis. Intraoperative data were collected by the investigators and postoperative data by nurses, residents in anesthesiology, and research medical students not involved in the trial. The Post-Operative Morbidity Survey (POMS) score was determined on the morning of postoperative day 2 (POD2) by two investigators who remained blinded to the group allocation at that time (A.J. and A.D.).

Anesthesia Procedures

All included patients were allowed solid foods up to 6 h before surgery and fluids up to 2 h before surgery. Bowel preparation was not performed in any patients except for those undergoing aortic surgery. No enhanced recovery after surgery programs were in place in either hospital during the study. In both groups, premedication consisted of 0.5 mg of alprazolam, given the morning of the surgery. Some patients had an epidural catheter placed prior to anesthesia induction in the operating room; however, most patients received only a spinal morphine injection. Standard monitoring for this surgery included a 5-lead electrocardiogram, pulse oximetry, noninvasive blood pressure, invasive radial arterial pressure, central venous pressure, rectal temperature, inspiratory and expiratory gas concentrations, urine output, and a processed electroencephalography monitoring (Spectral Entropy, GE Healthcare,

Finland, for Brugmann Hospital; and Bispectral Index monitor, Covidien, Ireland, for Erasme Hospital). Additionally, all subjects were monitored with a minimally invasive cardiac output monitoring device (EV-1000, Edwards Lifesciences, USA). Anesthesia was induced with lean body weight–adjusted doses of propofol (2 mg/kg), remifentanil (Minto Pharmacokinetics model: 2 to 6 ng/ml), and rocuronium (0.5 mg/kg), and was maintained with remifentanil (2 to 6 ng/ml) and volatile anesthetic (either sevoflurane or desflurane, depending on physician preferences). After intubation, a protective ventilation approach was applied, consisting of a tidal volume of 8 ml/kg of lean body weight, a positive end expiratory pressure of 5 to 7 cm H_2O, and recruitment maneuvers whenever necessary. The respiratory rate was set to achieve an end-tidal carbon dioxide partial pressure between 32 and 36 mmHg. Adequate prophylactic antibiotics were administered to all patients. Inhaled volatile anesthetic and remifentanil concentrations were adjusted intraoperatively in order to target bispectral entropy or Bispectral Index (BIS) values between 40 and 60. Anesthetic delivery adjustments were made at the discretion of the physician. Mean arterial pressure (MAP) was kept above 65 mmHg with either ephedrine and/or phenylephrine boluses. If additional vasopressors were needed, norepinephrine was used as a continuous infusion. Red blood cells were transfused in addition to closed-loop fluid boluses to maintain hemoglobin concentration between 7 and 9 g/dl perioperatively. After skin closure, most patients were extubated in the operating room. The postoperative recovery was done in the postanesthesia care unit (PACU) or in the intensive care unit (ICU), depending on the type of surgery. All physicians caring for patients in the perioperative period were blinded to the study fluid allocation.

Closed-loop Setup

The closed-loop software (Sironis, USA; versions 4.5K and 4.9K) was run on a Shuttle X50 Touchscreen PC (Shuttle Computer Group, USA) and an ACER laptop running Windows 7 (Microsoft Corp., USA). The system was connected to the serial output port of the EV-1000 for real-time capture of data.

A Q-Core Sapphire Multi-Therapy Infusion Pump (Q-Core, Israel) was used by the closed-loop to deliver 100-ml mini-fluid challenges of the study fluids. The Sapphire pump is a single-channel volumetric pump capable of flow rates from 0.1 to 999 ml/h. The pump was controlled by the closed-loop system using the software provided by Q-Core (Netanya, Israel) *via* serial connection (Commands Server R.00).

After the placement of the radial line, but before incision, the closed-loop target was selected and started by the anesthetist in charge of the patient. All study cases were started with a standard setting of 15%, meaning the system considered a bolus "effective" if the response to the bolus scaled to 500 ml would have been a 15% increase in stroke volume (SV).

Closed-loop System Description and Fluid Administration

The closed-loop system has been described extensively in our previous publications.[14–16,26,27] "As a short review, the system monitors SV, stroke volume variation (SVV), heart rate, and MAP and uses this information to optimize SV. The controller uses both a model layer to formulate a predicted response to a fluid bolus and an adaptive layer for bolus-based error-correcting during direct fluid management to correct for changes induced by surgical and anesthetic conditions. The final action to be taken by the controller is then determined by a rule-based layer taking into account data provided by the previous layers. The system is ultimately a slope-seeking controller and aims to optimize patients' fluid status and stroke volume to near the plateau of the Starling Curve." The senior anesthetist in charge of the patient had the option to interact with the automated system and deliver or halt a fluid bolus manually if needed. Visual and audio alerts were created for each fluid bolus to ensure the anesthesiologist was aware of each intervention. Additionally, in order to prevent possible over-administration of fluid by the closed-loop system, the software required the amount of total fluid the closed-loop could deliver at a time to be predefined by the anesthesiologist (limited to 500-ml study bags).

After anesthesia induction, a baseline isotonic balanced crystalloid infusion (Plasmalyte) was set at 3 ml · kg^{-1} · h^{-1} *via* an infusion pump (Volumat Agilia, Fresenius Kabi, Belgium) and administered for the duration of the procedure. Additional fluid boluses were delivered by a goal-directed fluid therapy strategy that used the closed-loop system and consisted of multiple 100-ml mini-fluid challenges of the study fluid (Plasmalyte or Volulyte). In both groups, an upper limit daily dose of 33 ml/kg of the study fluid was allowed. If the upper limit of the study fluid was reached, unblinded Plasmalyte was consistently used thereafter in all patients. Importantly, the closed-loop system delivers only 100-ml fluid boluses over 6 min and is therefore not designed for bleeding resuscitation but rather fluid optimization in line with goal-directed fluid therapy protocols. As a result, the anesthesiologist in charge of the patient also had the opportunity to administer additional Plasmalyte without using the closed-loop (as rescue) in case of hemodynamic instability related to acute bleeding or aortic unclamping. No other fluids were allowed in addition to the rescue crystalloid (Plasmalyte). Lastly, if the senior anesthetist felt that the patient was fluid optimized but MAP was less than 65 mmHg (despite appropriate anesthetic depth), vasopressors could be used.

The postoperative maintenance fluid for all patients was 1.5 ml · kg^{-1} · h^{-1}, 5% dextrose–NaCl, 0.45%, in Brugmann Hospital and Sterofundin B (B-Braun Medical SA, Belgium) in Erasme Hospital. If additional volume was required, Plasmalyte or saline was administered, depending on physician preference. In our institutions, this was mostly done to treat oliguria (urine output less than 0.5 ml · kg^{-1} · h^{-1}) and increased lactate concentrations. However, if hypotension

occurred, administration of modified fluid gelatin, 3% (Geloplasma, Fresenius Kabi GmbH), was permitted as another option to crystalloid solution to quickly restore intravascular volume.

Outcomes, Data Collection, and Analysis

The following intraoperative characteristics were collected for each patient from the medical chart: time of anesthesia, time of surgery, fluid volumes and net fluid balance, urine output, estimated blood loss, and amount of vasopressors. The closed-loop system also recorded advanced hemodynamic data (cardiac output, SV, SVV) provided by the EV-1000 at 2-s intervals, as well as fluid bolus deliveries.

The primary outcome was the POMS score at POD2. This score includes nine domains for which patients were assessed for diagnostic features (pulmonary, infectious, renal, cardiovascular, gastrointestinal, neurologic, hematologic, wound, and pain; see appendix 2). This score has been validated and used in a wide range of elective moderate and major surgeries.[28] Secondary outcomes were the number of postoperative complications up to 30 days after surgery. Major complications included: cardiac (acute coronary syndrome/arrhythmia), pulmonary (embolism, edema, or pneumonia), gastrointestinal (bowel and surgical anastomotic leak), renal (renal failure requiring dialysis), infectious (peritonitis/sepsis), coagulation (bleeding requiring redo surgery), wound dehiscence, stroke, reoperation, and all cause of mortality at 30 days. Minor complications included superficial wound infection, urinary and other infection, paralytic ileus, need for loop diuretics, postoperative confusion, postoperative nausea and vomiting, and incidence of pruritus. A definition of these different outcomes is presented in appendix 3. An additional important secondary outcome that has been rigorously examined was the effect of study fluids on postoperative renal function. This was assessed by quantifying the incidence of either an acute kidney injury, which was defined using the Kidney Disease: Improving Global Outcomes (KDIGO)[29] classification of 1 or higher, or the requirement of renal replacement therapy (RRT). Finally, amounts of fluid given and lost, exposure to blood products, transfusion rates, laboratory and arterial blood gas parameters measured at different time points, and ICU and hospital length of stay (defined as the time from the day of the surgery to the last day in the hospital or death) were also analyzed. Importantly, hospital length of stay was also quantified using "fit for discharge criteria,"[30] as discharge from the hospital was decided by surgeons without real objective criteria.

Study Power

A priori determination of the number of patients needed for each group was based on the recorded POMS score of previous patients in both hospitals. Previously, the mean POMS score at POD2 was 3.09 and SD was 2.13. Considering that the minimum clinically important difference was a 1-point difference in the primary endpoint, a study with a power of 80% and an alpha error of 0.05 will require 73 patients per group. As a result, we decided to include 160 patients (80 per group). No interim analysis was planned.

Statistical Analysis

Intention-to-treat analysis was performed on data. Continuous data were tested for normality using a Kolmogorov-Smirnov test. As they were not normally distributed, they were reported as median and interquartile range, and comparisons were made with a Mann-Whitney U test. Discrete data were presented as percentages and compared using a chi-square or a Fisher exact test when indicated. Significance was set at the 0.05 level. Data were analyzed using Minitab (France).

Results

A total of 198 patients were screened for eligibility from April 2015 through November 2016. Ultimately, 160 patients were recruited and prospectively randomized between the two groups. Ten patients presented exclusion criteria after randomization: six in the crystalloid group (unexpected suprarenal aortic clamping [n = 2]; surgery duration less than 3 h [n = 2]; protocol violation [n = 2]: administration of nonprotocol fluids) and four in the colloid group (unexpected suprarenal aortic clamping [n = 1]; surgery duration less than 3 h [n = 2]; missed preoperative exclusion criteria [n = 1]). All were included in the intention-to-treat analysis (fig. 1). Patient baseline characteristics are presented in table 1.

Intraoperative Data

Maintenance balanced crystalloid volume was not different between groups, and neither was the requirement for additional rescue fluid (table 2). The total volume of study fluid was 1,500 ml (interquartile range, 800 to 2,500 ml) in the crystalloid group and 900 ml (400 to 1,300 ml) in the colloid group. Study fluid volume, total amount of fluid, and net fluid balance were significantly lower in the colloid group compared to the crystalloid group ($P < 0.001$ for all). Moreover, only one patient (1%) in the colloid group reached the maximum study fluid dose (33 ml · kg^{-1} · day^{-1}) compared to 16 patients (20%) in the crystalloid group ($P < 0.001$). The need for any kind of blood component transfusion was not different between groups. However, the use of vasopressors was lower in the colloid group than in the crystalloid group (55% *vs.* 89%; $P < 0.001$). Patients in the colloid group had a significantly lower heart rate (67 [60 to 76] *vs.* 72 [64 to 82]; $P = 0.012$) and SVV (8 [7 to 9] *vs.* 10 [8 to 13]; $P < 0.001$), and a higher MAP (79 [74 to 84] *vs.* 75 [72 to 81]; $P = 0.036$) (table 3).

Outcome Variables

The POMS score (primary endpoint) was significantly lower in the colloid group (2 [1 to 3] *vs.* 3 [1 to 4]; –1 (–1

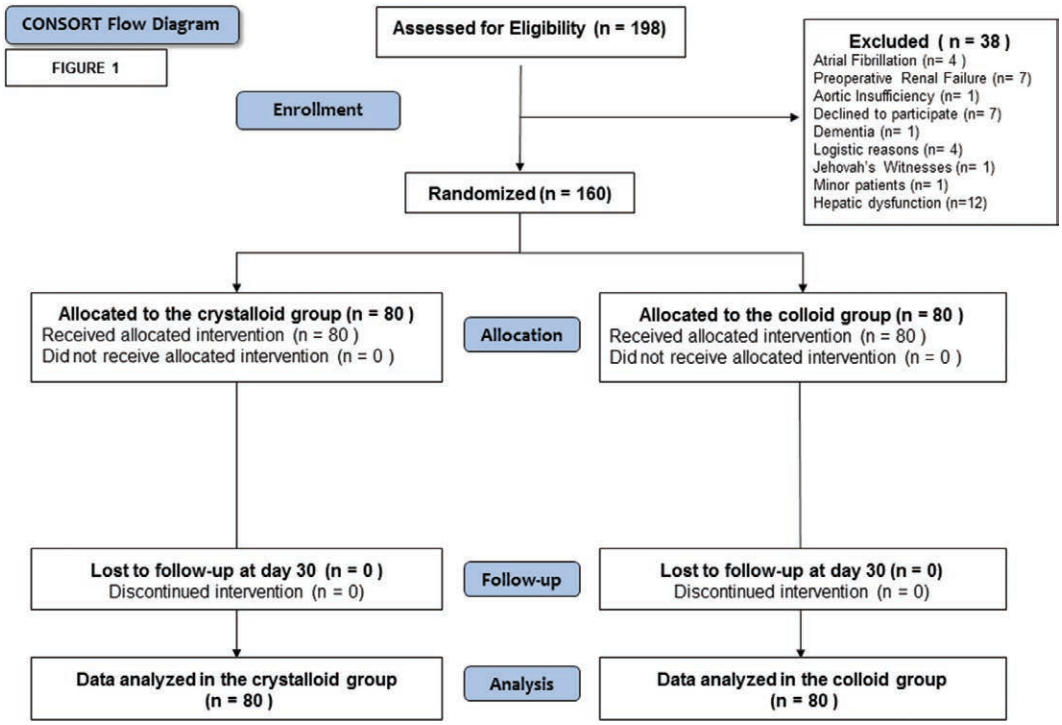

Fig. 1. Consolidated Standards of Reporting Trials flow diagram of the study.

to 0); $P < 0.001$). The incidence of complications was also significantly lower in the colloid group than in the crystalloid group (table 4). More specifically, the incidence of anastomotic leakage was significantly higher in the crystalloid group than in the colloid group for patients undergoing gastrointestinal anastomosis (table 4). Renal function assessed by the KDIGO classification[29] revealed no difference between groups. Two patients experienced RRT in the postoperative period (one in each group; patients had a suprarenal aortic clamping during their surgery). Length of stay in the ICU, PACU, and hospital did not differ between groups. Three patients died within 30 postoperative days—all in the crystalloid group. The first person died from hemorrhagic shock on POD1, the second from an anastomotic leak on POD7, and the third from pulmonary embolism after hospital discharge (POD15).

Laboratory and arterial blood gas parameters measured at different time points were not different between groups (data not shown). However, on arrival in the ICU/PACU, significantly fewer patients in the colloid group had lactate levels greater than 2 mEq/l (23% *vs.* 39%; $P = 0.029$).

Closed-loop Management

The anesthesiologists in charge of the patients never discontinued an active fluid bolus that was administered by the automated system. Additional fluid boluses were delivered manually through the closed-loop system by the anesthesiologist in charge of the patient in 41% of the cases in the crystalloid group and in 28% of the cases in the colloid group ($P = 0.07$). In these patients, the number of additional boluses did not differ between groups (crystalloid group: 2 [1 to 2]; colloid group: 1 [1 to 1]; $P = 0.12$). In most of the cases, the reason for additional fluid was acute bleeding.

Per-protocol analysis included 74 patients in the crystalloid group and 76 patients in the colloid group. Results of this analysis (data not shown) did not differ from the intention-to-treat analysis.

Discussion

In the conditions of our study, a colloid-based goal-directed fluid therapy was associated with a lower POMS score and fewer postoperative complications when compared with a crystalloid-based goal-directed fluid therapy in patients undergoing major abdominal surgery. These beneficial effects may be secondary to the significant decrease in intraoperative fluid and net fluid balance in the colloid group; however, given the study design, it is not possible to distinguish whether the type of fluid, the total volume, or a combination of both was responsible for the observed effect. Only two prospective, randomized, double-blinded studies have compared the efficacy of colloids and crystalloids when using a goal-directed approach for fluid management in patients undergoing abdominal surgery. In the first study, Yates *et al.*[31] reported no perioperative benefit of HES over crystalloids in terms of complications and need of vasopressors in 202 patients undergoing colorectal surgery, despite a lower amount of volume required. A continuous cardiac output monitor (LIDCO Rapid, United Kingdom) was used to standardize and guide fluid therapy in their patients. However, 38% of patients in the crystalloid group received

Table 1. Baseline Characteristics

Characteristics	Crystalloid Group (N = 80)	Colloid Group (N = 80)
Age (yr)	62 [48 to 70]	65 [53 to 73]
Male sex (%)	51 (64)	45 (56)
Weight (kg)	71 [63 to 82]	74 [64 to 83]
Height (cm)	170 [165 to 174]	170 [164 to 175]
BSA (m^2)	1.8 [1.7 to 2.0]	1.9 [1.7 to 2.0]
BMI (kg/m^2)	24.9 [22.4 to 27.4]	25.4 [22.8 to 29.1]
ASA physical status 2	45 (56)	48 (60)
ASA physical status 3	35 (44)	32 (40)
Medications (%)		
Aspirin	26 (33)	24 (30)
Clopidogrel	4 (5)	0 (0)
β blocker	20 (25)	27 (34)
ACEI	18 (23)	19 (24)
ARB	7 (9)	4 (5)
Calcium channel blocker	13 (16)	8 (10)
Diuretics	5 (6)	5 (6)
Statin	20 (25)	28 (35)
Oral hypoglycemic drugs	7 (9)	8 (10)
Insulin	3 (4)	3 (4)
Type of surgery (%)		
Pancreatectomy	19 (24)	22 (28)
Cystectomy	7 (9)	11 (14)
Aortic surgery	11 (14)	6 (8)
Gastrectomy	5 (6)	7 (9)
Major gynecologic	7 (9)	2 (3)
Nephrectomy	7 (9)	8 (10)
Colectomy	19 (24)	18 (23)
Other surgical procedure*	5 (6)	6 (8)
High-risk surgery (%)	46 (58)	42 (53)
Standard bowel preparation (%)	6 (8)	3 (4)
POSSUM physiology score	16 [14 to 18]	16 [15 to 19]
POSSUM operative score	14 [11 to 18]	13 [11 to 17]
POSSUM-predicted morbidity (%)	31 [18 to 53]	33 [21 to 54]
POSSUM-predicted mortality (%)	1.5 [0.8 to 2.8]	1.6 [0.8 to 3.3]
Surgery duration (min)	310 [211 to 375]	250 [183 to 312]
Anesthesia duration (min)	388 [271 to 450]	318 [242 to 388]
Mechanical ventilation time (min)	360 [249 to 431]	296 [226 to 370]
Lumbar spinal analgesia (%)	70 (88)	67 (84)

Population data are listed as value (%) and quantitative data as median [25th to 75th percentiles]. Note that high-risk surgeries are those where estimated surgical risk of 30-day cardiac event rates (cardiac death and myocardial infarction) were greater than 5%.

* Included prostatectomy, surrenalectomy, and retroperitoneal lymphadenectomy.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers; ASA = American Society of Anesthesiologists; BMI = body mass index; BSA = body surface area; POSSUM = Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity.

a rescue colloid (modified fluid gelatin), compared to 12% of patients in the HES group. As a result, this trial compared two groups that received a combination of crystalloid and colloid in different proportions. In the second study, Feldheiser *et al.*[32] reported that a balanced HES solution was associated with a higher stroke volume and a lower volume of fluid administered in 50 patients undergoing ovarian cancer surgery. In this study, a goal-directed fluid protocol was applied using the esophageal doppler. However, as it was a small pilot study, the trial was underpowered to assess the effects of study fluids on postoperative complications and hospital length of stay. When the results of these two previously published studies comparing balanced crystalloids to balanced colloids are examined together, they suggest that balanced colloids induce a larger volume expansion effect compared to crystalloids, and as a result, a lesser volume of colloids was needed to achieve a comparable hemodynamic endpoint. As no clear outcome benefit emerged from the previous studies, no recommendation regarding the use of colloids over crystalloids in the perioperative setting could be made. The present study makes a much stronger connection between fluid type, optimizing physiologic variables, and improving clinical outcome. Moreover, the use of the closed-loop system to remove intervention bias between groups is a feature that has not previously been possible in comparing fluids.

Table 2. Intraoperative Data

Variables	Crystalloid Group (N = 80)	Colloid Group (N = 80)	Difference (95% CI)	*P* Value
Maintenance crystalloid volume (ml · kg^{-1} · h^{-1})	3.8 [3.5 to 4.2]	3.8 [3.4 to 4.1]	0.1 (–0.1 to 0.3)	0.31
Study fluid volume (ml · kg^{-1} · h^{-1})	4.0 [2.6 to 6.2]	2.9 [1.9 to 3.9]	1.2 (0.5 to 1.9)	**< 0.001**
Patients reaching limit dose of study solution (%)*	20	1	19 (10 to 28)	**< 0.001**
Rescue fluid required (%)†	24	11	13 (1 to 24)	**0.035**
Rescue fluid volume (ml/kg)†	12.2 [4.2 to 18.8]	7.0 [4.7 to 12.2]	2.9 (–2.1 to 10.4)	0.31
Total in (ml · kg^{-1} · h^{-1})	9.5 [6.8 to 11.1]	7.1 [5.7 to 8.5]	2.0 (1.1 to 3.0)	**< 0.001**
Urine output (ml · kg^{-1} · h^{-1})	1.2 [0.8 to 1.9]	1.4 [0.9 to 2.3]	–0.2 (–0.5 to 0.0)	0.07
Estimated blood loss (ml · kg^{-1} · h^{-1})	1.7 [0.8 to 3.3]	2.1 [1.1 to 4.1]	–0.3 (–0.8 to 0.2)	0.18
Total out (ml · kg^{-1} · h^{-1})	3.5 [1.9 to 5.6]	4.5 [2.7 to 6.1]	–0.8 (–1.5 to –0.1)	**0.037**
Fluid balance (ml · kg^{-1} · h^{-1})	5.2 [3.2 to 7.5]	2.7 [1.5 to 4.1]	2.6 (1.8 to 3.5)	**< 0.001**
Blood component transfusion (%)				
PRBC	11	13	–1 (–11 to 9)	0.81
FFP	1	3	–1 (–5 to 3)	1.00
Platelets (6 to 8 unit bags)	0	1	–1 (–4 to 1)	1.00
Any blood product (%)	11	13	–1 (–11 to 9)	0.81
Ephedrine (%)	78	43	35 (21 to 49)	**< 0.001**
Phenylephrine (%)	26	16	10 (–3 to 23)	0.12
Norepinephrine (%)	39	11	28 (15 to 40)	**< 0.001**
Patients under vasoactive infusion agents (%)	89	55	34 (21 to 47)	**< 0.001**

Qualitative data are listed as value (%) and quantitative data as median [25th to 75th percentiles] and difference (95% CI). Doses of ephedrine and phenylephrine were not different between groups. Bold indicates significant results with *P* value < 0.05.

*33 (ml · kg^{-1} · day^{-1}). †Plasmalyte administered without the closed loop because of hemodynamic instability.

FFP = fresh-frozen plasma; PRBC = packed erythrocyte.

Table 3. Perioperative Hemodynamic Data

Variables	Crystalloid Group (N = 80)	Colloid Group (N = 80)	Difference (95% CI)	*P* Value
Intraoperative HR (beats/min)	72 [64 to 82]	67 [60 to 76]	5 (1 to 8)	**0.012**
Intraoperative MAP (mmHg)	75 [72 to 81]	79 [74 to 84]	–2 (–5 to 0)	**0.036**
Intraoperative SVI (ml/m^2)	38.2 [33.2 to 45.6]	40.9 [35.1 to 47.6]	–2.0 (–4.7 to 0.7)	0.17
Intraoperative cardiac index (l · min^{-1} · m^{-2})	2.67 [2.35 to 3.30]	2.66 [2.33 to 3.24]	0.04 (–0.15 to 0.23)	0.70
Intraoperative SVV (%)	10 [8 to 13]	8 [7 to 9]	2 (1 to 3)	**< 0.001**
Postoperative HR (beats/min)	82 [72 to 93]	79 [73 to 86]	3 (–1 to 7)	0.18
Postoperative MAP (mmHg)	77 [70 to 86]	78 [73 to 84]	–1 (–5 to 2)	0.46
Postoperative CVP (cm H_2O)	6.5 [5.0 to 8.0]	7.0 [4.0 to 9.0]	0 (–1 to 1)	0.91

Data are expressed as median [25th to 75th percentiles] and difference (95% CI). Intraoperative variables were recorded by the closed-loop system at 2-s intervals and averaged. Postoperative variables is an average of the variables recorded at four different time points in the postoperative period (at arrival at postanesthesia or intensive care unit, +6 h, +12 h postarrival, and morning of postoperative day 1). Bold indicates significant results with *P* value < 0.05.

CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; SVI = stroke volume index; SVV = stroke volume variation.

Several recent investigations have emphasized the positive effects of using a goal-directed fluid protocol to guide fluid administration.[30,33] This strategy has been recommended by professional societies in European countries.[34] Despite this, it is not commonly implemented in clinical practice.[35] Among the likely reasons is the fact that goal-directed fluid strategies require substantial training, attention, and effort for reliable and effective implementation. Even under perfect study conditions, compliance rates are often 50% or less.[10,11,36] Additionally, the recent OPTIMIZE trial emphasized that a learning curve is present when trying to apply a goal-directed fluid protocol.[7] Therefore, a closed-loop system may boost compliance to protocols and improve accuracy of implementation. Computers are ideally suited for repetitive and "attention-based" work, and are not limited by an inevitable decrease in vigilance when compared to that of humans.[37] Such systems consistently exhibit superiority in maintaining a set target over clinicians.[38]

In the current study, the use of our closed-loop fluid delivery system was beneficial as it involved a strict standardization of study fluid administration, which resulted in similar treatment of both groups. This system provided consistent, individualized, goal-directed fluid therapy for all cases while removing interprovider variability as a frequent confounder. Whether the beneficial effect observed with the use of colloids is secondary to improved optimization of central cardiovascular variables such as cardiac output or SV *versus* peripheral effects of fluid type is difficult to determine. The higher rate of postoperative

Table 4. Postoperative Data and Outcome Variables

Variables	Crystalloid Group (N = 80)	Colloid Group (N = 80)	Difference (95% CI)	*P* Value
POMS score at POD2	3 [1 to 4]	2 [1 to 3]	1 (0 to 1)	**< 0.001**
Patients under vasopressors (%)	18	4	14 (4 to 23)	**0.009**
Fluid balance at POD1 (ml/kg)	22.1 [11.7 to 40.9]	15.8 [9.2 to 26.0]	5.5 (–0.2 to 12.0)	0.06
Weight gain at POD2 (kg)*	0.25 [0 to 1.00]	0.00 [–0.20 to 0.10]	0.30 (0.0 to 1.00)	**0.028**
Blood components transfusion (%)				
PRBC	20	11	9 (–2 to 20)	0.13
FFP	3	1	1 (–3 to 5)	1.0
Any kind of blood product (%)	20	13	8 (–4 to 19)	0.20
Major complications (%)				
Patients with any major complications (%)	23	9	14 (3 to 25)	**0.015**
Anastomotic leakage†	8	0	8 (1 to 16)	**0.046**
Peritonitis	5	1	4 (–2 to 9)	0.37
Sepsis	6	4	3 (–4 to 9)	0.72
Wound dehiscence	5	1	4 (–2 to 9)	0.37
Bleeding requiring a redo surgery	5	0	5 (0 to 10)	0.12
Pulmonary embolism	4	0	4 (0 to 8)	0.25
Pulmonary edema	6	1	5 (0 to 11)	0.21
Pneumonia	4	3	1 (–4 to 7)	1.00
Acute coronary syndrome	0	1	-1 (–4 to 1)	1.00
Atrial fibrillation/arrhythmia	0	1	-1 (–4 to 1)	1.00
Stroke	0	1	-1 (–4 to 1)	1.00
Renal replacement therapy	1	1	0 (–3 to 3)	1.00
Reoperation	8	4	4 (–3 to 11)	0.50
30-day mortality	4	0	4 (0 to 8)	0.25
Minor complications (%)				
Patients with any minor complications (%)	63	44	19 (4 to 34)	**0.016**
Superficial wound infection	6	5	1 (–6 to 8)	1.00
Urinary and other infection	26	16	10 (–3 to 23)	0.12
Paralytic ileus	14	9	5 (–5 to 15)	0.32
Need for loop diuretics	11	5	6 (–2 to 15)	0.25
Postoperative confusion	5	3	3 (–3 to 8)	0.68
Postoperative nausea and vomiting	33	28	5 (–9 to 19)	0.49
Pruritus	6	6	0 (–8 to 8)	1.00
Acute kidney injury	23	19	4 (–9 to 16)	0.56
KDIGO I	11	13	–1 (–11 to 9)	0.81
KDIGO II	9	6	3 (–6 to 11)	0.55
KDIGO III	3	1	1 (–3 to 5)	1.00
Length of stay				
ICU/PACU (h)	20 [18 to 22]	20 [18 to 22]	0 (–1 to 1)	0.96
Hospital (days)	10 [6 to 16]	10 [6 to 13]	1 (–1 to 3)	0.43
Fit for discharge criteria (days)	10 [6 to 15]	9 [6 to 12]	1 (–1 to 3)	0.22
30-day readmission	5	8	–3 (–10 to 5)	0.75

Outcome data are presented as value (%) and/or median [25th to 75th percentiles] and difference (95% CI). Bold indicates significant results with *P* value < 0.05.
*Data were available for 62 patients in the crystalloid group and 67 patients in the colloid group. †Determined among the 102 patients who underwent gastrointestinal anastomosis.
FFP = fresh-frozen plasma; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes; PACU = postanesthesia care unit; POD = postoperative day; POMS = Post-Operative Morbidity Survey; PRBC = packed erythrocyte.

complications in the crystalloid group might be explained by the fact that the gastrointestinal tract and pulmonary system do not tolerate excessive fluid accumulation. The observation that the crystalloid group had a significantly higher rate of anastomotic leakage (table 4) supports this hypothesis.

The main strength of this study relies on the methodology used to standardized fluid therapy in our patients through a fully automated, closed-loop–assisted, intraoperative, goal-directed fluid therapy system. Of note, the proportions of patients for whom clinicians overrode the system did not differ between groups, nor did the number of additional fluid boluses per patient. In contrast to most studies that used boluses of 200 to 250 ml, we decided to use 100-ml boluses in our closed-loop system for two reasons. First, in working with different bolus sizes and performance of the controller, we observed that using boluses of 100 ml was the right

balance between the information content in bolus response and minimizing fluid delivered. Splitting a single 200-ml bolus into two 100-ml boluses provided the controller with two feedback data points instead of just one, thus improving future performance and reducing total administered volume. Second, some studies have demonstrated that 100-ml fluid challenges are indeed able to predict fluid-responsiveness.[39,40]

Limitations

The first limitation of our study was that procedures in the crystalloid group lasted about 1 h longer than in the colloid group. This was the reason why all data regarding fluid therapy were expressed as milliliter per kilogram per hour of surgery. Although we could not rule out that the time difference may have affected our results, incidence of high-risk surgery and preoperative Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM)–predicted morbidity and mortality were similar between groups. Additionally, intraoperative blood losses that might be considered a marker of surgical complexity were comparable in both groups. Second, crystalloids and colloids provide obviously differential intravascular volume. However, the exact ratio between both types of fluid remains largely debated and clearly depends on the clinical situation, as the volume effect of fluids is context sensitive.[41] As with most studies in the field, we decided to use the same volume of crystalloids and colloids to ensure the double-blind design of our study. Third, the results of the present study are limited to short-term outcomes; planned long-term outcomes, such as renal function and long-term quality of life, will be followed up at 1 yr in compliance with the registered protocol, and results will be published at that time. However, several authors have demonstrated the impact of early postoperative complications on long-term outcomes.[42,43] Fourth, as the study power was based on the POMS score, this study was underpowered to detect any differences in renal function (acute kidney injury, RRT) and mortality rate. Additionally, a 1-point difference in the POMS score may not be considered clinically significant. However, the lower POMS score observed in the colloid group was also associated with a lower incidence of major postoperative complications. Fifth, our results may not be generalized to other situations, as they are only relevant to the question of which fluid to use for goal-directed fluid therapy delivered by our closed-loop system in patients undergoing major open abdominal surgery. Finally, it should be noted that our study is a small trial and is therefore prone to type 1 error.

Conclusions

Under our study conditions, when fluid resuscitation was standardized and guided by a closed-loop system, a colloid-based goal-directed fluid therapy was associated with fewer postoperative complications than a crystalloid one. This beneficial effect may be related to a significantly lower intraoperative fluid balance, which is related to a lower fluid volume administration when a balanced colloid was used. However, given the limitations of the study design, the mechanism for the difference cannot be determined with certainty.

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Competing Interests

Dr. Van der Linden has received, within the past 5 yr, fees for lectures and consultancies from Fresenius Kabi GmbH (Bad Homburg, Germany) and Janssen-Cilag SA (Beerse, Belgium). Dr. Joosten is a consultant for Edwards LifeSciences (Irvine, California). Dr. Cannesson and Dr. Rinehart declare ownership interest in Sironis (Newport Beach, California), a company developing closed-loop systems, and consultancy for Edwards Lifesciences. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: Alexandre.Joosten@erasme.ulb.ac.be. Raw data available at: Alexandre.Joosten@erasme.ulb.ac.be.

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Appendix 1. Composition of Study Fluids

	Plasmalyte	Volulyte
Na+ (mmol/l)	140	137
K+ (mmol/l)	5	4
Mg++ (mmol/l)	1.5	1.5
Cl– (mmol/l)	98	110
Acetate (mmol/l)	27	34
Gluconate (mmol/l)	23	
Osmolarity (mOsm/l)	295	286

Appendix 2. Post-Operative Morbidity Survey Score

Morbidity Type	Criteria	Source Data
1) Pulmonary	*De novo* requirement for supplemental oxygen or other respiratory support (CPAP)	Observation of the PACU/ICU chart
2) Infectious	Currently on antibiotics or temperature > 38° in the last 24 h	Observation of the PACU/ICU chart
3) Renal	Oliguria (< 500 ml/day), increased serum creatinine (> 30% from baseline value), or urinary catheter in place for nonsurgical reasons	Observation of the PACU/ICU chart and lab results
4) Gastrointestinal	Unable to tolerate an enteral diet (either by mouth or feeding tube) for any reasons, including nausea, vomiting, and abdominal distension	Observation of the PACU/ICU chart and ward fluid balance chart
5) Cardiovascular	Myocardial infarction, hypotension requiring fluid therapy, atrial or ventricular arrhythmia, or pulmonary edema: Diagnostic tests or therapy within the last 24 h	Observation of the PACU/ICU chart and ward notes review
6) Neurologic	Presence of *de novo* focal deficit, coma, or confusion/delirium	Observation of the PACU/ICU chart and patient observation
7) Wound complications	Wound dehiscence requiring surgical exploration or drainage or pus from the wound	Observation of the PACU/ICU chart and pathology results
8) Hematologic	Requirement for any of the following within the last 24 h: PRBC, FFP, platelets transfusion	Observation of the PACU/ICU chart
9) Pain	Surgical wound pain requiring parenteral opiates or regional anesthesia	Observation of the PACU/ICU chart and patient questioning

CPAP = continuous positive airway pressure; FFP = fresh-frozen plasma; ICU = intensive care unit; PACU = postanesthesia care unit; PRBC = packed erythrocyte.

Appendix 3. Definitions of Outcomes

Major Complications

Anastomotic leakage: A defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extra-luminal compartments

Peritonitis: Infection or inflammation of the peritoneum caused by intestinal perforation, trauma, postoperative infection from drains, or direct spread of infected organ

Sepsis: Defined using criteria before the 2016 sepsis definition (*i.e.,* two or more features of the systematic inflammatory response syndrome plus evidence or suspicion of infection)

Wound dehiscence: Postoperative rupture of sutures and opening along the site of surgical incision

Bleeding requiring surgery: Postoperative bleeding requiring reoperation

Pulmonary embolism: Mechanical obstruction of pulmonary artery or arteriole confirmed by chest angiographic computerized tomography, ventilation perfusion scintigraphy, or autopsy

Pulmonary edema: Respiratory distress or impaired oxygenation *and* radiologic evidence of pulmonary edema requiring diuretic therapy

Pneumonia: The presence of new and/or progressive pulmonary infiltrates on chest radiograph plus two or more of the following

1. fever of 38.5°C or higher, or postoperative hypothermia less than 36°C;
2. leukocytosis of 10,000 white blood cell/mm^3 or greater or leukopenia less than 4,000 white blood cell/mm^3;
3. purulent sputum; and/or
4. new onset or worsening cough or dyspnea.

Acute coronary syndrome: Increase and gradual decrease in troponin level or a faster increase and decrease of creatine kinase isoenzyme as markers of myocardial necrosis in the company of at least one of the following: ischemic symptoms, abnormal Q waves on the electrocardiograph, ST segment elevation or depression, coronary artery intervention (*e.g.,* coronary angioplasty), or a typical decrease in an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for the troponin elevation

Arrhythmia: Electrocardiograph evidence of cardiac rhythm disturbance

Stroke: Embolic, thrombotic, or hemorrhagic cerebrovascular event with persistent motor, sensory, or cognitive dysfunction confirmed by computerized tomography, magnetic resonance imaging, or autopsy

Renal replacement therapy: Decided by the doctor in charge

Reoperation: Re-intervention within the 30 days after primary surgery

Mortality: Patient death within the 30 days after primary surgery

Minor Complications

Superficial wound infection:

(1) Infection occurs within 30 days after surgery,
(2) involves only skin and subcutaneous tissue of the incision, and
(3) the patient has at least one of the following:

   (a) purulent drainage from the superficial incision;
   (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
   (c) at least one of the following symptoms or signs of infection: pain or tenderness, localized swelling, redness or heat, and superficial incision deliberately opened by surgeon with culture positive or not cultured (a culture negative finding does not meet this criterion); and
   (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.

Urinary tract infection: Positive urine culture of at least 10^5 colony forming units per milliliter with no more than two species of microorganisms, and with at least one of the following symptoms or signs: fever (higher than 38°C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognized cause

Infection other: All other suspected or confirmed infections investigated by body fluid culture and treated with antibiotics

Paralytic ileus: Failure to tolerate solid food or defecate for three or more days after surgery

Loop diuretic therapy: Postoperative administration of loop diuretics other than that associated with blood product transfusion and chronic therapy

Postoperative confusion–delirium: Acute confusion or personality change with altered vigilance and no preexisting cause of cognitive impairment

Postoperative nausea and vomiting: Nausea or vomiting within 24 to 48 h of surgery and requiring antiemetic therapy

Pruritus: Severe itching of the skin during hospital stay

Other Definitions

Any blood transfusion: Including erythrocyte, fresh-frozen plasma, or platelet transfusion, from the commencement of surgery

Acute kidney injury: According to the Kidney Disease: Improving Global Outcomes (KDIGO) group criteria

KDIGO 1: Increase in serum creatinine 0.3 mg/dl or 150 to 200% from baseline (1.5- to 2-fold)

KDIGO 2: Increase in serum creatinine to 200 to 300% from baseline (2- to 3-fold)

KDIGO 3: Increase in serum creatinine to 300% or more (3-fold) or increase in serum creatinine to more than 4.0 mg/dl or initiation of renal replacement therapy