Personalized Versus Protocolized Fluid Management Using Noninvasive Hemodynamic Monitoring (Clearsight System) in Patients Undergoing Moderate-Risk Abdominal Surgery

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Advances in noninvasive hemodynamic monitoring systems allow delivery of goal-directed fluid therapy and could therefore be used in less-invasive surgical procedures. In this randomized controlled trial, we compared closed-loop–assisted goal-directed fluid therapy using a noninvasive cardiac output (Clearsight system) monitor (personalized approach) to a protocolized fluid therapy approach in 40 patients undergoing moderate-risk laparoscopic abdominal surgery. Cardiac output and stroke volume variations were not significantly different in both groups and remained within predefined target values >90% of the study time. Personalized fluid therapy does not seem to offer any hemodynamic advantage over a protocolized approach in this population. (Anesth Analg 2019;129:e8–e12)

Considerable evidence indicates that goal-directed fluid therapy (GDFT) can improve patient outcomes after high-risk surgery.1–4 However, there is still debate regarding the benefit of GDFT strategies in moderate-risk surgery. Most GDFT protocols require invasive monitoring devices with insertion of an arterial catheter, and substantial effort is needed to ensure that the protocols are applied correctly. Recently, we demonstrated that a closed-loop fluid management system linked to a noninvasive cardiac output (Clearsight system) monitor was associated with a high rate of GDFT protocol compliance in patients undergoing moderate-risk surgery.7 Among the available noninvasive hemodynamic monitors, the Clearsight system (Edwards Lifesciences, Irvine, CA) has the advantage that it directly measures flow variables, in contrast with the Masimo system (Irvine, CA), which only provides the pleth variability index.

A study by Stens et al8 recently reported no additional value of advanced noninvasive CO monitoring to conventional hemodynamic monitoring with regard to postoperative complications in patients undergoing moderate-risk abdominal surgery. However, from the data presented, it was not possible to determine whether hemodynamics was similarly maintained in both groups. Thus, we sought to further test GDFT strategies in a prospective randomized controlled trial in moderate-risk surgical patients targeting specific predefined hemodynamic end points. We compared a personalized approach (closed-loop–assisted GDFT approach guided by a noninvasive CO monitor) and a protocolized fluid therapy approach and hypothesized that there would be no significant differences between groups. Consistent with previous work,7,8 our primary outcome was time spent with either a cardiac index (CI) ≥2.5 L/min/m² or a stroke volume variation (SVV) <13%.

METHODS

The study was approved by the Ethics Committee of Erasme Hospital (No: P2016/526), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at clinicaltrials.gov (NCT03039946; principal investigator: A.J.; date of registration: February 1, 2017).

Adult low- to moderate-risk patients who did not require invasive arterial pressure monitoring and were listed for moderate-risk surgery (including only elective laparoscopic–robotic colorectal, gynecological, or urological procedures) were included. Exclusion criteria included <18 years of age, an American Society of Anesthesiologists score >3, a left ventricular ejection fraction <30%, significant cardiac arrhythmias or aortic regurgitation, coagulation disorders (activated partial thromboplastin time >15 normal value), preoperative renal insufficiency (serum creatinine >2 mg/dL, oliguria, anuria, or hemodialysis), emergency surgery, preoperative infection, and participation in another trial.
Randomization, Blinding, and Data Collection
Randomization was conducted using Internet-based software (http://www.randomization.com), and the randomization numbers were placed in sealed envelopes containing the group assignments. The list of codes was kept in a designated area by the departmental secretary. Data were collected in the postanesthesia care unit by the nurses in charge of the patient who were blinded to the group allocation and on the ward (record of postoperative data and complications) by the investigators (A.J., S.R.L., A.C., or S.C.).

Anesthesia Procedures
All included patients were allowed to take solid foods until 6 hours before surgery and fluids until 2 hours before surgery. None of the patients had bowel preparation. In both groups, premedication consisted of 0.5 mg of alprazolam given on the morning of surgery. Standard monitoring included a 5-lead electrocardiogram, pulse oximetry, noninvasive blood pressure, inspiratory and expiratory gas concentrations, urine output, and processed electroencephalography monitoring (BIS monitor; Covidien, Dublin, Ireland). In addition to standard monitoring, all patients had a noninvasive CO monitor (Clearsight; Edwards Lifesciences) positioned before anesthesia induction. Anesthesia was induced with sufentanil (0.2 μg/kg), propofol (2 mg/kg), and rocuronium (0.6 mg/kg). Anesthesia was maintained with sevoflurane or desflurane depending on preference and sufentanil boluses at the discretion of the anesthesia team. Any necessary adjustments were made at the discretion of the primary anesthesia providers to keep the bispectral index level between 40 and 60. Patients were mechanically ventilated using a volume control mode with a tidal volume of 8 mL/kg of ideal body weight and a positive end-expiratory pressure of 5 cm H₂O using the Zeus Infinity C700 Anesthesia workstation (Dräger Medical GmbH, Lübeck, Germany). Respiratory rate was adjusted to achieve end-tidal CO₂ between 32 and 36 mm Hg.

Fluid Therapy
All patients received 100 mL of isotonic saline during the induction of anesthesia. In the protocolized group, patients received a baseline infusion of 4 mL/kg/h of isotonic balanced crystalloid solution (PlasmaLyte; Baxter, Lessines, Belgium), and the anesthesiologist was blinded to the information provided by the Clearsight system. Providers were permitted to administer additional fluids as deemed necessary. In the personalized group, no baseline fluid therapy was used. The closed-loop system used in the personalized group has been described extensively in our previous publications. The Clearsight monitor was linked to the closed-loop system (Figure) that delivered 100-mL boluses of isotonic balanced crystalloid (PlasmaLyte) through a Sapphire infusion pump (Q-Core, Tel Aviv, Israel) based on the incoming data. The anesthesiologist in charge of

Figure. Schematic representation of our closed-loop system linked to the noninvasive hemodynamic monitoring device (Clearsight System; Edwards Lifesciences, Irvine, CA). The closed-loop system was connected to the serial output port of the EV1000 monitor for real-time capture of data. A Q-Core Sapphire Pump was used by the closed loop to deliver 100-mL boluses of balanced crystalloid solution (PlasmaLyte; Baxter, Lessines, Belgium). The Sapphire Pump was controlled by the closed-loop system using the software provided by the Q-Core via serial connection (Commands Server R.00). In brief, the system monitors stroke volume, stroke volume variation, heart rate, and mean arterial pressure, and it uses this information to optimize stroke volume. The controller uses a model layer to formulate a predicted response to a fluid bolus and an adaptive layer for bolus-based error correcting 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.
the patient could interact with the automated system and deliver or halt a fluid bolus manually if necessary; he/she could also deliver additional fluid outside of the closed loop (rescue fluid therapy). In both groups, anesthesiologists could compensate intraoperative blood loss using a 1-to-1 ratio of colloid (6% hydroxyethyl starch 130/0.4; Fresenius Kabi GmBH, Bad Homburg, Germany) if deemed necessary. Boluses of ephedrine were allowed when severe arterial hypotension (mean arterial pressure, <65 mm Hg) persisted after appropriate fluid administration.

Outcome Variables
The primary outcome was the percentage of intraoperative time spent within hemodynamic targets, as defined by a CI ≥2.5 L/min/m² and/or an SVV <13%. Secondary outcomes were the times-in-target for the separate CI and SVV subcomponents of the primary outcome, total volume of fluid administered, fluid balance, incidence of postoperative complications within 30 days, and lengths of stay in the postanesthesia care unit and in the hospital.

Statistical Analysis
The assumption of normality for the primary outcome, assessed using the Shapiro-Wilk test, was not fulfilled, so continuous variables are shown as medians (25th–75th percentiles). Categorical variables are reported as counts and percentages. Group comparisons for continuous variables were made using a Mann-Whitney U test, and for categorical variables using a χ² test, or Fisher exact test when individual cell counts were <5. Statistical significance was set at P < .05. Statistical tests were performed with SPSS (IBM Corp, Armonk, NY) or R statistics (www.r-project.org).

Previous internal data showed that patients managed with the closed-loop system spent approximately 90% ± 10% of intraoperative time within the hemodynamic targets. Assuming similar performance of the closed loop in this study, we determined a priori that a 10% difference between groups would be clinically significant, and the study was powered to this end. Monte Carlo power analysis using a normal sampling distribution showed that to detect 10% difference in time-in-target over the protocolized group with a power of 0.8 and a significance level of 0.05, 20 patients per group would give a power of approximately 0.85.

RESULTS
Forty consecutive patients were recruited. One patient was subsequently excluded because of an anaphylactic reaction during induction, which resulted in cancellation of the surgery. Demographic data for the 2 groups are shown in Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/C438.

There was no statistically significant difference in time-in-target between groups: 97.5% (93.5%–100%) of intraoperative time for the protocolized group and 99.9% (97.2%–100%) for the personalized group (P = .10). The time-in-target measures for the SVV and CI components were 91% (75%–95%) and 94% (77%–98%) for SVV (P = .19) and 92% (49%–100%) and 98% (94%–100%) for CI (P = .30) for the protocolized and personalized groups, respectively (Table). Intraoperative and postoperative heart rate and mean arterial pressure were not statistically significantly different in the 2 groups (Table). The volumes of crystalloid administered intraoperatively and use of vasopressors were not significantly different. Intraoperative fluid balance was significantly lower in the personalized than in the protocolized group (Supplemental Digital Content 2, Table 2, http://links.lww.com/AA/C439). No patient in either group required rescue fluid boluses. All patients were extubated in the operating room at the end of the surgery. The incidence of major and minor complications was not significantly different between groups. There was no

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Patient outcomes

| Patients with any major complications (%)         | 3 (16)                      | 3 (15)                      | .946    |
| Patients with any minor complications (%)        | 5 (26)                      | 2 (10)                      | .184    |
| Length of stay postanesthesia care unit (h)      | 3 (2–4)                     | 3 (2–4)                     | .708    |
| Length of stay hospital (d)                       | 3 (2–5)                     | 3 (2–6)                     | .478    |

Data are expressed as median (25th–75th percentiles). P values are by Mann-Whitney U test for continuous data and by χ² test for % measures, or by Fisher exact test when cell counts are <5. Intraoperative variables were recorded by the noninvasive cardiac output monitor at 20-s intervals and averaged. Postoperative hemodynamic variables are an average of the variables recorded at 4 different time points in the postoperative period (arrival in postanesthesia care unit, +1 h, +2 h postarrival, and +3 h postarrival).
significant difference between groups in postanesthesia care unit or hospital lengths of stay (Table; Supplemental Digital Content 3, Table 3, http://links.lww.com/AA/C440). The median hospital length of stay was 3 days in both groups.

DISCUSSION

Our results confirmed that a personalized approach, that is, a closed-loop–assisted GDFT guided by a noninvasive CO monitor, offered no significant advantage in maintaining CI or SVV in patients undergoing moderate-risk abdominal surgery compared to a protocolized approach. This observation is consistent with the results from the study by Stens et al9 mentioned earlier. However, adding to the results from that study, we also recorded advanced hemodynamic variables in the 2 groups and observed similar values, although the anesthesiologists in charge of the patients in the protocized group were blinded to these variables.

A major strength of this study was the use of the closed-loop–assisted system, which ensured high protocol compliance in the personalized group.7,9 Limitations include the relatively small number of patients, making the study underpowered to assess the impact of the fluid therapy approach on the incidence of postoperative complications. However, based on the incidence of major complications in the 2 groups, a Monte Carlo simulation of binomial proportion tests with an α of .05 suggests that around 35,000 patients per group would be needed to have 80% power to detect a significant difference between groups. Baseline maintenance fluid therapy of 4–8 mL/kg/h is usually recommended for GDFT, so we chose to administer 4 mL/kg/h for our patients undergoing moderate-risk laparoscopic surgery; lower maintenance rates are considered too restrictive by some experts.35 Finally, the results of our study should not be extrapolated to surgical procedures with significant blood loss and/or major fluid shifts.

CONCLUSIONS

Under our study conditions in patients undergoing moderate-risk abdominal surgery, a personalized approach using closed-loop–assisted GDFT (without baseline crystalloid infusion) does not seem to have any advantage over a protocolized approach in maintaining CI or SVV within predefined targets.

DISCLOSURES

Name: Alexandre Joosten, MD.
Contribution: This author helped design the study, recruit the patients, collect the data, and draft the final manuscript.
Conflicts of Interest: A. Joosten is a consultant for Edwards Lifesciences (Irvine, CA). He is a cofounder of Sironis and owns a patent on closed-loop–fluid management and hemodynamic optimization.

Name: Jean Louis Vincent, MD, PhD.
Contribution: This author helped analyze the data and draft the final manuscript.
Conflicts of Interest: None.

Name: Philippe Van der Linden, MD, PhD.
Contribution: This author helped analyze the data and draft the final manuscript.
Conflicts of Interest: P. Van der Linden has received, within the past 5 years, fees for lectures and consultancies from Fresenius Kabi GmbH and Janssen-Cilag SA, Belgium.

Name: Maxime Cannesson, MD, PhD.
Contribution: This author helped design the closed-loop system, analyze the data, and draft the final manuscript.

Conflicts of Interest: M. Cannesson is a consultant for Edwards Lifesciences (Irvine, CA), Covidiens (Boulder, CO), and Masimo Corp (Irvine, CA). He is a cofounder of Sironis and owns a patent on closed-loop fluid management and hemodynamic optimization.

Name: Joseph Rinehart, MD.
Contribution: This author helped design the closed-loop system, analyze the data, and draft the final manuscript.

Conflicts of Interest: J. Rinehart is a consultant for Edwards Lifesciences (Irvine, CA). He is a cofounder of Sironis and owns a patent on closed-loop fluid management and hemodynamic optimization.

This manuscript was handled by: Tong J. Gan, MD.

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