ANESTHESIOLOGY

Anesthetic Management Using Multiple Closed-loop Systems and Delayed Neurocognitive Recovery

A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Recommendations for anesthetic care are often difficult to implement in the intraoperative setting because of the requirement for continuous attention

What This Article Tells Us That Is New

- Closed-loop, automated management of anesthetic, analgesic, fluid, and ventilation parameters was superior to manual control and might influence postoperative outcomes

ABSTRACT

Background: Cognitive changes after anesthesia and surgery represent a significant public health concern. We tested the hypothesis that, in patients 60 yr or older scheduled for noncardiac surgery, automated management of anesthetic depth, cardiac blood flow, and protective lung ventilation using three independent controllers would outperform manual control of these variables. Additionally, as a result of the improved management, patients in the automated group would experience less postoperative neurocognitive impairment compared to patients having standard, manually adjusted anesthesia.

Methods: In this single-center, patient-and-evaluator-blinded, two-arm, parallel, randomized controlled, superiority study, 90 patients having noncardiac surgery under general anesthesia were randomly assigned to one of two groups. In the control group, anesthesia management was performed manually while in the closed-loop group, the titration of anesthesia, analgesia, fluids, and ventilation was performed by three independent controllers. The primary outcome was a change in a cognition score (the 30-item Montreal Cognitive Assessment) from preoperative values to those measures 1 week postsurgery. Secondary outcomes included a battery of neurocognitive tests completed at both 1 week and 3 months postsurgery as well as 30-day postsurgical outcomes.

Results: Forty-three controls and 44 closed-loop patients were assessed for the primary outcome. There was a difference in the cognition score compared to baseline in the control group *versus* the closed-loop group 1 week postsurgery (–1 [–2 to 0] *vs.* 0 [–1 to 1]; difference 1 [95% CI, 0 to 3], $P = 0.033$). Patients in the closed-loop group spent less time during surgery with a Bispectral Index less than 40, had less end-tidal hypocapnia, and had a lower fluid balance compared to the control group.

Conclusions: Automated anesthetic management using the combination of three controllers outperforms manual control and may have an impact on delayed neurocognitive recovery. However, given the study design, it is not possible to determine the relative contribution of each controller on the cognition score.

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There is increasing evidence that many different intraoperative anesthetic factors may influence various postoperative patient outcomes. Inappropriate anesthetic depth, too much or too little intravascular volume replacement, and overventilation have all been shown to increase the risk of postoperative complications.[1–5] As a result, specific recommendations exist to optimize these three factors by (1) titrating anesthetics drugs using a depth of anesthesia monitor in order to avoid burst suppression and/or overly deep anesthesia (defined as Bispectral Index [BIS] less than 40), (2) guiding fluid administration using an advanced hemodynamic monitoring device paired with a goal-directed fluid therapy protocol, and (3) applying a protective lung ventilation strategy during the intraoperative period.[6–9] However, while advanced monitoring devices are widely available at the bedside to achieve these goals, the application of best-practice recommendations

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utilizing them can largely be improved, especially regarding compliance to treatment protocols.[10–12] Part of the difficulty in maintaining compliance with such optimization strategies is that they require sustained continuous attention and frequent adjustments to maintain specific physiologic variables within predefined target ranges. In clinical environments, tightly controlled manual feedback is often not possible because of other important tasks, distractions, and the natural limitations of human attention.[13] By comparison, physiologic closed-loop systems do not have lapses in attention and are well-suited to repetitive trivial tasks.[14] For this reason, these systems have consistently been shown to improve the quality of drug and fluid delivery when compared to manual administration, allowing better accuracy in maintaining physiologic variables within a desired range, with a significant reduction in episodes of over- and underdosing.[15,16]

Recently, we have reported the clinical feasibility of combining two independent closed-loop systems operating in parallel to maintain predefined anesthetic depth and hemodynamic parameters for the majority of intraoperative case time in adult patients having major vascular surgery.[17] The next logical step is to evaluate the clinical impact of this closed-loop technology on a broader patient population undergoing elective noncardiac surgery. It has already been established that titrating anesthetics to avoid overly deep anesthesia can reduce cognitive impairment 3 months postsurgery.[18] Additionally, it has been recently suggested that more efficient maintenance of normocapnia and cardiac blood flow (by applying a goal directed fluid therapy strategy) might also decrease postoperative cognitive impairment in elderly patients undergoing noncardiac surgery.[4,19]

We hypothesized that a closed-loop management of (1) anesthetic depth (*via* processed EEG monitoring), (2) cardiac blood flow (*via* stroke volume optimization), and (3) lung ventilation (*via* optimization of tidal volume and respiratory frequency to maintain predefined end-tidal carbon dioxide [$ETCO_2$] targets) using three independent controllers would outperform manual control of these variables, and as a result, patients would present with less postoperative neurocognitive impairment compared to patients having standard, manually adjusted anesthesia.

Materials and Methods

Ethical Approval

This single-center, patient-and-evaluator-blinded, two-arm, parallel, randomized-controlled, superiority study was approved on April 20, 2017, by our Ethics Committee (Brussels, Belgium; P2017/234-B406201731981) and registered on May 11, 2017, in clinicaltrials.gov (NCT03148730, Principal Investigator: A.J.). The study was conducted at Erasme Hospital in Brussels, Belgium, between May 2017 and November 2017 with patient follow-up continued until February 2018. All patients provided written informed consent before surgery.

Patient Inclusion and Exclusion. Inclusion criteria were autonomous French-speaking patients (*e.g.*, living at home or in nonmedical institution) 60 yr or older, scheduled for elective intermediate- or high-risk noncardiac surgery under total intravenous anesthesia. Exclusion criteria included American Society of Anesthesiologists Physical Status score IV or greater, the presence of significant preoperative neurocognitive disorder (predefined as a Montreal Cognitive Assessment test score less than 23/30),[20] known neurologic deficits (stroke, Alzheimer disease, Parkinson disease), cardiac arrhythmias, pacemaker, preoperative chronic renal insufficiency (serum creatinine greater than 2 mg/dl, hemodialysis), or known allergy to propofol, remifentanil, or hydroxyethyl starch. Patients having neurosurgical procedures, participating in another trial, or living more than 40 miles from the institution were also excluded.

Randomization, Blinding, and Data Collection

Patients were randomized preoperatively into one of two groups. In the first group, anesthesia management was performed manually (control group), while in the second group, the titration of anesthesia, analgesia, fluids, and ventilation was performed by three independent closed-loop systems (closed-loop group).

The sequence of randomization for the study (1:1 allocation) was generated by the head of the neuropsychology department (H.S.), who was not involved in the cognitive assessment of the patients using internet-based randomization software (randomization plan created on April 20, 2017, 14:59:47). The day of the surgery, a sealed envelope containing the assigned patient number was opened. The envelopes were kept in the research unit of our hospital. Patients in the control group were managed by team members not involved in the study, while those in the closed-loop group were exclusively managed by one of the investigators (A.J., V.J., and L.B.). Perioperative data were collected by the investigators for all patients. Neurocognitive tests were performed by independent and experienced neuropsychologists and a psychiatrist recruited specifically for this study. To minimize bias, all patients and the evaluators assessing neurocognitive function were blinded to randomization assignments.

Anesthesia Procedures

No premedication was given the morning of the surgery. Standard monitoring included a five-lead electrocardiogram, pulse oximetry, noninvasive blood pressure upper arm cuff, rectal temperature, inspiratory and expiratory gas concentrations, and urine output. A BIS electrode was applied to the patient's forehead and temporal regions to capture frontal electroencephalogram (EEG) and electromyography signals before induction using a BIS monitor (Aspect Medical Systems Inc, USA). Insertion of a central venous catheter was left at the discretion of the attending anesthesiologist.

In the closed-loop group, all patients had a radial arterial catheter inserted before induction and linked to a cardiac output monitoring (EV1000, Edwards Lifesciences, USA) *via* the Flotrac sensor (Edwards Lifesciences, USA). In the manual group, the choice of hemodynamic monitoring was left to the discretion of the anesthesiologist in charge of the patient. In both groups, rocuronium (0.6 mg · kg^{-1}) was administered during induction of anesthesia and continuously administered during the procedure using a standard syringe pump adjusted by the anesthesiologist to maintain the train-of-four ratio less than 2 using a muscle relaxant monitor (TOF Scan, France). Last, perioperative pain management was standardized in both groups. All patients who underwent a laparotomy had a preinduction spinal morphine injection (250 μg). In addition, all patients included in the study received intravenous morphine (0.05 mg · kg^{-1}) at incision and 1 h before the end of surgery along with paracetamol and nonsteroidal antiinflammatory agents if there were no contraindications.

Propofol and Remifentanil Management

In the closed-loop group, two Base Primea infusion pumps (Fresenius Kabi, Belgium) were used and connected to the Infusion Toolbox 95 (version 4.11) software[21] *via* their RS 232C serial interfaces. The dual proportional-integral-derivative algorithm of the closed-loop system was used to deliver a target controlled infusion of propofol and remifentanil during induction and maintenance of anesthesia in order to maintain BIS values between 40 and 60. The controller adjusted both propofol and remifentanil concentrations according to the BIS index, the signal quality index, the electromyographic activity, and the percentage of burst suppression ratio collected from the BIS monitor. The controller measures and continuously calculates the difference between the set point and the most recently measured BIS values. Using the assumption that intraoperative BIS changes are caused by fluctuations in the severity of noxious stimuli, only the remifentanil concentration is modified if the changes are small, while both remifentanil and propofol concentrations are modified if the difference is larger. The controller has been described extensively in previous randomized controlled trials.[22,23] For safety reasons, upper and lower limits for propofol (0.5 to 3 μg · ml^{-1}) and remifentanil (3 to 8 ng · ml^{-1}) target concentrations were defined in the system. Importantly, the anesthesiologist in charge of the patient could override the system in order to keep the BIS within the predefined range of 40 to 60.

In the manual group, the anesthesiologist in charge of the patient used the same Infusion Toolbox 95, but the adjustment of propofol and remifentanil concentrations was done manually using target controlled infusion systems (based on the pharmacokinetic models of Schnider *et al.*[24] and Minto *et al.*,[25] respectively) with the goal of keeping BIS values between 40 and 60 (no upper and lower limits predefined). In both groups, data from the BIS monitor and the two infusion pumps were recorded every 5 s.

Fluid Management

In the manual group, the amount and type of intravenous fluids were completely left at the discretion of the anesthesiologist treating the patient.

In the closed-loop group, a maintenance balanced crystalloid solution (Plasmalyte, Baxter, Belgium) was administered throughout the procedure at 3 ml · kg^{-1} · h^{-1} *via* an infusion pump (Volumat Agilia, Fresenius Kabi, Belgium). Additional fluid boluses were delivered as part of a goal-directed fluid therapy strategy. The details of the closed-loop fluid delivery system have been described extensively in previous publications.[26–29] We have also included a more detailed description in Supplemental Digital Content, appendix 1 (http://links.lww.com/ALN/C78). Briefly, the controller monitors stroke volume, heart rate, mean arterial pressure, and stroke volume variation and subsequently uses this information to optimize stroke volume as part of an established goal-directed fluid therapy protocol. The controller uses both a model layer to formulate a predicted response to a fluid bolus and an adaptive layer for bolus-based error correction during direct fluid management to correct for changes induced by surgical and anesthetic conditions. The system delivers 100-ml boluses of a balanced tetrastarch (Volulyte, Fresenius Kabi, Germany) more than 6 min. A 24-h upper limit dose of 33 ml · kg^{-1} was established and if reached, Plasmalyte was used as a rescue fluid. 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 EV-1000 serial output ("IMFout") was captured at a rate of one sample every 2 s. The closed-loop system delivered fluid boluses *via* a Q-Core Sapphire Multi-Therapy Infusion Pump (Q-Core, Israel). Control was achieved by the closed-loop system using a serial connection and the Commands Server R.00 software provided by Q-Core. Before surgical incision, the system was started by the anesthetist in charge of the patient and resuscitation targets chosen. Similar to the dual propofol and remifentanil closed-loop system, the anesthesiologist in charge of the patient could interact with the system and manually deliver or halt a fluid bolus, if needed. Importantly, the anesthesiologist could also administer additional fluid without using the closed loop in case of hemodynamic instability related to acute bleeding or aortic unclamping.

Postoperative fluid administration was standardized in both groups and consisted of 1.5 ml · kg^{-1} · h^{-1} of a balanced crystalloid solution containing 5% glucose (Sterofundin B, B-Braun Medical SA, Belgium). If additional volume was required, Plasmalyte was administered based on individual physician preference.

Ventilation Management

In the manual group, ventilation management followed our departmental guidelines. Patients were ventilated using volume control mode with a Zeus Infinity C700 Anesthesia workstation machine (Dräger Medical GmbH, Germany). Tidal volume was set at 7 ml · kg^{-1} of predicted body weight, and respiratory rate adjusted to achieve an $ETCO_2$ between 32 and 38 mmHg. A positive end expiratory pressure of 5 cm H_2O was applied to all patients and recruitment maneuvers applied if deemed necessary during the procedure.

In the closed-loop group, anesthesiologists used the recently added closed-loop mode (smart ventilation control) available on our Zeus Anesthesia workstation machines. This closed-loop system automatically analyzes ventilation parameters, which *ensures* the consistent application of a "lung protective ventilation strategy" using adaptive tidal volume (between 6 and 8 ml/kg predicted body weight) and respiratory frequency to maintain predefined $ETCO_2$ targets (32 to 38 mmHg).

Hypotension and Transfusion Management

In both groups, the type and dose of vasoconstrictor used were left at the discretion of the anesthesiologist in charge of the patient. However, the goal was to maintain the mean arterial pressure (MAP) strictly greater than 60 mmHg (departmental guidelines). Hemoglobin concentration was kept above 7 to 9 g · dl^{-1} perioperatively. At the end of the procedure, patients went to the postanesthesia care unit (PACU) or the intensive care unit depending on the type of surgery and the patient's clinical condition. All team members managing the postoperative care of the patients were completely blinded to the study purpose and group allocation.

All intraoperative data were extracted from our electronic medical record system (Innovian, Draeger, Inc., United Kingdom).

Neurocognitive Assessment

Cognitive function was assessed using multiple neurocognitive tests including both global and specific measures of cognition. All patients were evaluated by an experienced team including one psychiatrist and two neuropsychologists.

The Montreal Cognitive Assessment test (version 7.1, French edition) was used as a global cognitive measure. This cognition score consists of a single page, 30-item test that measures abilities in different cognitive domains including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation.[30] It is a sensitive and widely used screening assessment test for detecting mild cognitive impairment and dementia, with a sensitivity and specificity of 90% and 87%, respectively.[31,32]

Classic neurocognitive tests based on standardized procedures and well-established theoretical models were also used to assess specific cognitive functions that have been described as frequently affected by surgery or anesthesia or hypoxia[33]: forward and backward digit span (working memory); Free and Cued Selective Reminding Test (verbal episodic memory); and Stroop test (executive function: inhibition). These tests are described in Supplemental Digital Content, appendix 2 (http://links.lww.com/ALN/C78).

Quality of Recovery and Quality of Life Assessments

In addition to neurocognitive tests, we also assessed both the quality of recovery using the Quality of Recovery-15 questionnaire and patient's health-related quality of life using the EQ-5D-5L questionnaire. Each scale has been described in recent guidelines on outcome measures.[34] Last, frailty was also assessed in each patient using the Edmonton Frail scale, which is a multidimensional assessment tool that can be done in less than 10 min.[35] The score ranges from 0 to 17 points with cutoffs used to grade the severity of frailty: no frailty (0 to 5), vulnerable to frailty (6 to 7), mild frailty (8 to 9), moderate frailty (10 to 11), and severe frailty (12 to 17).

Timeline

Patients were assessed three times: the day before the surgery (preoperatively), within the first week postsurgery (between postoperative days 3 and 5 for moderate-risk surgery and between days 7 and 10 for high-risk surgery), and 3 months postsurgery. To ensure consistency, each patient was assessed by the same evaluator whenever possible. Once again, all evaluators were blinded to the study group allocation. Figure 1 represents the timeline of the different tests. Last, multiple versions of the cognition score were used to decrease possible learning effects.

Outcomes, Data Collection, and Analysis

The primary outcome of this study was the change of the cognition score from the preoperative period to the first week postsurgery. Secondary outcomes included change of the cognition score from the preoperative period to 3 months postsurgery, the patient's performance on the specific cognitive function tests between the preoperative period and the first week postsurgery and again 3 months postsurgery, quality of life and quality of recovery measured using EQ-5D-5L and QoR-15, amount of intravenous drugs used (propofol, remifentanil, and vasopressors), total fluid infused, percentage time spent with BIS values between 40 and 60 (also less than 40 and greater than 60), $ETCO_2$ ranges (less than 32 mmHg, 32 to 38 mmHg, and greater than 38 mmHg), occurrence of awareness and incidence of burst suppression ratio (defined as a period of isoelectric cortical signal at 10% for more than 1 min), hemodynamic variables, percentage of case time with MAP less than 60 mmHg, incidence of postoperative major and minor complications at 30 days postoperatively (definitions given in our previous publications[28,36]), length of stay in the intensive care unit, PACU, and hospital, and mortality at 30 and 90 days. Of note, there

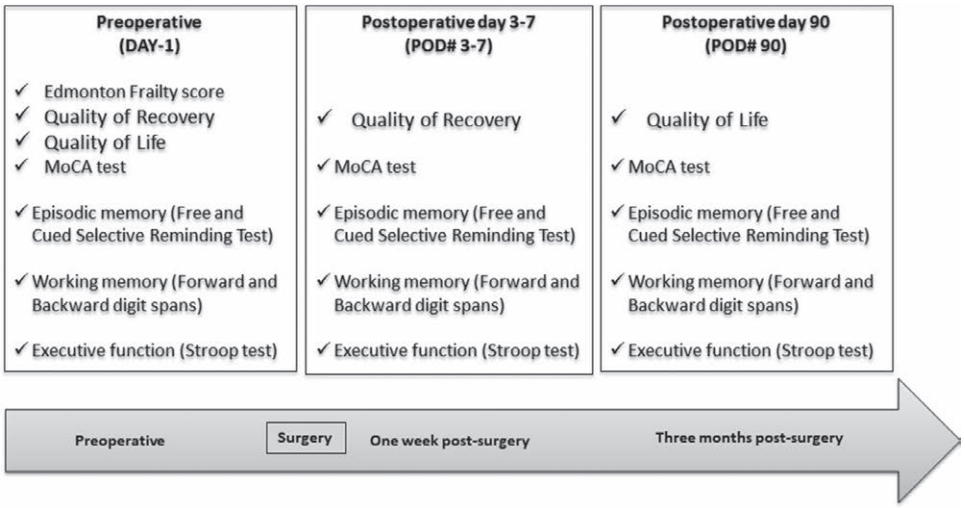

Fig. 1. Battery of Neurocognitive Tests. MoCA, Montreal Cognitive Assessment; POD, postoperative day.

was no predefined criterion to determine intensive care unit and PACU discharge.

Statistical Analysis

We *a priori* determined the number of patients needed for each group based on the recorded cognition score of a previous group of 10 patients in our institution. In this small sample, the cognition score decreased by 2.2 ± 3.3 (mean ± SD) in the immediate postoperative period. We hypothesized that, in contrast to the control group, the cognition score would not decrease in the closed-loop group. Thus, assuming a mean difference in groups of 2.2 and a pooled SD of 3.3, we find a standardized effect size of 0.667. Therefore, 37 patients per group would be required to test our hypothesis with a power of 80% and an alpha error of 0.05. As a result, we chose to include 90 patients (45 per group). Intention-to-treat analysis was performed with no planned interim analysis. Missing cognition data at 3 months follow-up was tested for randomness of missing values using the method described by Jamshidian and Jalal.[37] If data were found to be missing *completely* at random, then complete case analysis would be sufficiently unbiased for analysis. If data were found to be missing at random or missing not at random, multiple imputation would provide more unbiased effect estimates and would therefore be used to impute the missing values.[38]

The primary outcome and secondary outcomes were compared using the Mann–Whitney U test. For other intraoperative and postoperative comparisons, continuous data were tested for normality using a Shapiro–Wilk test. Data normally distributed were compared using a paired *t* test (for tests in the same patients at different time points) and unpaired *t* test (for comparisons between groups) and presented as mean ± SD. Data not normally distributed were compared using a Mann–Whitney U test and reported as median (25th to 75th) percentiles with 95% CIs. When indicated, discrete data were presented as a percentage and compared using a chi-square or a Fisher exact test. Statistical significance was set at a P value less than 0.05, and all tests were two-tailed. Correlations were examined using Pearson's r. Data were analyzed using Minitab (France) and R version 3.3.3.[39]

Results

We recruited 90 patients in total. One patient in the control group voluntarily withdrew from the study before completing the baseline testing. Baseline characteristics of the remaining 89 patients were similar in both groups (table 1). The CONSORT (Consolidated Standards of Reporting Trials) flow chart is shown in figure 2.

Regarding our primary outcome, there was a significant decrease in the cognition score compared to baseline when comparing the control group *versus* the closed-loop group at 1 week postsurgery (–1 [–2 to 0] *vs.* 0 [–1 to 1]; difference 1 [95% CI, 0 to 3], $P = 0.033$). This effect persisted at 3 months postsurgery (–1 [–3 to 0] *vs.* 0 [–2 to 2]; difference 1 [95% CI, 0 to 2], $P = 0.017$). Timing of cognitive assessments (at 1 week and 3 months) did not differ between groups (Supplemental Digital Content, appendix 1, http://links.lww.com/ALN/C78). The additional battery of cognitive tests did not show any difference between the groups at 1 week postsurgery (all $P > 0.05$; Supplemental Digital Content, appendix 2, http://links.lww.com/ALN/C78) and at 3 months postsurgery (data not shown). Finally, there was no significant difference in EQ-5D-5L and QoR-15 scores between groups (Supplemental Digital Content, appendix 1, http://links.lww.com/ALN/C78).

Table 1. Baseline Characteristics

Variables	Control Group (N = 44)	Closed-loop Group (N = 45)
Age (yr)	62 [60–72]	64 [60–86]
Male sex, n (%)	27 (61)	30 (67)
Weight (kg)	77 [60–85]	76 [61–87]
Height (cm)	169 ± 8	172 ± 10
Body mass index (kg · m^{-2})	26 [23–30]	26 [22–29]
Montreal Cognitive Assessment score	27 [25–29]	27 [25–28]
Edmonton Frail Scale	3 [2–4]	3 [2–4]
No. of patients with American Society of Anesthesiologists Physical Status II/III	30/14	26/19
Baseline hemoglobin (g · dl^{-1})	14 [13–15]	13.9 [13–14]
Baseline creatinine (mg · dl^{-1})	0.80 [0.8–1.1]	0.90 [0.8–1.1]
Baseline estimated glomerular filtration rate (ml · min^{-1} · 1.73 m^{-2})	87 [65–95]	84 [68–90]
Type of surgery, n (%)		
Major gynecological surgery	3 (7)	4 (9)
Major urologic surgery*	10 (23)	11 (24)
Major aortic surgery	4 (9)	4 (9)
Major peripheral vascular surgery	8 (18)	7 (16)
Colectomy	5 (11)	10 (22)
Other abdominal procedure†	14 (32)	9 (20)
Medications, n (%)		
Aspirin and/or clopidogrel	19 (43)	21 (47)
β Blockers	15 (34)	15 (33)
Angiotensin-converting enzyme inhibitor	14 (31)	13 (29)
Calcium channel blocker	5 (11)	4 (9)
Diuretics	2 (5)	1 (2)
Statin	11 (25)	15 (33)
Insulin or other oral hypoglycemic drugs	4 (9)	10 (22)
Physiologic and operative severity score for the enumeration of mortality and morbidity		
Physiology score	15 [14–17]	16 [14–17]
Operative score	9 [8–11]	10 [8–12]
Predicted morbidity	16 [11–21]	17 [13–26]
Predicted mortality	2.8 [2–3.8]	3.0 [2.4–4.6]
Comorbidities, n (%)		
Hypertension	26 (59)	22 (49)
Hyperlipidemia	11 (25)	16 (36)
Ischemic heart disease	3 (7)	7 (16)
Previous myocardial infarction	3 (7)	3 (7)
Asthma and chronic obstructive pulmonary disease	3 (7)	6 (13)
Diabetes	9 (20)	15 (33)

Data are listed as mean ± SD or median [25th to 75th percentiles] and number and percentage (%).

*Major urologic procedure included open prostatectomy, open cystectomy, open nephrectomy. †Other abdominal surgery included hepatectomy (open or laparoscopic), cholecystectomy, gastrectomy (open or laparoscopic), huge umbilical hernia (open), and exploratory laparotomy (open).

Sensitivity analysis to the decision to use modified intention-to-treat analysis (*i.e.*, excluding deceased patients from the primary outcome assessment) was performed by replacing deceased patients with both zero values and lowest observed values at 1 week postsurgery. Neither replacement strategy resulted in a change in statistical significance ($P = 0.037$ for zero replacement, and $P = 0.038$ for lowest observed value replacement).

Finally, a *post hoc* sensitivity analysis of the decision to use change in scores from baseline as the primary analysis was performed by analyzing the primary outcome instead with analysis of covariance, using preoperative cognition score as a covariate and group assignment as a fixed effect. When analyzed in this manner, group assignment at 1 week and 3 months postsurgery follow-up was found to be nonstatistically significant (point estimate 0.7 with 95% CI = –0.2 to 1.6, $P = 0.14$; and point estimate 1.1 with 95% CI = 0 to 2.2, $P = 0.056$, respectively).

Secondary analysis showed a significant correlation between case time with a BIS time less than 40 and decrease in cognition score between preoperative and 1 week postsurgery scores ($r = 0.22$; $P = 0.042$). There was no significant correlation between $ETCO_2$ less than 32 mmHg and decrease in cognition score ($P = 0.883$) or between MAP less than 60 mmHg and decrease in cognition score ($P = 0.631$).

Intraoperative Data

All intraoperative data are shown in table 2. Anesthesia and surgery duration were similar in both groups. Patients in the control group received more crystalloids and less colloids than those in the closed-loop group. Total

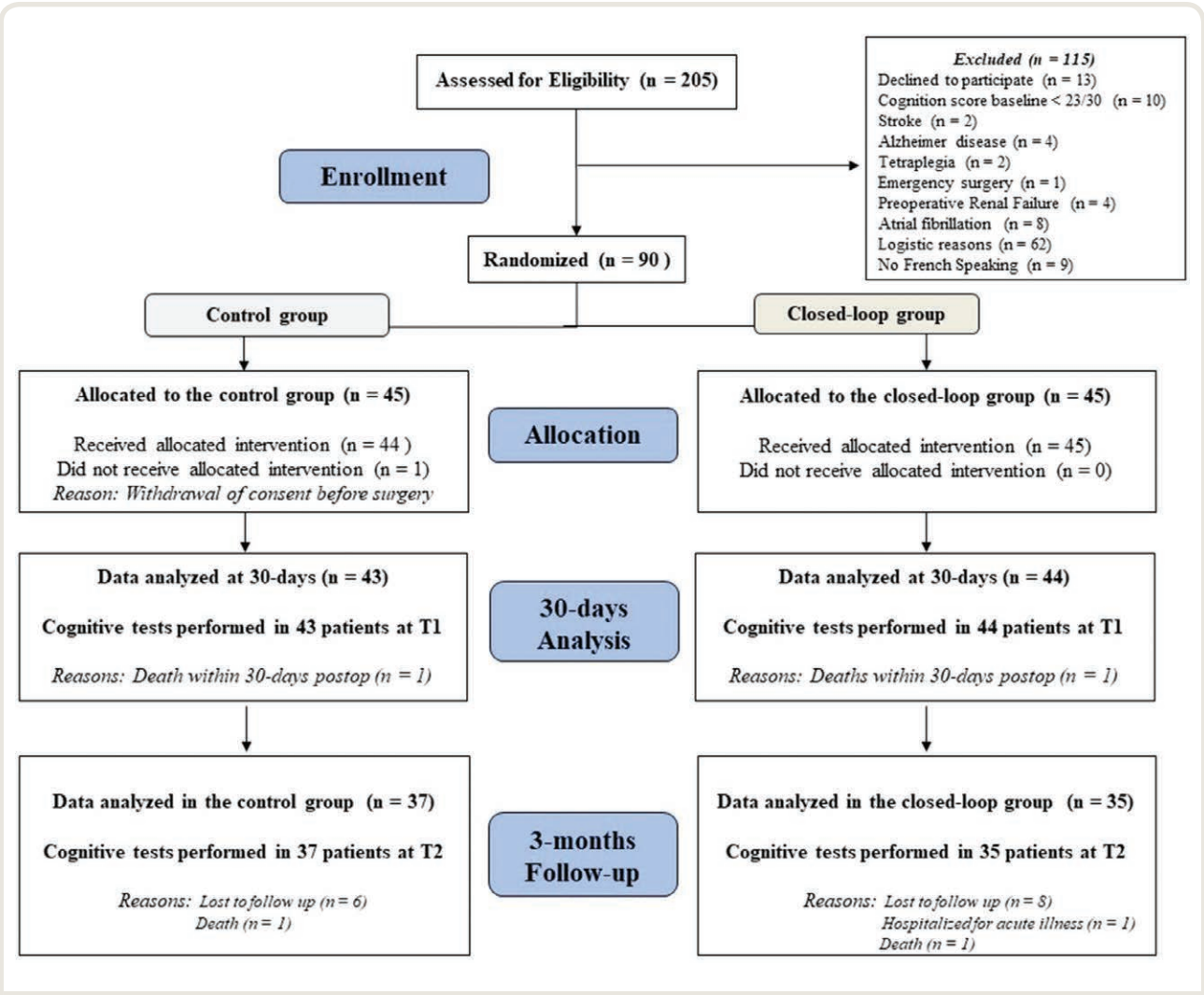

Fig. 2. CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram.

intraoperative fluid balance was higher in the control group than in the closed-loop group. Percentage of case time in the BIS target range 40 to 60 was significantly lower in the control group compared to the closed-loop group. Also, percentage of case time with BIS less than 40 was significantly *higher* in the control group. Percentage of case time with an $ETCO_2$ less than 32 mmHg was significantly lower in the closed-loop group compared to the control group. Unsurprisingly, the control group had significantly fewer adjustments of propofol, remifentanil, and ventilatory settings compared to the closed-loop group. Last, patients in the closed-loop group received significantly less propofol and more remifentanil than the control group (table 2). In the intervention group, upper propofol and remifentanil concentrations were overridden in 9 and 13 patients, respectively. This was done to maintain the BIS target within the range of 40 to 60 with no patient requiring more than one override.

Neurocognitive Follow-up

In the control group, one patient died 13 days postoperatively due to pulmonary aspiration. In the closed-loop group, one patient died on the first postoperative day due to pulmonary embolism. Both patients did not undergo the 1 week postoperative cognitive evaluation and were excluded from analysis at 1 week postsurgery (modified intention-to-treat analysis; sensitivity to this decision is explored below). Therefore, 43 patients in the control group and 44 patients in the closed-loop group did have the cognitive tests and were included in the primary analysis. At 3 months, 38 patients in the control group and 36 in the closed-loop group completed the cognitive tests. The others were lost to follow-up or readmitted to the hospital for a complication (fig. 2). Analysis of missing data revealed the values to be missing completely at random, and thus complete-case analysis would be relatively unbiased and was used for subsequent group comparisons.

Table 2. Intraoperative Data

Variables	Control Group (N = 44)	Closed-loop Group (N = 45)	Point Estimate (95% CI)	*P* Value
Anesthesia duration (min)	265 ± 144	274 ± 101	9 (–44 to 62)	0.732
Surgery duration (min)	177 [117 to 267]	203 [139 to 300]	23 (–19 to 62)	0.313
Crystalloid volume (ml)	2,000 [1,000 to 2,483]	900 [688 to 1,210]	–950 (–1,209 to –600)	**< 0.001**
Colloid volume (ml)	0 [0 to 0]	700 [400 to 1500]	600 (400 to 900)	**< 0.001**
Blood component transfusion (%)				
Packed red blood cells	1 (2.3)	1 (2.2)		> 0.999
Fresh frozen plasma	0	0		> 0.999
Platelets	0	0		> 0.999
Total IN (ml)	2,000 [1,500 to 2,688]	1,600 [1,011 to 2,610]	–225 (–600 to 192)	0.299
Urine output (ml)	300 [150 to 488]	330 [238 to 500]	75 (–25 to 150)	0.152
Estimated blood loss (ml)	150 [50 to 488]	250 [100 to 725]	50 (0 to 200)	0.202
Total OUT (ml)	535 [255 to 1,015]	780 [400 to 1,300]	200 (0 to 430)	0.063
Fluid balance (ml)	1,250 [850 to 1,888]	875 [488 to 1380]	–350 (–650 to –50)	**0.028**
Ephedrine (mg)	0 [0 to 9]	0 [0 to 18]	0 (0 to 2)	0.405
Phenylephrine (μg)	0 [0 to 0]	0 [0 to 0]		> 0.999
Patients under norepinephrine (%)	11 (25)	12 (27)	1.7 (–17 to 20)	0.857
Patients under any kind of vasopressor agents, n (%)	28 (64)	31 (69)	5 (–14 to 25)	0.600
Percentage case time with Bispectral Index [40 to 60] (%)	56 [38 to 75]	84 [74 to 89]	22 (14 to 31)	**< 0.001**
Percentage case time with Bispectral Index < 40 (%)	29 [12 to 50]	10 [3 to 19]	–18 (–28 to –9)	**< 0.001**
Percentage case time with Bispectral Index > 60 (%)	7 [1 to 13]	3 [2 to 8]	–2 (–5 to 0)	0.128
Number of episode with suppression ratio > 10 > 1 min	0 [0 to 1]	0 [0 to 0]	0 (0 to 0)	0.707
Intraoperative heart rate (beats/min)	65 [59 to 74]	68 [63 to 76]	4 (0 to 8)	0.094
Intraoperative mean arterial pressure (mmHg)	90 [82 to 95]	84 [78 to 94]	–4 (–8 to 1)	0.130
Percentage case time with MAP < 60 mmHg	0.8 [0 to 3.6]	1.0 [0 to 3.2]	0 (–0.5 to 0.4)	0.703
Number of effect site propofol modifications per hour	5 [3 to 8]	24 [18 to 32]	18 (15 to 22)	**< 0.001**
Number of effect site remifentanil modifications per hour	4 [2 to 5]	24 [21 to 30]	21 (19 to 22)	**< 0.001**
Total propofol consumption ($mg \cdot kg^{-1} \cdot h^{-1}$)	4.4 [3.3 to 5.5]	3.8 [3.0 to 4.5]	–0.71 (–1.37 to –0.05)	**0.033**
Total remifentanil consumption ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.12 ± 0.05	0.14 ± 0.04	0.02 (0.01 to 0.04)	**0.012**
24-h morphine consumption (mg)	4 [2 to 10]	4 [2 to 8]	–0.5 (–4.0 to 0.0)	0.313
Mean tidal volume ($ml \cdot kg^{-1}$)	6.6 [6.1 to 6.9]	6.9 [6.7 to 7.1]	0.31 (0.08 to 0.52)	**0.012**
Percentage case time with end-tidal carbon dioxide [32 to 38] mmHg (%)	48 [21 to 80]	80 [56 to 92]	20.5 (5.5 to 37.6)	**0.004**
Percentage case time with end-tidal carbon dioxide < 32 mmHg (%)	24 [5 to 54]	8 [3 to 30]	–8 (–23 to 0)	**0.037**
Percentage case time with end-tidal carbon dioxide > 38 mmHg (%)	2.2 [0.5 to 12.8]	4.3 [1.1 to 7.7]	0.4 (–1.2 to 2.1)	0.537
Total number of ventilation parameters modifications	3 [2 to 5]	13 [3 to 33]	6 (1 to 18)	**0.001**

Data are listed as number and percentage (%), or mean ± SD for continuous variables that were normally distributed or median [25th to 75th percentiles] if not normally distributed. Point estimates for group differences were estimated for Mann–Whitney U test as the median difference in the set of values representing all differences in pairings between the two groups. Bold indicates significant results with *P* value < 0.05. IN includes all fluid and blood products received during surgery. OUT includes estimated blood loss and urine output.

MAP, mean arterial pressure.

Adverse Events

No patient experienced intraoperative awareness. There was no significant difference in major or minor complications in the intensive care unit and PACU, and no difference in hospital length of stay (table 3). The 30-day mortality rate was 1 of 45 patients in each group (2.2%). Last, we did not observe any adverse events related to the use of our closed-loop systems during the study.

Discussion

Under our study conditions, we demonstrated that closed-loop anesthetic management using the combination of three independent controllers outperformed manual control of depth of anesthesia, $ETCO_2$, and fluid balance. This management was associated with a significant difference in the cognition score compared to baseline in the control group *versus* the closed-loop group at 1 week postsurgery (–1 [–2 to 0] *vs.* 0 [–1 to 1]; difference 1 [95% CI, 0 to 3], $P = 0.033$). This effect persisted at 3 months follow-up. Taken together, these results suggest that automated anesthetic management may have a positive impact on delayed neurocognitive recovery.[40] However, given the study design, it was impossible to draw strong conclusions on the impact of each controller's individual effect on the cognition score.

These observations could be of major interest as delayed neurocognitive recovery and postoperative neurocognitive disorder and their adverse consequences are not only a significant burden to patients but also a financial burden on our healthcare system (estimated $150 billion annual expense).[41] Not surprisingly, the battery of specific neurocognitive tests did not confirm this result, as they did not show any significant difference between the groups from baseline. Indeed, these neurocognitive tests do not capture all aspects of cognition as they evaluate different, potentially

Table 3. Postoperative Data

Variables	Control Group (N = 44)	Closed-loop Group (N = 45)	Point Estimate (95% CI)	*P* Value
Total fluid infusion at postoperative day 1 (ml)	1,325 [400 to 2,638]	1,625 [500 to 2,648]	100 (–300 to 700)	0.534
Major complications, N (%)				
Patients with any major complications	5 (11)	2 (4)	–7 (–18 to 4)	0.224
Pulmonary embolism	1 (2)	0 (0)	–2 (–7 to 2)	0.312
Pulmonary edema	1 (2)	0 (0)	–2 (–7 to 2)	0.312
Pneumonia	2 (5)	0 (0)	–5 (–10 to 2)	0.241
Incidence of acute kidney injury*	4 (9)	2 (4)	–5 (–15 to 6)	0.382
30-day mortality	1 (2)	1 (2)	0 (–6 to 6)	0.987
90-day mortality	1 (2)	1 (2)	0 (–6 to 6)	0.987
Minor complications, N (%)				
Patients with any minor complications	10 (23)	11 (24)	2 (–16 to 19)	0.849
Superficial wound infection	1 (2)	1 (2)	0 (–6 to 6)	0.987
Urinary infection	1 (2)	0 (0)	–2 (–7 to 2)	0.312
Paralytic ileus	1 (2)	1 (2)	0 (–6 to 6)	0.987
Postoperative confusion†	2 (5)	0 (0)	–5 (–10 to 2)	0.241
Postoperative nausea and vomiting	5 (11)	7 (16)	4 (–10 to 18)	0.561
Other infections	3 (7)	3 (7)	0 (–11 to 10)	0.977
Hemoglobin at discharge ($g \cdot dl^{-1}$)	11.7 ± 1.7	11.8 ± 2.1	0.1 (–0.8 to 0.9)	0.892
Creatinine at discharge ($mg \cdot dl^{-1}$)	0.9 [0.7 to 1.0]	0.8 [0.6 to 1.0]	–0.1 (–0.2 to 0)	0.052
Estimated glomerular filtration rate at discharge ($ml \cdot kg^{-2} \cdot 1.73\ m^{-2}$)	85 [74 to 95]	96 [80 to 103]	8 (0 to 15)	0.059
Intensive care or postanesthesia care unit length of stay (h)	6 [3 to 19]	17 [4 to 19]	1 (–1 to 3)	0.419
Hospital length of stay (day)	4 [3 to 7]	4 [3 to 8]	1 (0 to 1)	0.259
90-day readmission	12 (27)	11 (24)	–3 (–21 to 15)	0.761

Data are presented as number and percentage, (%) or median [25th to 75th percentiles] or mean ± SD. Point estimates for group differences were estimated for Mann–Whitney U test as the median difference in the set of values representing all differences in pairings between the two groups.

*Included Kidney Disease Improving Global Outcomes I to III. †Assessed by nurses in the postanesthesia care unit.

less affected, cognitive domains than the cognition score. Attention functions, visual–spatial abilities, and language were not assessed by these specific tests, while they were all assessed as part of the cognition test. Interestingly, there was a significant correlation between percentage of case time with a BIS value less than 40 and a decrease in the cognition score, confirming that a deep anesthetic level may impact postoperative cognitive function in elderly patients undergoing noncardiac surgery.[42] It should be mentioned, however, that Wildes *et al*. recently put into question the benefit of a BIS monitor to decrease the incidence of postoperative delirium.[43]

Whether a 1-point decrease in the 30-item cognition score is meaningful remains an open question. On the one hand, this small change is probably nondetectable in terms of activities of daily living or function. On the other hand, most patients would be unhappy to learn of *any* possibility of a persistent cognitive decline, no matter how small, that may last for months after a procedure. Additionally, as the average surgical patient ages and their survival increases with improved perioperative techniques, clinicians and patients are increasingly concerned with quality of life outcomes, including cognitive performance. It is worth noting that patients enrolled in the current study were not frail based on the Edmonton frail scale. As a result, our primary outcome might have been even more significantly affected in a more frail and vulnerable population.

Our results are in agreement with those of the only published study that assessed the impact of closed-loop intravenous anesthesia guided by BIS monitoring on cognitive function in patients scheduled for abdominal surgery.[44] In this study, Cotoia *et al*. reported better performance in the Mini Mental State Examination test performed 15 min after awakening in the closed-loop group (coadministration of propofol and remifentanil) compared to a control group, where anesthesia was manually titrated with either intravenous or inhaled agents. The authors also reported that the percentage of time with a BIS less than 40 was significantly lower in the closed-loop group compared to the manually titrated group. As a possible consequence of the anesthetic closed-loop algorithm, patients in the intervention group received more remifentanil and less propofol than those in the control group, which has already been observed by Cotoia *et al*.[44] It is worthy of future consideration to more objectively quantify the impact of the closed-loop algorithm on anesthetic potency using parameters evaluating the synergic interaction between propofol and remifentanil as described by Luginbühl *et al*.[45] However, we do not think the difference in remifentanil doses between the two groups significantly impacted postoperative induced hyperalgesia as postoperative opioid requirements were not different between the groups.

In the current study, the closed-loop system used to titrate the depth of anesthesia was used alongside two other

closed loops, one in control of fluid titration to optimize stroke volume, and another to adjust ventilation parameters in order to ensure end-tidal normocapnia. Total fluid administration and intraoperative fluid balance were lower in the closed-loop group than in the control group. Previous studies applying goal-directed fluid therapy using a closed-loop system have also demonstrated a reduction in the net fluid balance, which was associated with a decrease in the incidence of postoperative complications.[28,46] However, the current study did not have the appropriate power to detect a difference in the incidence of postoperative complications between the two groups based on different fluid titration strategies. Of note, all patients in this study had a radial arterial line placed, but previous studies have demonstrated that such a closed-loop system works well with noninvasive hemodynamic monitoring.[27,47]

The use of the closed-loop mode on our ventilator resulted in a significantly lower percentage of case time with $ETCO_2$ less than 32 mmHg, which has been recently associated with postoperative delirium.[4] This recent study by Mutch *et al.* clearly emphasized the importance of maintaining adequate normocapnia in elderly patients undergoing noncardiac surgery.[4] Putting all these data together, our results confirm the usefulness of closed-loop systems to maintain multiple physiologic variables within a desired range as compared to manual adjustments, with a significant reduction in episodes of over- and undershooting.[15,16]

Additionally, and perhaps more importantly, the results of the current study emphasized the concept that closed-loop systems might represent an interesting approach to ensure standardization and consistent application of physiologic-based recommendations, particular if these recommendations are strict.[11] It is unfortunate that closed-loop systems are still predominantly considered to be simply a research tool, although their increasing acceptance into clinical environment in upcoming years is expected.

Strengths of the current study include extensive evaluation of cognitive function performed by expert administrators from the preoperative period until 3 months postsurgery. The use of the well-defined closed-loop systems for the various interventions also represents another strength, as their performance will be consistent and repeatable in future work. Last, the comparison of three independent controllers to manual adjustments in the operating room is a novel technique that is only recently possible as the necessary technology has only recently become available. Comparing an automated intraoperative approach using three controllers to manual management is something that has never been possible in the field of automation and closed-loop systems.

Limitations

First, a *post hoc* sensitivity analysis using analysis of covariance suggested the strength of our conclusions may be limited by some sensitivity of the results to the manner of analysis we chose. Certainly, using this study's estimated effect sizes indicates a more robustly powered study could be undertaken. Second, although this study was powered to detect a difference in cognition score, this is still a relatively small sample of patients, and larger studies are definitely warranted, in particular for patients at higher risk of cognitive impairment. Indeed, as per the study design, patients included in our study did not have any preoperative cognitive impairment, and patients were not frail according to the Edmonton frail scale. Therefore, the results of the current study should not be extrapolated to a population with preexisting cognitive decline or to frail patients preoperatively. Third, this study was also clearly not powered to detect other postoperative complications or mortality, which have commonly been assessed by studies investigating the "double-low" or "triple-low" in recent literature.[48,49] The blood pressure in the current study was not specifically regulated in either group, although the average MAP was well above 80 mmHg in both groups. In a recent study, Futier *et al.* demonstrated that tighter blood pressure control was associated with fewer postoperative complications, including a lower incidence of alteration in consciousness among high-risk patients undergoing major abdominal surgery.[50] In the current study, the percentage time spent with MAP less than 60 was around 1% in both groups, suggesting tight hemodynamic management occurred in both groups. Fourth, the absence of cardiac output and stroke volume values in the control group prevented the determination of the true impact of a closed loop–assisted goal-directed fluid strategy on our primary outcome. Regardless, these previous and current observations strengthen the importance of carefully titrating the level of anesthesia to reduce the incidence of cognitive impairment. Fifth, the current study used lower tidal volumes than those usually recommended when stroke volume variation is applied to predict fluid responsiveness.[51] The influence of stroke volume variation on the controller as a guide for fluid therapy is extremely complex and variable depending on the predictability of the hemodynamic response to previous boluses. Nevertheless, the reduction in tidal volume below $10\,ml \cdot kg^{-1}$ may have, on average, made the controller less sensitive to mild hypovolemia, and this in turn may have led to different management than if $10\,ml \cdot kg^{-1}$ had been used. Sixth, the depth of anesthesia within the control group was adjusted by anesthesiologists who had expertise in utilizing the BIS monitor, whereas in the intervention group, this was performed by one of the three closed-loop system "experts" within our department, all of whom also have significant experience using the BIS monitor. Allocating anesthesiologists with different expertise into two separate groups will inevitably introduce some bias. On the one hand, if the intervention group was managed by the same anesthesiologists who managed the control group, some additional user variability or errors may have decreased the performance of the intervention. This could have introduced a potential methodologic bias.

On the other hand, if the three experts (A.J., V.J., L.B.) involved in the study had also performed anesthesia in the control group, this would have also introduced a potential bias and would have hardly been considered "standard practice." Moreover, using three novel closed-loop systems simultaneously requires a learning curve that is only currently mastered by the three authors. Unfortunately, both situations introduce possible bias to the study. Last, we want to point out that clinicians from the control group were all familiar with target-controlled intravenous anesthesia using BIS monitoring as they have been using such a system for multiple years. This was supported by the low occurrence of burst suppression and hypotension in the control group and could explain the low incidence of postoperative adverse events. Results might therefore be different (likely worse) in institutions where total intravenous anesthesia and the use of BIS monitoring are not yet the standard of care.

Future Directions

Prevention of delayed cognitive recovery in surgical patients may reduce the rate of postoperative complications in this population. Promoting the development of interventions such as physiologic closed-loop systems to optimize perioperative anesthesia management represents an appealing strategy in this context.

In the current work, each physiologic closed-loop system worked independently as purely "isolated controllers." Each system responded to a specific intervention (propofol and/or remifentanil adjustments, fluid loading, and ventilator parameter modifications) only in regard to how these interventions affect their specific target variable. In the future, closed-loop systems will be built to work *together* to control multiple aspects of patient care simultaneously.

Conclusions

Among older, nonfrail patients undergoing moderate and high-risk noncardiac surgery, an automated anesthetic management using the combination of three independent closed-loop systems outperformed manual control and may have an impact on delayed neurocognitive recovery. However, given the study design, it is impossible to draw strong conclusions on the impact of each controller's individual effect on the cognition score. Future studies are needed to further assess the impact of this approach in more vulnerable patients and on other postoperative complications.

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Competing Interests

Drs. Joosten, Cannesson, and Rinehart are consultants for Edwards Lifesciences (Irvine, California). Drs. Cannesson and Rinehart have ownership interest in Sironis (Newport Beach, California), which has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences. Edwards Lifesciences, Sironis, and any other commercial entity have provided no funding, directly or indirectly, in support of the current work, to the individual authors, or any of their respective departments. Dr. Joosten is a consultant for Aguettant (Lyon, France) and Fresenius Kabi GmbH (Bad Homburg, Germany). Dr. Van der Linden has received, within the past 5 yr, fees for lectures and consultancies from Fresenius Kabi GmbH, Aguettant, and Nordic Pharma (Antwerpen, Belgium). Dr. Liu is a cofounder and holds equity interest in MedSteer (Paris, France). The company's patented technologies focus on drug delivery solutions guided by the cortical activity of the patient. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: joosten-alexandre@hotmail.com.
Raw data available at: joosten-alexandre@hotmail.com.

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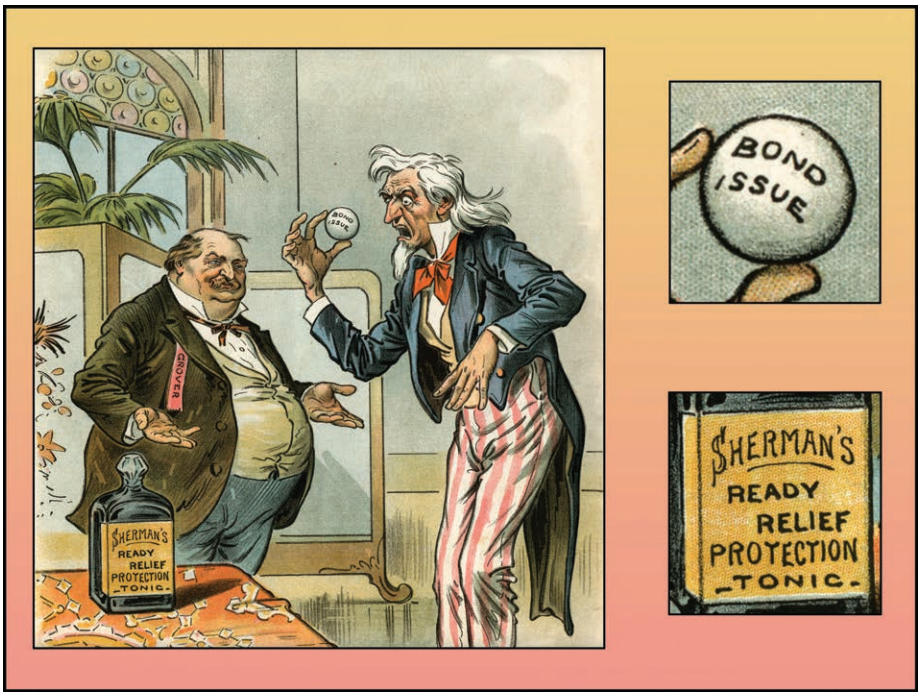
Bitter Gold Analgesia: Grover Cleveland's Remedy



In the post–Civil War era, the Republican Party—that of Lincoln, Grant, and the Union—and the Democratic Party—that of the bygone Confederacy—had remained divided by geography. Economic unrest in the late nineteenth century, however, weakened old political ties. Farmers and industrial workers began to despise Wall Street and the "money trust." Free silver, as opposed to the gold standard, became the Populist mantra and cut across party lines. Passed under Republican leadership, the Sherman Silver Purchase Act (1890) committed the federal government to purchasing surplus mined silver for minting. In 1892, the Democrats' selection of a pro-silver running mate (Adlai Stevenson) eased the re-election of gold-devoted Grover Cleveland to a non-consecutive second presidential term. Facing the Panic of 1893, Cleveland panicked and repealed the Sherman Silver Purchase Act. In this cover cartoon (*left*) of a January 1896 issue of *Judge*, a satirical pro-Republican weekly, an unsightly "Doctor Cleveland" offers "A Bitter Pill," as opposed to Sherman's Ready Relief Protection Tonic (*lower right*), to an appalled Uncle Sam. The pill, his fourth Treasury "Bond Issue" (*higher right*), aimed to restore the nation's depleted gold reserves by increasing federal debt—an unpopular move by which Cleveland hoped to rebuild long-term security. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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