Feasibility of Fully Automated Hypnosis, Analgesia, and Fluid Management Using 2 Independent Closed-Loop Systems During Major Vascular Surgery: A Pilot Study

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Automated titration of intravenous anesthesia and analgesia using processed electroencephalography monitoring is no longer a novel concept. Closed-loop control of fluid administration to provide goal-directed fluid therapy has also been increasingly described. However, simultaneously combining 2 independent closed-loop systems together in patients undergoing major vascular surgery has not been previously detailed. The aim of this pilot study was to evaluate the clinical performance of fully automated hypnosis, analgesia, and fluid management using 2 independent closed-loop controllers in patients undergoing major vascular surgery before implementation within a larger study evaluating true patient outcomes. (Anesth Analg XXX;XXX:00–00)

Given the safety record that automation has achieved in fields ranging from manufacturing to commercial flight, many researchers have developed devices using self-contained feedback technologies (closed-loop systems) for delivery of intravenous anesthetic drugs,[1,2] fluids,[3] and vasopressors.[4–6] Overall, these systems have been shown to improve the consistency of interventions when compared to manual interpretation and modifications.[7,8]

In recent years, members of our group have developed a dual closed-loop controller allowing the automated coadministration of propofol and remifentanil with dosing adjusted based on feedback using the bispectral index (BIS).[2] We have also created an adaptive closed-loop system for fluid titration using goal-directed fluid therapy strategies that are guided by a stroke volume (SV) and SV variation (SVV) monitor.[9] The main objective of this pilot study was to assess the clinical performance of fully automated hypnosis, analgesia, and fluid administration guided via a combination of several physiological variables (BIS, SV, and SVV) and controlled with 2 independent closed-loop systems in a series of patients undergoing major vascular surgery. This pilot study was also undertaken to verify that no serious or unexpected negative interactions between the 2 systems would take place when operating in parallel while also ensuring that both systems would prove suitable for a large population of high-risk surgical patients.

METHODS

This study was approved on July 2016 by our Ethics Committee (Comité D'éthique de l'hopital Erasme) and registered before the enrollment of the first included patient (September 1, 2016) with ClinicalTrials.gov (NCT02886806, principal investigator: L.B.). All patients provided written informed consent. Adult patients scheduled for various elective major vascular surgeries were included in this study (Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/C367). Exclusion criteria included American Society of Anesthesiologists score >3, left ventricular ejection fraction <30%, cardiac arrhythmias, preoperative renal disorder (serum creatinine >2 mg/mL, oliguria, anuria, or hemodialysis), supraspinal neurological disorder, and patients with a pacemaker.

All patients received standard monitors (pulse oximeter, noninvasive blood pressure, electrocardiogram, rectal temperature). A radial arterial line was inserted before induction and linked to SV and SVV monitoring (EV-1000; Edwards Lifesciences, Irvine, CA). BIS electrodes were placed on the patient's forehead before induction and connected to a BIS XP monitor (Aspect Medical System, Inc, Natick, CA). Rocuronium (0.6 mg·kg^{-1}) was administered during the induction of anesthesia and continuously administered during the case using a standard syringe pump adjusted by the anesthesiologist to maintain the train-of-four ratio <2 using a curarization monitor (Tof Scan; Idmed, Marseille, France). After tracheal intubation, ventilation was performed using a tidal volume of 7 mL·kg^{-1} of ideal body weight, a positive end-expiratory pressure of 5 cm H_2O, and recruitment maneuvers when necessary.

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The respiratory rate was set to achieve an end-tidal carbon dioxide between 32 and 36 mm Hg. All patients required anticoagulation during the procedure, and this was achieved using heparin (1.5 mg·kg^{-1}) to keep activated clotting time over 250 seconds. This was reversed with protamine (1:2 ratio) at the end of the clamping period. Intravenous morphine was administered (0.05 mg·kg^{-1}) at incision, or a spinal injection of morphine (300 μg) was given before induction at the anesthesia team's discretion. Additionally, morphine was given again 1 hour before the end of surgery along with paracetamol (with nonsteroidal agents if no contraindications).

Intraoperative Anesthesia Management

Two Base Primea infusion pumps (Fresenius Kabi, Bruxelles, Belgium) and the BIS XP monitor (Aspect Medical Systems, Inc, Newton, MA) were connected to the Infusion Toolbox 95 (version 4.11) software[10] via their RS 232C serial interfaces. The ToolBox software required patient demographic data (sex, age, weight, and height) to calculate the effect-site concentrations of propofol and remifentanil using the pharmacokinetic models of Schnider et al[11] and Minto et al,[12] respectively. 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.[2] This system is described more extensively in Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C368. The anesthesiologist could modify the upper and lower limits of desired drug concentrations and override the system if necessary. Thereafter, modifications of propofol and remifentanil effect-site target-calculated concentrations were only controlled by the dual-loop algorithm with lower and upper limits for propofol (0.5–3 ng·mL^{-1}) and remifentanil (2–8 ng·mL^{-1}). Both of these infusions were discontinued at the start of skin closure, and a neuromuscular reversing agent was given to all patients if the train-of-four ratio was <0.9.

Patients received a maintenance crystalloid infusion (PlasmaLyte; Baxter, Lessines, Belgium) through a Hotline fluid warmer system (Smiths Medical , Bruxelles, Belgium) at a rate of 3 mL·kg^{-1}·hour^{-1} delivered by a standardized pump (Volumat Agilia; Fresenius Kabi, Bruxelles, Belgium). Additional fluid was given using a goal-directed fluid therapy protocol using information from the EV-1000 monitor (Edwards Lifesciences) that was linked to our closed-loop system. This consisted of multiple 100-mL boluses of colloid (Geloplasma; Fresenius Kabi GmbH, Bad Homburg, Germany). This closed-loop system has been reported in detail elsewhere[3] and in Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C368. Blood loss management was treated by anesthesiologists independently of our controllers. If hypotension occurred (predefined as mean arterial pressure [MAP] <70 mm Hg), it was treated consistently using a norepinephrine infusion that was manually adjusted by the anesthesiologist using an infusion pump (BasePrimea; Fresenius, Belgium). In the postoperative period, all patients received a crystalloid infusion (Sterofundin B; B-Braun, Diegem, Belgium) at a rate of 1.5 mL·kg^{-1}·hour^{-1}. Additional fluid infusions were given at the discretion of the provider taking care of the patient. The Figure describes the closed-loop system set-up in our operating room.

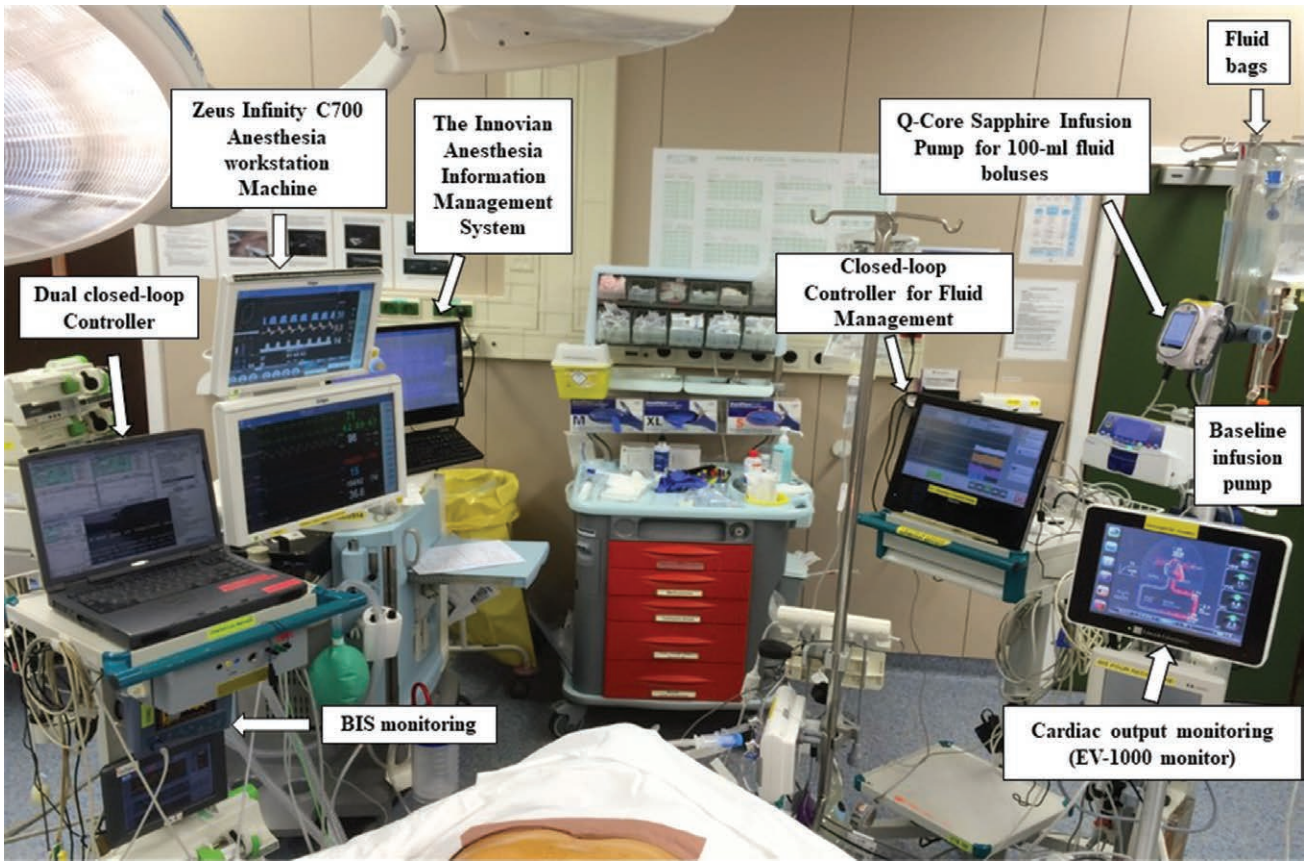

Figure. Closed-loop systems set up in our operating room in Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.

Table. Intraoperative Variables and Controller Performances of Both Closed-Loop Systems

Case	Crystalloid (mL)	Colloid (mL)	EBL (mL)	Urine Output (mL)	Net Fluid Balance (mL)	NE (μg)	PF Mean Infusion Rate, mg·kg^{-1}·hour^{-1}	No. of PF Target Modifications	RF Mean Infusion Rate ∫, μg·kg^{-1}·minute^{-1}	No. of RF Target Modifications	% Case-Time With BIS (40–60)	% Case-Time With BIS (30–40)	% Case-Time With BIS >60	% Case-Time BSR >10% for >1 min	% Case-Time in Preload Independent State[a]
1	1330	1700	1700	825	505	146	3.3	219	0.16	205	57	39	1	0	94
2	1476	400	300	475	1101	18	3.16	170	0.12	153	96	3	1	0	100
3	950	1500	450	1325	926	0	2.79	258	0.21	220	81	19	0	2	100
4	2000	2500	2255	1475	2509	136	2.68	341	0.16	289	76	22	1	0	100
5	1100	1100	300	1300	600	51	3.90	197	0.14	164	96	3	2	2	99
6	1250	2200	1000	1275	1461	283	3.63	292	0.17	291	63	33	3	0	97
7	925	900	350	500	975	0	2.42	142	0.13	122	84	14	2	0	97
8	2350	2500	2900	500	2616	992	4.06	363	0.19	328	89	9	1	0	99
9	1703	600	500	250	1553	0	3.42	276	0.15	240	88	12	0	2	100
10	1873	2000	500	1200	2455	61	3.81	350	0.15	316	97	1	2	0	99
11	900	100	200	450	350	0	2.10	116	0.10	90	76	23	0	1	99
12	870	1600	500	450	1520	42	3.96	201	0.15	154	87	13	0	0	94
13	800	1700	500	1600	400	45	3.99	205	0.20	171	72	26	2	1	93
Median	1250	1600	500	825	1101	45	3.42	219	0.15	205	84	14	1.2	0	99
25th IQ	925	900	350	475	600	0	2.80	197	0.14	154	76	9	0.4	0	97
75th IQ	1703	2000	881	1300	1553	136	3.90	292	0.17	289	89	23	2.0	1	100

Abbreviations: BIS, bispectral index; BSR, burst suppression ratio; CI, cardiac index; EBL, estimated blood loss; IQ, interquartile; NE, norepinephrine; PF, propofol; RF, remifentanil; SVV, stroke volume variation.
[a]Preload independent state defined as SVV <13% and/or CI ≥2.5 L·minute^{-1}·m^{-2}.

Study Objectives

The primary objective was to assess the clinical performance of both closed-loop systems with respect to an adequate depth of anesthesia (defined as a percentage of BIS 40–60) and an adequate hemodynamic profile (defined as preload independent state: SVV <13% and/or a cardiac index ≥2.5 L·minute^{-1}·m^{-2}) for at least 85% of the case-time in individual patients. In regard to the closed-loop fluid management system, 85% of case-time within the target range was the primary objective of previous studies.[13,14] As such, we decided to use this same target as the goal for each patient in our study. As for the dual-loop closed loop (propofol–remifentanil), the original study comparing this to manual control had 85% and 76% median time-in-target, respectively.[2] We once again decided to use the higher value as our goal for overall median time spent with a BIS 40–60. Secondary outcomes included an estimate of the number of manual closed-loop system overrides by the attending anesthesiologist, time to tracheal extubation (time between the discontinuation of propofol and remifentanil infusion and tracheal extubation), number of system errors, time of BIS value <40 or >60 (overshoot and undershoot of hypnosis), occurrence of burst suppression ratio >10% for at least 1 minute, mean anesthetic drugs infusion rate, frequency of drugs concentrations modifications, net fluid balance, incidence of intraoperative awareness, dose of norepinephrine, hospital length of stay, and mortality rate at 30 and 90 days. Last, we also attempted to explore if there were any significant treatment errors (defined as changes in therapy inappropriate for the clinical setting) during large hemodynamic perturbations. This was investigated by assessing the treatment approach of both systems during hypotensive events (defined as MAP <70 mm Hg for at least 5 consecutive minutes) and during the aortic clamping and unclamping period of aortobifemoral bypass surgeries. These time periods were chosen as they were the most dynamic periods of patient physiology (Supplemental Digital Content 3, Appendix 2, http://links.lww.com/AA/C369).

Statistical Analysis

Data are expressed as median (25th–75th percentiles) or percentages (%). Confidence intervals (CIs) are calculated for proportions with the exact Poisson method. For a pilot study, it has been suggested that a minimum sample size of 12 patients is needed.[15] Therefore, 13 consecutive patients were recruited in our study.

RESULTS

Thirteen patients were included. Baseline characteristics are shown in Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/C367, and hemodynamic variables in Supplemental Digital Content 4, Table 2, http://links.lww.com/AA/C370. The median (interquartile range) patient case-time with a BIS 40–60 was 84% (76–89) and with hemodynamics within goal was 99% (97–100). On a per-patient basis, 6 of 13 (46%, 95% CI, 19%–75%) patients had BIS values within target for 85% of the case duration. Error, when present, was consistently a BIS value below target in the range of 30–40 (Table). The dual closed-loop system maintained anesthesia for 4707 minutes and made a total of 3130 propofol and 2743 remifentanil target

concentration modifications for all patients (Table). The systems were not overridden by the supervising anesthesiologist in any cases. For the case which lost 2900 mL of blood, the patient (No. 8) received 4 units of packed red blood cells and 2 units of fresh frozen plasma via pressure bags independent of the closed-loop fluid management system. This manual resuscitation did not disrupt either closed-loop system as input variables were still present and accurate. This case and another uncomplicated example (patient No. 5) are presented in Supplemental Digital Content 5, Appendix 3, http://links.lww.com/AA/C371.

Importantly, overshoot (BIS >60) and undershoot (BIS <40) occurred in 1.2% (0.4–2.0) and 14% (10–23) of case-time. No patient experienced intraoperative awareness when asked in the postoperative period, although our sample size is too small to effectively address this concern (0/13; 95% CI, 0–24). The median number of burst suppression episodes per patient was (0 [0–1]; Table).

Patients spent at least 85% of total case-time in a preload independent state for all 13 patients (13/13; 95% CI, 76–100). The primary anesthesiologist never stopped a fluid bolus and never changed the controller from the standard SVV target of 11%. Five patients received blood transfusion. The median fluid balance was positive 1101 mL (600–1553). MAP was effectively maintained at a steady level as patients spent 92% (86–97) of the anesthesia time with a MAP >70 mm Hg. Nine of the 13 patients (95% CI, 39–91) received a continuous infusion of norepinephrine as part of their care. We did not observe any negative interaction of the infusion with either system, but we did not examine this question in complete detail. There were no system errors recorded, and times for tracheal intubation (6.5 ± 2.9 minutes) and extubation (4.7 ± 2.0 minutes) were within standard practice. The length of stay in the hospital was 8 (6–19) days. There were no mortalities during 90-day follow-up period.

DISCUSSION

This pilot study describes the simultaneous use of 2 independent closed-loop systems to assist clinicians in titrating hypnosis, analgesia, and fluid therapy in patients undergoing major vascular surgery. The dual anesthesia controller performed comparably to the results reported by Liu et al[2] (84% and 85% time-in-target, respectively, as median for the entire cohort), despite the fact that our patients underwent longer, more complex, and high-risk vascular surgeries. This latter fact may have contributed to the lower per-patient rate (46%) of time in BIS target 40–60. The median cohort times are also higher than hand-titrated results reported previously by Puri et al,[16] Bould et al,[17] and Liu et al.[2] The number of episodes of burst suppression was also low compared to the total duration of anesthesia. The clinical performance of the fluid management controller was comparable with our previous publications.[5,6] Overall, both controllers managed the cases with no physician interaction required once targets were set. Our results might be somewhat expected given that both of these controllers have already been well described in the literature and the interaction between the 2 controllers were likely minimal. However, a key difference is that we performed this study in high-risk surgical patients undergoing major vascular surgeries, while previous studies by our group were done in moderate-risk patients undergoing mainly moderate-risk surgery. Anesthesia durations were also almost twice as long in the present study compared to both previous publications.[5,13] Our patients had a median (interquartile range) anesthesia time of 328 (278–476) minutes. Additionally, while it is true that both systems have been shown to function acceptably independently guided by their own inputs (BIS versus SV/SVV), it does not necessarily follow that they will not interact in potentially negative ways, especially during periods of hemodynamic instability often present during major vascular surgery. This study demonstrated that both systems do continue to function well during large hemodynamic changes. Supplemental Digital Content 3, Appendix 2, http://links.lww.com/AA/C369, details the behavior of both controllers during hypotensive episodes and aortic clamping and unclamping, and Supplemental Digital Content 6, Table 3, http://links.lww.com/AA/C372, shows the closed-loop controller's reactions to these hypotensive episodes. We did not observe any degradation in stability of either system by the presence of the other, although we did not extensively assess this. This issue may require specific engineering or directed in vivo studies to completely answer. On a deeper level, there is likely a significant opportunity to improve both systems with the addition of cross-communication software and coordination of operation. Certainly work like this has been done in the fields of control engineering (which would include the aviation industry), but this was outside the scope of the current article. At some point, if separate closed-loop systems are to be joined and cross-communication implemented effectively, stability testing would be a key component in the validation of the final controller system.

Limitations and Future Direction

This trial is a small series of patients performed in single center. However, based on previously published studies,[5,6] 13 patients were determined to be sufficient for such a simple demonstration of performance in realistic condition. The clinical applicability and ease of use cannot be fully addressed without the addition of practitioners who are naive to our technology. Our group is working on the development of an optimized user workstation interface before attempting to evaluate this concern more fully in the future. Additionally, a larger randomized study in the future will allow for additional evaluation of expected and unexpected safety concerns. We would also like to explore higher infusion rates that can help manage more acute hemodynamic changes, although this has the potential to significantly change the safety profile of our system. Closed-loop vasopressor protocols are also of great interest for our group as they can help manage hypotensive patient who are fluid optimized. Our next step will be a randomized controlled trial comparing the impact of this strategy (fully automated anesthesia) versus patients having completely manually titrated anesthetic on the incidence of postoperative cognitive dysfunction in elderly surgical patients.

CONCLUSIONS

This study demonstrates the clinical ability in realistic conditions of dual closed-loop systems to maintain their anesthetic and hemodynamic targets for the majority of the

case-time in patients undergoing major vascular surgery. Additional research will be required to demonstrate any true benefits of this strategy on patient outcome and realistic clinical applicability.

DISCLOSURES

Name: Alexandre Joosten, MD.
Contribution: This author helped design the study, recruit the patients, collect and analyze the data, and draft the final manuscript.
Conflicts of Interest: A. Joosten is the Consultant for Edwards Lifesciences (Irvine, CA).
Name: Vincent Jame, MD.
Contribution: This author helped design the study, recruit the patients, collect and analyze the data, and draft and approve the final manuscript.
Conflicts of Interest: None.
Name: Brenton Alexander, MD.
Contribution: This author helped analyze the data and draft the final manuscript.
Conflicts of Interest: None.
Name: Thierry Chazot, MD.
Contribution: This author helped analyze the data and draft the final manuscript.
Conflicts of Interest: T. Chazot is a cofounder of MedSteer, a company dedicated to creating closed-loop systems for the delivery of anesthesia drugs.
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Conflicts of Interest: J. Rinehart is a consultant for Edwards Lifesciences, and he is also a cofounder of Sironis, a company developing closed-loop fluid management systems.
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Contribution: This author helped design the study, analyze the data, and draft the final manuscript.
Conflicts of Interest: None.
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