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Clinical Performance of a Bispectral Index Controlled Closed-Loop Administration System for Simultaneous Administration of Propofol and Remifentanyl

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Closed-loop control of total intravenous anesthesia (TIVA) uses computer-based systems to autonomously regulate propofol infusion based on a quantitative indicator of depth of hypnosis (DoH), thereby maintaining the desired clinical effect and reducing anesthesiologist workload.¹

However, due to the lack of a reliable quantitative measure of analgesia, the administration of remifentanyl remains in charge of the anesthesiologist.²

Current protocols involve measuring DoH alone and impose a balance between propofol and remifentanyl. In Liu's approach (Dual-Loop),³ remifentanyl infusion rate is implicitly embedded in the rule-based controller. In West's approach (iControl-RP),⁴ the system allows the user to choose a desired baseline level of remifentanyl infusion.

We propose an alternative approach where the opioid-hypnotic balance is explicitly determined by imposing an adjustable ratio between the infusion rates of propofol and remifentanyl, thus leaving the anesthesiologist complete control over it.

The objective of this study was to evaluate the performance of this approach in a prospective series of patients undergoing TIVA for surgery.

METHODS

The study was approved by the Ethics Committee of Brescia (NP-2861), authorized by the Italian Ministry of Health, and registered at clinicaltrials.gov (NCT04432974, principal investigator: Massimiliano Paltenghi, date of first registration: June 9, 2020).

We consecutively recruited adult patients (18 years or older) with written informed consent scheduled for elective plastic surgery at the Spedali Civili University Hospital in Brescia, Italy.

Control System Specification

The Automatic Control of Total Intravenous Anesthesia (ACTIVA) closed-loop anesthesia system is based on a proportional-integral-derivative (PID) control algorithm (Figure). Its architecture, implementation, and preliminary clinical experimental results have been previously published by the authors⁵⁻⁷ and are summarized in Supplemental Digital Content 1, Supplemental Material 1, <http://links.lww.com/AA/F87>.

The control algorithm is executed on a personal computer. It receives the value of the bispectral index (BIS), and based on that, calculates the infusion rates of propofol and remifentanyl that are sent to the syringe pumps. The anesthesiologist can supervise the system's operation through a graphical user interface (Supplemental Digital Content 2, Supplemental Figure 1, <http://links.lww.com/AA/F88>).

The opioid-hypnotic balance is constrained by imposing a ratio between the infusion rates of remifentanyl and propofol, expressed in $\mu\text{g/s}$ and mg/s , respectively. During anesthesia, the anesthesiologist can dynamically adjust the ratio value between 0.5 and 15⁵ to select the most appropriate opioid-hypnotic balance for the specific clinical situation. In this study, we imposed a fixed remifentanyl/propofol ratio value of

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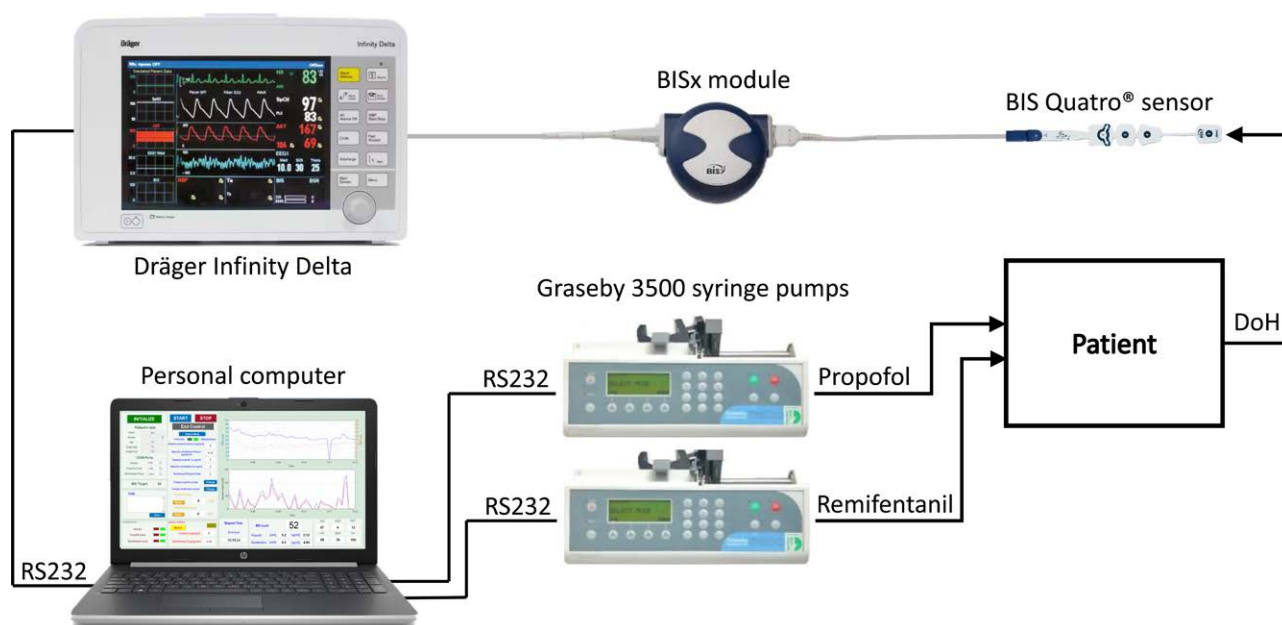


Figure. Schematic representation of the ACTIVA closed-loop anesthesia system. ACTIVA indicates Automatic Control of Total Intravenous Anesthesia; BIS, bispectral index scale; DoH, depth of hypnosis.

2 for the entire duration of surgery since the goal was to test the performance of the overall approach of the ACTIVA system and compare it with published studies.

This specific value was established after the methodology explained in Schiavo et al,⁶ in accordance with the infusion pattern proposed by Vuyk et al.⁸

Anesthesia Protocol

The ACTIVA system was started by setting a target BIS of 50. Then, it automatically administered the drugs to quickly reach the target BIS and to maintain it throughout the surgical procedure. Automatic control was suspended, thus stopping drugs infusions, after skin suture was completed.

Performance Evaluation

The performance of ACTIVA was evaluated for both anesthesia induction and maintenance phases. For the induction phase, we evaluated the induction time, the lowest DoH value, and the drug induction doses. For the maintenance phase, we evaluated the percentage of time with adequate anesthesia ($40 \leq \text{DoH} \leq 60$), the percentage of time of deep anesthesia ($\text{DoH} < 40$) and the drugs median infusion rates. We also evaluated the indexes based on the performance error (PE),² which is the percentage difference between the target DoH and the measured DoH. These indexes are as follows: the median performance error (MDPE), which is a measure of bias and describes whether the measured DoH values are systematically distributed either above (positive values) or below (negative values) the target DoH; the median absolute performance error (MDAPE), which reflects the inaccuracy

of the controller as quantitative measure of how much the measured DoH deviates from the target DoH; the wobble, which is an index of PE variability, and the Global Score (GS), which is calculated as $(\text{MDAPE} + \text{wobble}) / (40 \leq \text{DoH} \leq 60)$ and characterizes the overall performance. The closer these PE-based indexes are to zero, the better the performance.

Our results were compared with the data taken from 2 high-quality clinical trials assessing the Dual-Loop and iControl-RP systems,^{3,4} which served as reference standard. Data are presented as median (IQR).

RESULTS

One hundred and thirty-nine patients (41 males and 98 females) were enrolled in the study and included in the analysis.

Patients' characteristics were as follows: age, 57 (46–69) years; weight, 70 (59–82) kg; height, 165 (160–171) cm.

The ACTIVA system automatically performed both anesthesia induction and maintenance for all the patients and no severe adverse events occurred.

The performance indexes obtained by ACTIVA are presented in the Table, along with those of Dual-Loop and iControl-RP.

An overview of the time courses of BIS and infusion rates is shown in Supplemental Digital Content 3, Supplemental Figure 2, <http://links.lww.com/AA/F89>.

DISCUSSION

The results show that the performance of ACTIVA compares favorably with that of Dual-loop and

Table. Performance Indexes Regarding Anesthesia Induction and Maintenance Phases

Performance index	ACTIVA (n = 139)	Dual-Loop (n = 83)	iControl-RP (n = 75)
Induction phase			
Induction time ^a (min)	1.72 (1.32 to 2.70)	4.72 (3.37–6.07)	4.08 (3.27–5.18)
Lowest DoH ^b (BIS/WAV _{CNS})	42 (36–45)	NA	41 (35–47)
Propofol induction dose ^c (mg · kg ⁻¹)	1.90 (1.63–2.19)	1.10 (0.9–1.6)	1.59 (1.12–2.19)
Remifentanil induction dose ^c (μg · kg ⁻¹)	2.16 (1.73–2.61)	2.1 (1.5–2.7)	0.72 (0.51–0.97)
Maintenance phase			
Maintenance duration ^d (min)	105 (67–178)	117 (89–176)	108 (82–157)
40≤DoH≤60 ^e (% of maintenance duration)	79.4 (68.6–87.1)	85 (73–91)	88.2 (83.1–93.4)
DoH<40 ^f (% of maintenance duration)	16.2 (10.0–26.2)	12 (6–22)	7.6 (4.4–12.4)
MDPE ^g (% of target DoH)	-10 (-16 to -6)	-6 (-12 to -2.8)	-3.33 (-6.07 to -1.73)
MDAPE ^h (% of target DoH)	12 (10–16)	10.5 (9.0–14.0)	7.00 (5.59–10.31)
Wobble ⁱ (% of target DoH)	8 (6–10)	8 (7–10)	6.05 (4.82–7.62)
GS ^j (dimensionless)	26.3 (22.2–36.7)	23 (19–30)	14.6 (11.6–20.7)
Propofol median infusion ^m (mg · kg ⁻¹ · h ⁻¹)	6.2 (5.1–7.3)	4.5 (3.7–5.7)	5.8 (4.7–7.2)
Remifentanil median infusion ^m (μg · kg ⁻¹ · min ⁻¹)	0.16 (0.13–0.21)	0.20 (0.17–0.27)	0.15 (0.13–0.17)

Data are presented as median (IQR).

The data reported in the dual-loop and iControl-RP columns are taken from Liu et al³ and West et al,⁴ respectively.

Note that iControl-RP uses the WAV_{CNS} in place of the BIS to measure DoH.

Abbreviations: BIS, bispectral index scale; DoH, depth of hypnosis; NA, not available; WAV_{CNS}, wavelet-based anesthetic value for central nervous system monitoring.

^aElapsed time from the start of infusions until the BIS first drops below 60 and stays there for 30 s.

^bLowest DoH value in the 60 s after the induction time.

^cInduction dose administered during the induction time.

^dElapsed time between induction time and end of automatic control.

^e40≤DoH≤60, percentage of time with adequate anesthesia (the higher, the better).

^fDoH<40, percentage of time with deep anesthesia (the lower, the better).

^gMDPE, median performance error (the closer to zero, the better).

^hMDAPE, median absolute performance error (the lower, the better).

ⁱWobble (the lower, the better).

^jGS, global score (the lower, the better).

^mMedian infusion rate calculated over the maintenance duration.

iControl-RP systems. Moreover, the percentage of time with adequate anesthesia was in the range of 75%–94%, and the medians of GS and MDAPE were well below the thresholds for successful anesthesia of 50 and 20, respectively, reported in systematic reviews.^{9,10} The ACTIVA system performs reasonably well in maintaining adequate anesthesia with a stable plane of DoH from the induction until the end of surgery. Given these promising results, future studies should fully evaluate the ACTIVA system, particularly taking advantage of the possibility of the anesthesiologist dynamically changing the remifentanil/propofol ratio during surgery and tailoring it to the patient's needs.

It is worth noting that all patients enrolled in this study were scheduled for elective plastic surgery, were relatively young, and had similar demographic characteristics, which limits the generalizability of the results. Future studies should include a more diverse population to better understand the system's applicability across broader clinical settings. ■

DISCLOSURES

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