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ORIGINAL CLINICAL RESEARCH REPORT

Influence of Remifentanil on the Control Performance of the Bispectral Index Controlled Bayesian-Based Closed-Loop System for Propofol Administration

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BACKGROUND: This study investigated the clinical performance of a model-based, patient-individualized closed-loop (CL) control system for propofol administration using the bispectral index (BIS) as a controlled variable during the induction and maintenance of anesthesia with propofol and remifentanil and studied the influence of the targeted effect-site concentration of remifentanil (Ce_{REMI}) on its clinical performance.

METHODS: In 163 patients, propofol was administered using a CL system (BIS target [BIS_{TARGET}] between 40 and 50). Initial Ce_{REMI} targets between 2 and 7.5 ng/mL were selected as deemed clinically required. Performance parameters during induction were the time required to initially cross the target BIS, the time required to reach the maximal drug effect after induction ($T_{PEAK, BIS}$) and the corresponding BIS at this moment, and the time required to regain the target BIS at the end of induction. Performance during maintenance was defined as the percentage of case time with target BIS ± 10 from target and the amount of performance error (PE) between the observed and target BIS values and its derived median PE (MDPE) as a measure of control bias, median absolute PE (MDAPE) as a measure of control inaccuracy, divergence as a measure of the time-related trend of the measured BIS values relative to the target BIS values, and wobble as a measure of intrasubject variability in prediction error. The secondary end point was the hemodynamic stability of the patient during CL control.

RESULTS: The applied CL system induced and maintained anesthesia within clinically accepted ranges. The percentage of case time [mean (standard deviation [SD]) across all study participants] with BIS ± 10 from the target was 82% (14%). The mean (SD) population MDPE and MDAPE were −6.6% (5.5%) and 11.2% (5.5%), respectively. A negative divergence [−0.001 (0.004)] and acceptable wobble [9.7% (4.0%)] were found. The correlation between the system PE and Ce_{REMI} was low and only influenced by a Ce_{REMI} <2.8 ng/mL. Hemodynamic stability stayed within the clinically acceptable range.

CONCLUSIONS: The applied CL system for propofol administration has an acceptable performance in the Ce_{REMI} range of 2.8–7.5 ng/mL during the induction and maintenance of anesthesia. There was no evidence of a strong association between Ce_{REM} and the CL performance. This study also shows that when the Ce_{REMI} is <2.8 ng/mL, it might be more challenging to prevent arousal during propofol anesthesia. (Anesth Analg 2020;130:1661–9)

KEY POINTS

- **Question:** What is the influence of coadministered remifentanil on the clinical performance of the bispectral index (BIS) controlled Bayesian-based closed-loop (CL) system for propofol administration?
- **Findings:** The applied CL system has an acceptable clinical performance during the induction and maintenance of anesthesia, and there was no evidence of a strong association between the remifentanil effect-site concentration and the system performance when targeted between 2.8 and 7.5 ng/mL.
- **Meaning:** This study offers the next step in the clinical validation of BIS-guided CL systems for propofol administration.

A closed-loop (CL) system for drug administration enables continuous adjustments of drug infusion to achieve and maintain a target level of a measured drug effect (defined as the controlled variable) using a specific computer-based control algorithm.[1] The bispectral index (BIS; Medtronic, Dublin, Ireland), a processed electroencephalographic variable, has been used previously as the controlled

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variable to guide CL propofol administration. Two recent meta-analyses listed the available BIS-guided, automated systems and concluded that they provided better clinical performance and safety compared to manual control.[2–4] Although these meta-analyses of previous work showed a more stable control of BIS when using CL control than manual control, neither of these studies focused on the influence of the opioid level on the clinical performance of the various propofol CL systems during clinical anesthesia.[2–4] A disequilibrium in the balance between nociception and antinociception during anesthesia might result in more instability in the required anesthetic-hypnotic background due to arousal and might challenge the clinical performance of the hypnotic CL system.[5]

Sahinovic et al[6] used a previously validated model-based, patient-individualized CL control system for propofol administration using BIS as the controlled variable to target various BIS levels.[7,8] They found an accurate performance using various levels of remifentanil under controlled study conditions and when applying experimental noxious pain stimuli. However, this CL system for propofol administration might only become clinically and regulatory acceptable if it secures stable control during clinical anesthesia using various levels of antinociception control.[9]

As such, the aim of this study was to assess the overall clinical performance of this BIS-guided propofol CL system during the induction and maintenance of anesthesia with propofol and remifentanil and to study the influence of the targeted effect-site concentration of remifentanil (Ce_{REMI}) on its clinical performance. Clinical performance parameters during induction were the time required to reach the target BIS, the time required to reach the maximal drug effect ($T_{PEAK, BIS}$) after induction and the corresponding BIS at this moment, and the time required to regain the target BIS at the end of induction. Clinical performance during maintenance was defined as the percentage of time the system was able to maintain BIS in a desired target range and the amount of performance error (PE) between the observed and targeted BIS values and its derived median PE (MDPE) as a measure of control bias, median absolute PE (MDAPE) as a measure of control inaccuracy, divergence as a measure of the time-related trend of the measured BIS values relative to the target BIS values, and wobble as a measure of intrasubject variability in prediction error. The secondary end point was the hemodynamic stability of the patient during CL control.

METHODS

Study Population

This study was approved by the Institutional Ethics' Committee (University Hospital Ghent, Belgium, EC2008/250). The trial was registered before patient enrollment at ClinicalTrials.gov (NCT00764855, principal investigator: M.M.R.F.S., date of first registration: October 2, 2008). The study methodology was prospective, observational, and cohort based. We received the approval of the Ethics' Committee to approach and include a maximum of 200 patients. This number was set arbitrarily based on our previous experience of testing CL technology. No formal power analysis was performed; however, statistical precision was evaluated for accuracy post hoc by computing a 95% confidence interval for the Spearman correlation and assessing its width. American Society of Anesthesiologists (ASA) physical status I, II, and III patients, 18 to 65 years of age, scheduled for elective gynecological or head and neck surgery under general total intravenous (IV) anesthesia were assessed for eligibility for this trial. Patient recruitment throughout the study is shown according to the Consolidated Standards of Reporting Trials (CONSORT) group statement (Figure 1). Patients with an allergy or inability to tolerate general anesthetics or patients who had participated in a clinical trial within the past 30 days were excluded. After written informed consent, patients were prospectively included in this cohort study.

Clinical Procedure

All subjects fasted and refrained from smoking 6 hours before anesthesia. On the morning of surgery, patients

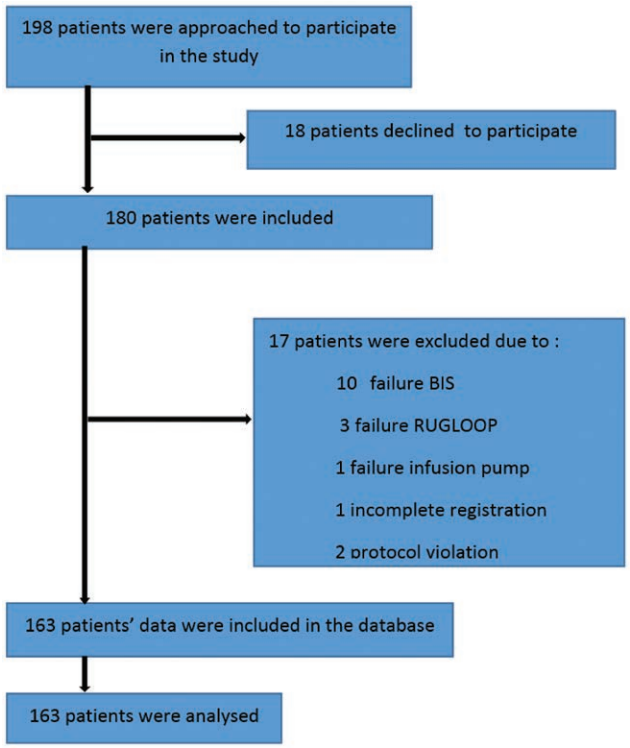

Figure 1. CONSORT flow chart. RUGLOOP is the software/hardware solution applied in this study. BIS indicates bispectral index; CONSORT, Consolidated Standards of Reporting Trials.

were allowed to take their routine medication. No premedication was given. On arrival in the operating theater, an IV cannula of 18 gauge was inserted and a crystalloid infusion was administered at a rate of 500 mL/h to deliver the required drugs and fluids during the study period. Standard monitoring was used throughout the procedure (AS3; GE Healthcare, Helsinki, Finland), including electrocardiogram (ECG), pulse oximetry, end-tidal oxygen and carbon dioxide concentrations, and BIS (BIS Vista monitor, BIS version 3.03). The BIS sampling frequency as a control variable for the CL algorithm was 3 seconds.

Blood pressure measurements were performed noninvasively at 1-minute intervals. RUGLOOP II software (Demed, Temse, Belgium) was used to record all numerical and waveform data and to steer the CL and target-controlled infusion (TCI) software.

Three minutes before the start of the propofol (Diprivan 1%; AstraZeneca, Brussels, Belgium) infusion, remifentanil (Ultiva; GlaxoSmithKline, Genval, Belgium) administration was started using an effect-compartment TCI system. At the discretion of the anesthesiologist, an initial Ce_{REMI} was selected between 2 and 7.5 ng/mL. Propofol was delivered using a propofol CL system[8] with a BIS target (BIS_{TARGET}) set between 40 and 50, as clinically required.

After loss of consciousness (LOC), rocuronium 0.6 mg/kg was given to facilitate laryngeal mask or endotracheal tube insertion. The lungs were ventilated mechanically with oxygen-enriched air (fractional inspired oxygen between 0.4 and 0.6) adjusted to keep the end-tidal carbon dioxide around 35–40 mm Hg. Anesthesia was initially maintained with the selected Ce_{REMI} and the Bayesian-based CL system administering propofol to target the desired BIS level. If signs of inaccurate anesthesia were detected and not covered by the propofol CL system, the anesthesiologist was allowed to adapt the Ce_{REMI}. In the case of anesthetic instability, the anesthesiologist was allowed to administer an escape bolus of propofol 30 mg by pushing the "bolus override function" on the CL computer screen. This bolus was taken into account when calculating the next online estimated propofol plasma and effect-site concentrations.

Approximately 1 hour before the end of the procedure, paracetamol 1 g was given. When the surgeon began skin closure, remifentanil was stopped and piritramide 0.05 mg/kg IV was given to provide postoperative pain relief. At the end of the procedure, the target of the CL system was reset at a target BIS of 100 to stop drug infusion and Ce_{REMI} was set at zero.

CL System

The details of the applied model-based, patient-individualized CL control system for propofol administration using BIS as the controlled variable have been published previously.[7,8] In brief, the model-based adaptive controller uses a patient-individualized pharmacodynamic sigmoidal E_{max} relationship between BIS and the propofol effect-site concentration (Ce_{PROP}). At each time point, the required effect-site concentration is calculated by the controller and is sent to a standard TCI algorithm steering a specific Ce_{PROP}. This system uses the pharmacokinetic-dynamic model by Schnider et al.[10,11] The measured BIS is used as a controlled variable. To enable CL at induction followed by individualization of the pharmacodynamic relationship between BIS and Ce_{PROP}, a Bayesian-based sigmoid E_{max} model estimator was used. This algorithm starts from a standard, population-based response model providing the prior distribution of parameter values. These values are adjusted to reflect the patient's own parameters over time, based on the observed response of the individual patient under varying conditions. This process makes use of specific modeling weights, called Bayesian variances, which determine how the patient-specific model can deviate from the population model. These Bayesian variances need to be optimized for control performance in a target population. This has been described previously.[7] For this study, the initial pharmacodynamic model parameters were the BIS value at no drug effect (E_0) = 100, the BIS value at the maximum effect (E_{MAX}) = 0, Gamma = 2.62, defined as the steepness of the Hill curve; and the Ce_{PROP} at 50% drug effect (EC_{50}) = 4.98 µg/mL. The delay in BIS was initially set at 10 seconds, and the BIS sample fade out time, defined as the time after which incoming BIS values were no longer taken into account, was set at 120 seconds. The BIS sample frequency for updating the model and CL control commands was 3 seconds.

To increase safety, additional algorithms are incorporated into the CL system. For example, the maximum allowed Ce_{PROP} is set at 15 µg/mL. When the incoming BIS values are corrupted by noise, making CL control unavailable, a BIS signal quality index (SQI) <50% automatically "opens" the loop, continuing the propofol infusion at the most recent Ce_{PROP}, and the anesthesiologist is notified. CL control remains active, and the system will "close" the loop when accurate BIS levels become available again. Additionally, the anesthesiologist can always take over control of drug infusion, if he/she does not trust the system.

Evaluation of the Controller Performance. The control performance was analyzed during induction and maintenance. We defined the start of induction as the beginning of propofol administration and the end of induction as when the patient lost consciousness. The maintenance period started from this time point and continued until termination of the propofol infusion at the end of surgery. Recovery was initiated by setting

the BIS_{TARGET} at 100. The control performance during induction was assessed using the following parameters: BIS at the moment of LOC (BIS_{LOC}), the time required to reach the target BIS ($T_{BIS\ TARGET}$), the time required to reach the maximal drug effect ($T_{PEAK,\ BIS}$), the observed BIS at $T_{PEAK,\ BIS}$ (BIS_{PEAK}), and the time required to regain the target BIS (T_{EQ}). Control performance during maintenance was evaluated by the percentage of case time BIS was 5 and 10 BIS units above or below the target.

Additionally, various controller PE criteria were computed from LOC until termination of propofol administration, as described by Varvel et al.[12] Individual PE, MDPE, MDAPE, divergence, and wobble were calculated as follows:

$PE_{ij} = (BIS_{ij} - BIS_{target})/BIS_{target} \times 100$

$MDPE_i = \text{Median}\ \{PE_{ij},\ j = 1,\ldots, N_i\}$

$MDAPE_i = \text{Median}\ \{|PE_{ij}|,\ j = 1,\ldots, N_i\}$

$Wobble_i = \text{Median}\ \{|PE_{ij} - MDPE_i|,\ j = 1,\ldots, N_i\}$

where N_i is the number of PEs obtained in the ith subject.

MDPE is a measure of bias for the ith individual. It indicates the direction of the PE rather than the size. MDAPE reflects the size of the inaccuracy of the control method in the ith subject. Divergence demonstrates the time-related trend of the measured BIS values relative to the target BIS values. It is defined as the slope of the linear regression equation of |PE| against time. Divergence was calculated between the moment of $T_{BIS\ TARGET}$ until the termination of propofol administration. Divergence was calculated separately for each individual. Wobble represents the intrasubject variability in PEs.

The other CL performance parameters we evaluated were as follows: (1) the percentage of case time BIS data were unavailable due to a low SQI (<50), defined as "time missing BIS"; (2) the percentage of case time CL control was unavailable due to no or corrupted BIS data; (3) the percentage of case time the CL was executed; and (4) the percentage of case time the Bayesian CL estimator was not able to update the model due to computer limitations or any other performance issues. (The computer always prioritized the primary CL control above the Bayesian estimator algorithm to ensure operational safety.) The BIS sample frequency for the evaluation of controller performance was 30 seconds.

Furthermore, we evaluated hemodynamic instability from the start of propofol administration until the end of propofol administration as the percentage of case time during which the heart rate was <50 or >90 beats/min, indicating bradycardia and tachycardia, respectively. We also evaluated hypotensive and hypertensive episodes as the percentage of case time patients showed a mean arterial blood pressure (MAP) <65 mm Hg[13] or a systolic blood pressure (SYS) >140 mm Hg.[14]

Statistics

A statistical analysis was performed using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean ± standard deviation (SD) or median (interquartile range) depending on the distribution of the specific dataset. Normality of the data was tested using a Shapiro–Wilk test. The correlation between the controller PE criteria (PE, MDPE, MDAPE, divergence, and wobble) and Ce_{REMI} was analyzed using the Spearman Rank test. To predict one of the PE criteria for any given mean Ce_{REMI}, a loess smooth curve with 95% confidence intervals was fitted through the different controller PE values for each individual versus the mean Ce_{REMI} for that individual. We calculated the mean Ce_{REMI} for each individual because Ce_{REMI} varied during the procedure. Locally weighted regression, or loess, is a procedure for estimating a regression surface using a multivariate smoothing procedure (more information at http://www.netlib.org/a/dloess). The significance level was set at $P < .05$.

RESULTS

The inclusion and exclusion criteria can be found in the CONSORT Figure 1. As shown, 163 patients were included in the analysis, consisting of 11 males and 152 females. Anesthesia care was provided to all patients by 1 consultant anesthesiologist (M.N.). The mean ± SD for age, height, and weight were 42 ± 13 years, 167 ± 7 cm, and 69 ± 13 kg, respectively. Sixty-four patients were scheduled for head and neck surgery (mostly thyroid surgery), 66 for a gynecological laparoscopy, 19 for gynecological laparotomy, and 14 for mamma surgery. The induction of anesthesia was successfully managed in all patients by the CL system without interference from the responsible anesthesiologist. BIS and the time at/to LOC, $T_{BIS\ TARGET}$, $T_{PEAK,\ BIS}$, BIS_{PEAK}, and T_{EQ} values are shown in Table 1.

The time courses of measured BIS, Ce_{PROP}, and Ce_{REMI} between the start and termination of propofol administration, defined as the entire duration of control, are plotted in Figure 2. Table 1 shows the mean population measured BIS, mean target BIS, and mean Ce_{PROP} and Ce_{REMI} calculated from the mean data during maintenance for each individual. As not all cases had similar case times, a graph showing the number of patients in the analysis at any time point is included (lower plots) to clarify the origin of increasing and missing ranges in the other plots in Figure 2.

The percentage of artifactual BIS leading to control unavailability and the overall active control time are shown in Table 1. The ability of BIS to obtain and maintain a specific target is shown as PE over time in Figure 2.

Table 1. Induction, Maintenance, and Controller Performance Error Criteria Analysis

	Mean ± SD or Median (Interquartile Range)
Induction	
BIS_{LOC}	67 ± 16
T_{LOC} (s)	110 ± 34
$T_{BIS\ TARGET}$ (s)	215 ± 79
BIS_{PEAK}	31 ± 7
$T_{PEAK,\ BIS}$ (s)	259 ± 85
T_{EQ} (s)	412 ± 245
Maintenance	
BIS[a]	41 ± 3
BIS target[b]	44 ± 3
% case time with BIS ± 10 from target	82 (75–88)
% case time with BIS ± 5 from target	60 (52–68)
Effect-site concentration propofol (μg/mL)	3.5 ± 0.8
Effect-site concentration remifentanil (ng/mL)	4.9 ± 1.4
HR (beats/min)	67 ± 9
% of case time HR between 50 and 90 beats/min	94 (84–98)
% of case time HR <50 beats/min	0 (0–2)
% of case time HR >90 beats/min	0 (0–3)
Systolic blood pressure (mm Hg)	110 ± 11
MAP (mm Hg)	81 ± 8
Diastolic blood pressure (mm Hg)	66 ± 7
% of case time with MAP <65 mm Hg	7 (0–17)
% of case time with SYS >140 mm Hg	0 (0–7)
% of case time with missing BIS data	1 (0–2)
% of case time with "control unavailable"	0 (0–2)
% of case time with "model old"	0 (0–0)
% of case time with "closed-loop control"	100 (100–100)
Total case time (s)	5066 ± 2482
BIS at end	44 ± 9
Propofol effect-site concentration at end	2.7 ± 1.0

Results are shown as mean ± standard deviation (SD) or median (interquartile range) depending on the distribution of the data.

Abbreviations: BIS, bispectral index; BIS_{LOC}, BIS at the moment of loss of consciousness; BIS_{PEAK}, the observed BIS at $T_{PEAK,\ BIS}$; HR, heart rate; MAP, mean arterial pressure; SYS, systolic blood pressure; $T_{BIS\ TARGET}$, time required to reach the target BIS; T_{EQ}, the time required to regain the target BIS following BIS_{PEAK}; T_{LOC}, time from the start of propofol administration until loss of consciousness; $T_{PEAK,\ BIS}$, the time required to reach the maximal drug effect after induction.

[a]BIS is calculated from the mean BIS values during maintenance for every individual.

[b]BIS is calculated from the mean BIS target values during maintenance for every individual.

The population data for the percentage of case time with BIS within a 5% and 10% margin are shown in Table 1. The overall population mean and SDs for PE, MDPE, MDAPE, divergence, and wobble are listed in Table 2.

The influence of the mean Ce_{REMI} for each individual on the controller performance for that individual was analyzed using a Spearman Rank correlation (Table 3). Although a significant difference from zero was observed for all the controller PE criteria, all the Spearman Rank correlation coefficients indicated an overall weak correlation between mean individual Ce_{REMI} and PE, MDPE, MDAPE, divergence, and wobble as each of the intervals in Table 3 excludes the possibility (with 95% confidence) of correlations that are >0.4 in absolute value.

Table 2 also shows the 95% confidence intervals for the Spearman correlation coefficients determined by bootstrap analysis. The confidence intervals are such that none of the intervals include zero and their width is acceptable, indicating that our sample size was adequate and the precision of the reported correlation coefficients was sufficient to justify our conclusion that they are (at the 5% level of significance) significantly different from zero.

To illustrate a more detailed trend in controller PE with various mean Ce_{REMI} values, loess smooth curves with 95% confidence were used as shown in Figure 3. For all indicators, performance was stable among different Ce_{REMI} values and a decrease in performance was only observed at a target Ce_{REMI} <2.8 ng/mL (visual inspection of the loess smooth curve). This might indicate that there is some evidence that the CL controller might have reduced performance among individuals for whom Ce_{REMI} is small; however, one has to be careful interpreting these data due to the small number of observations.

Figure 2 also shows the time course of the heart rate and blood pressure during the induction and maintenance of anesthesia. The heart rate was found to be between 50 and 90 beats/min for approximately 94% of the case time (median result). Some very short episodes of bradycardia (<50 beats/min) and tachycardia (>90 beats/min) were observed as shown in Table 2. As shown in Figure 2, blood pressure dropped after induction and returned to higher values during surgical stimulation, as clinically expected. The overall systolic, diastolic, and mean blood pressure was within clinical ranges. Table 1 also shows the percentage of case time with elevated systolic blood pressure and hypotension. Oxygen saturation and end-tidal CO_2 data were within clinical ranges as expected during mechanical ventilation (data not shown).

DISCUSSION

This study shows that the applied model-based, patient-individualized CL control system for propofol administration using BIS as the controlled variable[7,8] has an acceptable clinical performance during anesthesia using a wide range of Ce_{REMI}. Except at very low concentrations of Ce_{REMI}, no clinically relevant influence of Ce_{REMI} was found on the CL controller performance.

Although the advantages of CL control for anesthetic drug administration have been widely advocated[3,15] and evidence of its benefit has been shown under experimental and well-controlled clinical conditions,[2–4] a rigid validation path is required, including a clinical study during routine care, before regulatory approval can even be considered.[9] The CL system in this study has been previously tested during clinical anesthesia using a fixed and rather high dose of remifentanil[16] during deep sedation with only a small dose of opioids[8] and under controlled study

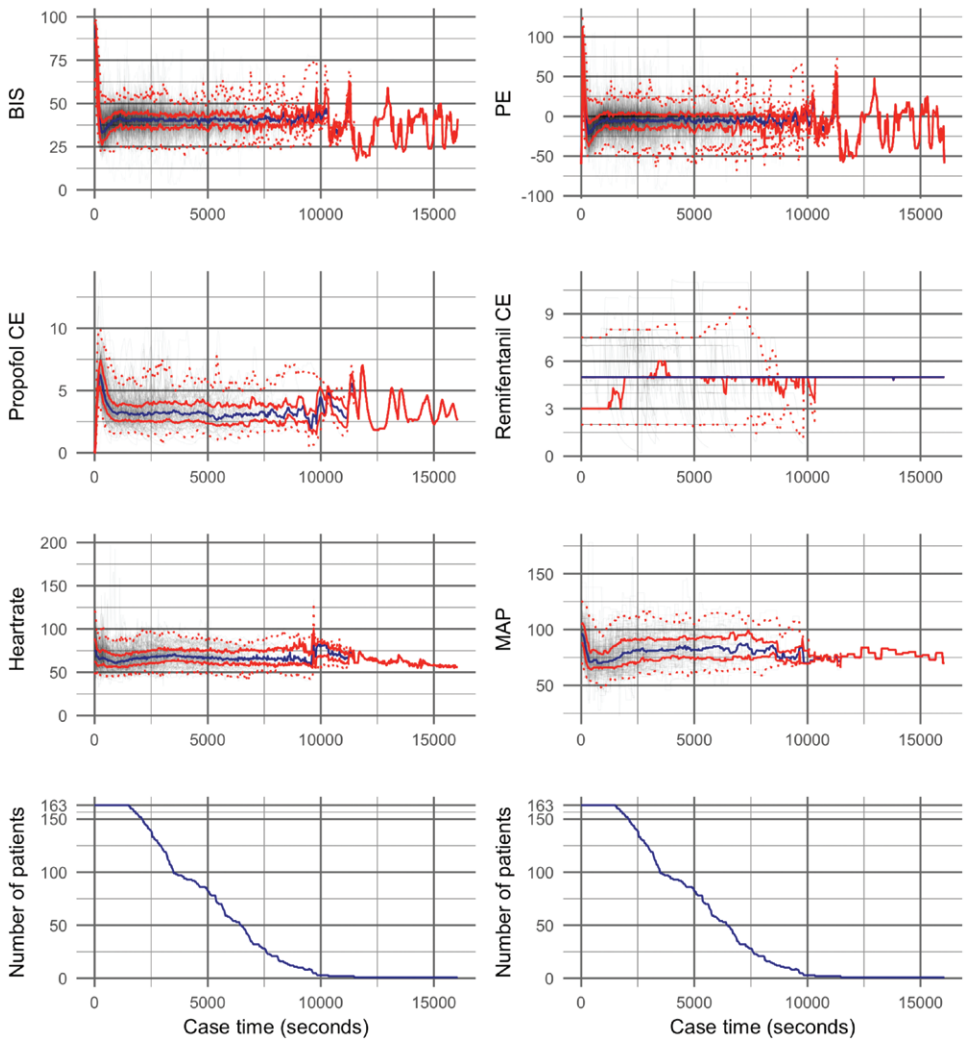

Figure 2. Individual, unfiltered, time-based data (gray lines) for bispectral index (BIS), performance error (PE), propofol effect-site concentration (Propofol CE), remifentanil effect-site concentration (Remifentanil CE), heart rate, mean arterial blood pressure (MAP), and the number of patients in the analysis at a specific time point. The blue line represents the median, the red line represents the interquartile range, and the red dotted line represents the 95% probability range versus time.

conditions applying experimental noxious pain stimuli and various Ce_{REMI}[6] and revealed an acceptable clinical performance.

In this clinical cohort study, CL control was used for both the induction and maintenance of propofol-based anesthesia in all cases. BIS was artifactual in around 1% of the case time (median), resulting in a control unavailability of around 0%–2% of the case time (interquartile range). Although these values demonstrate the robustness of the BIS sensor and monitor as a controlled variable, these results should be interpreted carefully, as other types of surgery might result in the generation of more noise and corrupt the quality of the EEG. The Bayesian CL estimator was able to update the model in nearly the entire case, shown by the 0% of "model old." As such, CL control was always available during control. The reader should be aware that the system has an automatic fall-back option toward effect-site targeted propofol administration using the last available Ce_{PROP} as the target concentration when no controlled variable BIS data are available. The control stays "active" and an alarm will sound.

The induction characteristics such as BIS_{LOC}, $T_{BIS\ TARGET}$, $T_{PEAK,\ BIS}$, BIS_{PEAK}, and T_{EQ} are comparable to our previous work[8] and that of others,[17–19] except for BIS_{PEAK}, which was lower than previously reported. This might be due to the somewhat lower target BIS selected by the clinicians in this study.

Control performance during maintenance was evaluated by the percentage of case time BIS was 5 and 10 BIS units above or below the target and was found to be clinically acceptable and similar[20,21] or somewhat higher[22,23] than others. The applied Ce_{PROP} and Ce_{REMI} during maintenance in this study were within the clinical and pharmacological accepted range[24] and even lower than the concentrations used in other CL systems for propofol and remifentanil administration.[23] It is important to note that the higher the applied drug concentrations of remifentanil during anesthesia, the lower the "workload" of the controller to maintain a stable level of the hypnotic component of anesthesia.[5]

The controller showed an acceptable performance and no strong association between Ce_{REMI} and the controller performance was found as further evidenced

Table 2. Controller Performance Error Criteria

Varvel Performance	Mean ± SD
PE	−6.705 ± 5.218
MDAPE (%)	11.243 ± 5.461
Divergence (% min)	−0.001 ± 0.004
MDPE (%)	−6.634 ± 5.492
Wobble (%)	9.746 ± 3.988

Abbreviations: MDAPE, median absolute prediction error; MDPE, median prediction error; PE, prediction error; SD, standard deviation.

Table 3. Correlation Between Controller Performance Error Criteria and Mean Ce_{REMI}

	Spearman ρ	*P* Value	95% CI
PE	0.237	.002	0.083 to 0.39
MDAPE	−0.234	.003	−0.383 to −0.087
Divergence	0.168	.033	0.008 to 0.324
MDPE	0.208	.008	0.046 to 0.368
Wobble	−0.187	.017	−0.335 to −0.035

Abbreviations: CI, confidence interval; Ce_{REMI}, effect-site concentration of remifentanil; MDAPE, median absolute prediction error; MDPE, median prediction error; PE, prediction error.

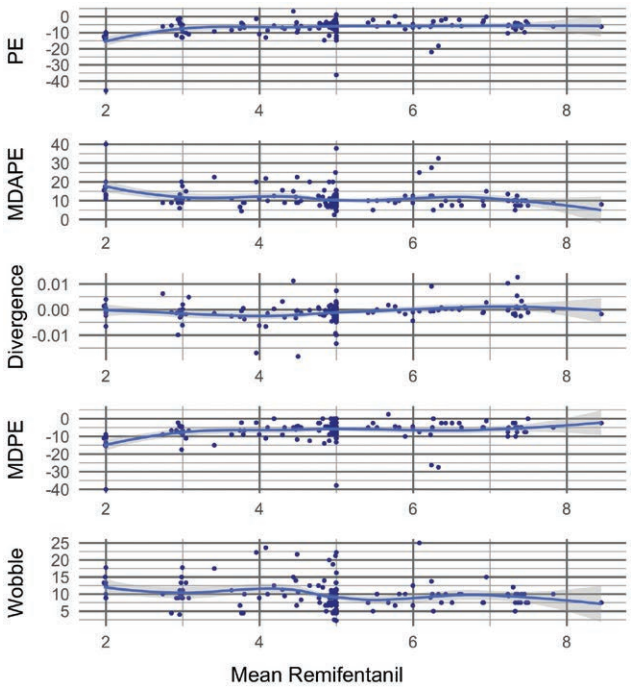

Figure 3. Loess plots for controller performance error (PE) criteria versus effect-site concentration of remifentanil (Ce_{REMI}) with a 95% confidence interval. MDAPE indicates median absolute performance error; MDPE, median performance error.

by the data shown in Figure 3. The overall prediction error from the target BIS was approximately −7 BIS values, except below a Ce_{REMI} of 2.8 ng/mL, where the loess curve gradually deviates toward a maximum of −16 BIS units at a Ce_{REMI} of 2 ng/mL (Figure 3). This resulted in an overall mean MDPE and MDAPE of approximately −7% and 11%, respectively, with a similar deviation in the loess curve toward an MDPE of −15% and an MDAPE of 18% at the lowest Ce_{REMI}, as shown in Figure 3. These results are comparable to the performance data found during deep sedation using the same controller, of approximately 8% and 12% for MDPE and MDAPE, respectively.[8] Therefore, our values are comparable to others. In their meta-analysis, Pasin et al[4] found an MDAPE range between 7% and 12% when screening the available publications on BIS-guided propofol CL controlled administration. This MDAPE range favors the use of CL control because the manually controlled groups in these studies showed an MDAPE range between 12% and 24%.[4] Our study also shows that at a Ce_{REMI} <2.8 ng/mL, it might be more challenging for our controller to maintain the required anesthetic-hypnotic background to prevent arousal during propofol anesthesia. However, as this statement is based on a small amount of observations, this information should be viewed as hypothesis-generating, rather than as providing definitive evidence.

Anesthesia consists of 2 components, the hypnotic component and the analgesic component, the latter one being the result of the balance between nociception and antinociception,[25] and both components interact.[26] It is well understood that the opioid concentration influences the stability of the hypnotic level of anesthesia over time due to noxious stimuli causing arousal. As a result, the BIS variability caused by the nociceptive input at the cerebral level might be inversely related to the amount of opioids administered.[27] This BIS variability might challenge the clinical performance of the controller if it is too difficult to handle. Wobble quantifies the oscillation of the controller behavior, and divergence indicates the tendency of the controller to converge on (when negative) or diverge from (when positive) the target over time. When studying the influence of Ce_{REMI} on the controller stability, divergence and wobble are important performance measures. In this study, the overall divergence is negative, although very close to zero, and showed only a weak correlation with the target Ce_{REMI}. The loess regression analysis showed beneficial divergence values throughout the entire Ce_{REMI} range. Additionally, wobble was weakly correlated to Ce_{REMI} and showed comparable results to previous work. The results for both divergence and wobble demonstrate that the applied CL controller has an acceptable clinical performance in the applied Ce_{REMI} range.

As clinically expected, heart rate and blood pressure decreased after induction and stabilized shortly afterward. This resulted in clinically acceptable cardiovascular stability, as shown in Table 2 and Figure 2.

The findings of this study are limited to the studied population of mostly ASA I and II physical status patients during head and neck and gynecological surgery; therefore, one should avoid extrapolation of our results to other populations and types of surgery.

Additionally, because this is an observational study where Ce_{REMI} was not protocolized, it is possible that the relationship between Ce_{REMI} and CL performance was confounded by other patient factors affecting both propofol pharmacokinetics and pharmacodynamics as well as the clinician's choice of Ce_{REMI}.

In conclusion, the BIS-controlled, Bayesian-based CL system for propofol administration has a clinically acceptable performance during the induction and maintenance of anesthesia in the Ce_{REMI} range of 2.8–7.5 ng/mL. There was no evidence of a strong association between Ce_{REM} and the CL performance. This study also shows that at Ce_{REMI} levels <2.8 ng/mL, it might be more challenging to prevent arousal during propofol anesthesia.

DISCLOSURES

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Contribution: This author helped conceive and design the study; acquire, analyze, and interpret the data; and draft the manuscript.
Conflicts of Interest: None.
Name: Jan-Willem H. L. Boldingh, MD.
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Name: Tom De Smet, PhD.
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Name: Michel M. R. F. Struys, MD, PhD, FRCA.
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