CME

Closed-Loop Coadministration of Propofol and Remifentanil Guided by Bispectral Index: A Randomized Multicenter Study

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BACKGROUND: We have developed a proportional-integral-derivative controller allowing the closed-loop coadministration of propofol and remifentanil, guided by a Bispectral Index (BIS) monitor, during induction and maintenance of general anesthesia. The controller was compared with manual target-controlled infusion.  

METHODS: In a multicenter study, 196 surgical patients were randomly assigned to dual closed-loop or manual administration of propofol and remifentanil. Comparison between groups was evaluated by calculating a global score that characterized the overall performance of the controller including the percentage of adequate anesthesia, defined as BIS between 40 and 60, the median absolute performance error, and wobble. Secondary outcomes included occurrence of burst suppression ratio, time to tracheal extubation, and drug consumption.  

RESULTS: Eighty-three patients assigned to dual-loop control and 84 patients assigned to manual control completed the study. The global score and the percentage of time with BIS between 40 and 60 were better in the dual-loop group (26 ± 11 vs 43 ± 40, P < 0.0001; 82% ± 12% vs 71% ± 19%, P < 0.0001). Overshoot (BIS < 40), undershoot (BIS > 60), and burst suppression ratio were all significantly less common in the dual-loop group. Modifications to the propofol and remifentanil infusions were more frequent, and adjustments smaller in the dual-loop group. Remifentanil consumption was greater (0.22 ± 0.07 vs 0.16 ± 0.07 μg·kg⁻¹·min⁻¹; P < 0.0001) and the speed to tracheal extubation was shorter (10 ± 4 vs 11 ± 5 minutes; P = 0.02) in the dual-loop group.  

CONCLUSION: The controller allows the automated delivery of propofol and remifentanil and maintains BIS values in predetermined boundaries during general anesthesia better than manual administration. (Anesth Analg 2011;112:546–57)
with BIS values within predetermined boundaries (i.e., the interval 40–60) and limit BIS oscillation as compared with manual administration.

**METHODS**

**Study Population**

With the approval of the Ethics Committee, the French Regulatory Office (Afsaps), and written informed consent, 196 patients scheduled for elective surgery requiring general anesthesia or combined regional/general anesthesia expected to last >30 minutes and requiring tracheal intubation were enrolled at 4 different hospitals: Hôpital Foch (Suresnes), Centre Hospitalier Victor Dupouy (Argenteuil), Centre Hospitalo-Universitaire de Besançon and of Angers. All investigators were clinically experienced in the use of target-controlled infusion (TCI) of propofol and remifentanil and in BIS monitoring, and all had received 2 days’ training on the closed-loop controller in Hôpital Foch. Patients were aged 18 to 90 years with ASA physical status I to IV. Exclusion criteria included psychiatric illness, supraspinal neurological disorders, cranial neurosurgical procedures, and patients equipped with a pacemaker.

**Procedures**

Patients were randomly assigned to dual closed-loop (dual-loop group) or manual (manual group) TCI of propofol and remifentanil. Treatments were segregated into blocks of 10 at each participating center, and randomization was determined using a random number generator. Assignments were kept in sequentially numbered opaque envelopes until just before surgery.

On arrival in the operating room, a dedicated IV cannula was placed, and routine monitoring commenced including temperature and monitoring of neuromuscular function at the adductor pollicis. The BIS electrode (Zipprep; Bispectral Index, Covidien, Mansfield, MA) was positioned on the patient’s forehead and connected to either an A-2000 XP (version 3.11) BIS monitor (Covidien) or a BIS module (Datex-Ohmeda S/5™, Helsinki, Finland).

All patients received total IV anesthesia in TCI mode using the population pharmacokinetic sets of Schnider et al.¹³ and Minto et al.¹⁴ for propofol and remifentanil, respectively. Infusion Toolbox 95⁰ version 4.11 software¹⁵ implemented in a personal computer served as a platform: (1) calculation of effect-site concentrations of propofol and remifentanil; (2) display of these concentrations in real time on the screen of the personal computer; (3) user interface to enter the patient’s demographic data (sex, age, weight, and height) and to modify these concentrations; (4) steering of the infusion pumps, one for propofol and the other for remifentanil (Alaris Medical, Hampshire, UK); and (5) collection of the data every 5 seconds (BIS, calculated site-effect drug concentrations, hemodynamic data when an AS/5 Datex-Ohmeda S/5™ monitor was used).

In both groups, the induction phase was defined as the time from the start of propofol and remifentanil administration to BIS <60 for 30 seconds and the maintenance phase from this point to the end of propofol and remifentanil administration.

In the manual group, the investigator chose the initial propofol and remifentanil effect-site target concentrations for induction according to his/her clinical judgment. Therefore, the investigator modified the effect-site target concentrations of both drugs without minimum or maximum concentration limits to maintain BIS at approximately 50 within a range of 40 to 60 to the extent possible. Only manual ventilation via a facemask was performed during the induction phase to avoid noxious stimuli (such as laryngoscopy or tracheal intubation). Throughout the procedure, signs of inadequate analgesia (tachycardia, hypertension, sweating, flushing, movement, or swallowing) or hypnosis (BIS value outside of the range 40 to 60) were treated by increasing remifentanil or propofol at the discretion of the attending physician.

In the dual-loop group, the investigator chose the initial propofol effect-site target concentration according to his/her clinical judgment and the controller fixed the first remifentanil concentration according to the following rules. If the initial propofol target was <2.5 µg·mL⁻¹, then the initial remifentanil target was 4 ng·mL⁻¹, if the initial propofol target was between 2.5 and 2.9 µg·mL⁻¹, then the initial remifentanil target was 5 ng·mL⁻¹, if the initial propofol concentration was >3 µg·mL⁻¹, then the initial remifentanil target was 6 ng·mL⁻¹. Thereafter, modifications of propofol and remifentanil effect-site target concentrations were decided by the controller with lower and upper limits for propofol (1.3 and 5 µg·mL⁻¹) and for remifentanil (3 and 12 ng·mL⁻¹). As in the manual group, only manual ventilation via a facemask was permitted during the induction phase. Throughout the procedure, the investigator could adjust the targets if necessary or switch between closed-loop and manual control. Detailed description of the controller is provided in Figure 1, the Appendix, and in Table 1.

Other than administration of the study drugs, patient management was based on current standards of care. No specific recommendations were given for the treatment of hemodynamic abnormalities and for the use of a neuromuscular blocking drug. Nitrous oxide was not used. Morphine was given at the discretion of the physician 45 minutes before the presumed end of surgery.

In both groups, propofol and remifentanil were stopped simultaneously upon completion of surgery, and if necessary, a neuromuscular blockade reversing drug was given. Tracheal extubation was performed when all of the following were present: patient responsive and cooperative, SpO₂ >95% with an oxygen inspiratory fraction <50%, T4/T1 ratio >90%, no hemodynamic instability (continuous infusion of vasoactive drugs), and temperature >36.0°C.

The primary outcome was the global score (GS),⁵ which characterized the overall performance of the controller including the percentage of adequate anesthesia, defined as BIS between 40 and 60 and the oscillation of the BIS determined by the median absolute performance error (MDAPE) and the wobble.¹⁶ The controller performances were calculated according to following equations.

- The performance error, or PE, calculated as the difference between actual and desired values (set point):

\[ PE_{ij} = \left( \frac{BIS_{\text{measuredij}} - BIS_{\text{set point}}}{BIS_{\text{set point}}} \right) \times 100 \]

- The bias or median performance error (MDPE):

\[ MDPE_i = \text{median} \left[ PE_{ij}, j = 1, \ldots, N_i \right] \]
increased.

concentration more than 3 times, then the propofol concentration is

ately amplifies the correction of the drugs when a measured BIS

thus remifentanil modifications are made more frequently. The
time interval is shorter for remifentanil

concentrations are changed. The minimal interval between 2 con-

remifentanil is changed; if the BIS error is higher, the 2 drug

mines which drug will be modified: if the BIS error is small, only the

propofol and/or remifentanil concentration. The error size deter-

(EMG) activity, and the percentage of burst suppression ratio (SR). If

Index (BIS) monitor if the signal quality index (SQI) is

anesthetics. The controller uses the parameters from the Bispectral

Figure 1. Main algorithm. The controller has a cascade structure

including a dual proportional-integral-derivative (PID) algorithm and a
target-controlled infusion (TCI) system for the administration of IV

Table 1. Proportional Gain of the Controller

<table>
<thead>
<tr>
<th>BIS error</th>
<th>( K_{propofol} )</th>
<th>( K_{remifentanil} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>-9</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>-8</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>-7</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>-6</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>-5</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>-4</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>-3</td>
<td>( \infty )</td>
<td>65</td>
</tr>
<tr>
<td>-2</td>
<td>( \infty )</td>
<td>65</td>
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<tr>
<td>-1</td>
<td>( \infty )</td>
<td>( \infty )</td>
</tr>
<tr>
<td>0</td>
<td>( \infty )</td>
<td>( \infty )</td>
</tr>
<tr>
<td>1</td>
<td>( \infty )</td>
<td>( \infty )</td>
</tr>
<tr>
<td>2</td>
<td>( \infty )</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>( \infty )</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>10 or feedforward</td>
<td>50</td>
<td>40</td>
</tr>
</tbody>
</table>

Bispectral index (BIS) is the difference between the set point of 50 and the
current BIS value; \( K_{propofol} \) and \( K_{remifentanil} \) are the gain constants for propofol and remifentanil. These values were determined empirically using the simu-
lator included in the Infusion Toolbox 95 software.

- The inaccuracy or MDAPE:

\[
MDAPE_i = \text{median}[|PE_i|, j = 1, \ldots, N_i]
\]

- The wobble, which measures the intraindividual vari-

ability in PE:

\[
\text{Wobble}_i = \{|PE_i - MDPE_i|, j = 1, \ldots, N_i\}
\]

where \( i \) = subject number, \( j \) = \( j \) th (one) measurement of observation period, \( n \) = total number of measurements during the observation period.

The GS was calculated according to the following equation:

\[
\text{GS} = (\text{MDAPE} + \text{wobble})/\% \text{ of time BIS value}
\]

Excellent performance is characterized by a low MDAPE

and wobble and high percentage of BIS value in the range 40 and 60, thus a low GS.

Secondary outcomes included the percentage of ade-
quate anesthesia (defined as BIS between 40 and 60),
overshoot (BIS < 40) and undershoot (BIS > 60) periods,
occurrence of suppression ratio (SR) defined as SR > 10%

lasts at least a minute, and parameters of Varvel et al.16

(PE, MDPE, MDAPE, and wobble). Secondary outcomes
also included the following clinical data: drug consumption,
number of somatic events (i.e., movements, grimacing),
time to tracheal exubation (i.e., time from discontinuation
of propofol and remifentanil infusions until extubation), and
recall of intraoperative events as determined by a standard-
ized interview performed in the postanesthesia care unit
and on the second or third postoperative day.17

This study is registered with ClinicalTrials.gov, number
NCT00392158.

Statistical Analyses

In a previous study, the GS was 50 ± 62 (mean ± SD) using
manual propofol and remifentanil infusions and 21 ± 8
using closed-loop control of propofol and manual remifen-
tanil infusion; therefore, we expected an improvement of

>50% using the closed-loop system. We thus estimated that
144 patients (72 per group) would provide a 95% power for
a 2-sided \( \alpha \) error of 0.01. We planned to recruit 200 patients
under the assumption that some would be excluded for
various reasons.

Categorical variables, expressed as numbers and fre-

quencies, were compared by means of \( \chi^2 \) test or Fisher

exact test as appropriate. Continuous variables were de-
scribed as mean ± SD and median and interquartile range
and compared using the Mann-Whitney \( U \) test. Compari-
son of serial measurements was performed with repeated-
measures analysis of variance (with Bonferroni correction),
and post hoc analyses were performed with nonparametric
tests. Time from discontinuation of propofol and remifen-
tanil infusions until tracheal extubation was compared
using a Kaplan-Meier survival analysis followed by log-
rank test. Probability values < 0.05 were considered statis-
tically significant. Data analysis was performed using
SPSS® version 11.0 (SPSS, Inc., Chicago, IL).
RESULTS

Of the 200 patients who were approached, 196 were enrolled in the study, and 98 were randomized to each group. However, 15 patients in the dual-loop group and 14 patients in the manual group were excluded from analysis because of neurological disorders, BIS artifact, recording system failure, and other reasons (Fig. 2). There were thus 83 patients in the dual-loop group and 84 in the manual group available for analysis.

The groups were well balanced with respect to demographic, morphometric, and treatment characteristics. More than one-third of the study population received preoperative cardiovascular treatments and/or had a major surgical procedure (Table 2). Study participants had cardiac bypass, thoracic, vascular, urologic, orthopedic, gynecologic, or otolaryngologic surgery.

This study was conducted at 4 different sites, involving 17 anesthesiologists and 22 nurse anesthetists. No significant site differences or group-by-site interaction were found for any end points. Results were therefore pooled from all sites for analysis.

The closed-loop system maintained anesthesia for 312 hours. During this time, 3843 propofol and 4981 remifentanil target modifications were made automatically. The loop was opened in 2 cases; both were manual remifentanil modifications related to an episode of hypertension during laparoscopic procedures. Data for these patients were analyzed in the dual-loop group.

BIS values and calculated effect-site concentrations of propofol and remifentanil from induction to discontinuation of infusion are shown for dual-loop and manual groups in Figure 3.

Induction phase duration was significantly shorter in the dual-loop group than in the manual group (289 ± 110 vs 345 ± 166 seconds, \( P = 0.01 \)). The initial effect-site concentrations and the amount of propofol were similar between the 2 groups whereas these values were larger for remifentanil in the dual-loop group (Table 3). There were more propofol and remifentanil modifications in the dual-loop group than in the manual group (Table 3). Overshoot, undershoot, and occurrence of SR were all less frequent in the dual-loop group during induction (Table 3).

During maintenance, the mean GS was 26 ± 11 in the dual-loop group versus 43 ± 40 in the manual group (\( P = 0.0001 \), Table 4, Fig. 4). The amount of time that BIS was maintained between 40 and 60 was significantly longer in the dual-loop group compared with the manual group (Table 4 and Fig. 5). MDAPE was significantly lower in the dual-loop group whereas wobble was similar between groups (Table 4). Overshoot, undershoot, and occurrence of SR were all less frequent in the dual-loop group.

### Table 2. Characteristics of Patients at Entry

<table>
<thead>
<tr>
<th></th>
<th>Manual group (n = 84)</th>
<th>Dual-loop group (n = 83)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61 ± 16, 59 (49–74)</td>
<td>57 ± 15, 59 (49–68)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male gender</td>
<td>45 (54)</td>
<td>54 (64)</td>
<td>0.18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 7, 170 (164–173)</td>
<td>169 ± 9, 168 (162–175)</td>
<td>0.58</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>073 ± 15, 71 (65–80)</td>
<td>071 ± 14, 70 (59–80)</td>
<td>0.38</td>
</tr>
<tr>
<td>ASA physical status III/IV</td>
<td>14 (17)</td>
<td>15 (18)</td>
<td>0.60</td>
</tr>
<tr>
<td>Preoperative cardiovascular treatment</td>
<td>32 (38)</td>
<td>39 (46)</td>
<td>0.31</td>
</tr>
<tr>
<td>Major surgery</td>
<td>32 (38)</td>
<td>30 (35)</td>
<td>0.67</td>
</tr>
<tr>
<td>Combined general/regional anesthesia</td>
<td>15 (18)</td>
<td>10 (12)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are mean ± SD, median (interquartile range); and number (%).

Preoperative cardiovascular treatment = beta blocker, calcium channel blocker, angiotensin converting enzyme inhibitor or diuretics.
Table 3. Comparison of Anesthetic Procedures During the Induction Phase

<table>
<thead>
<tr>
<th></th>
<th>Manual group (n = 84)</th>
<th>Dual-loop group (n = 83)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9 (11)</td>
<td>6 (7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>67 (80)</td>
<td>61 (73)</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>8 (9)</td>
<td>16 (19)</td>
<td></td>
</tr>
<tr>
<td>Duration (s)</td>
<td>345 ± 166, 322 (228–436)</td>
<td>289 ± 122, 283 (202–364)</td>
<td>0.01</td>
</tr>
<tr>
<td>Propofol dose (mg · kg⁻¹)</td>
<td>1.3 ± 0.7, 1.1 (0.9–1.7)</td>
<td>1.3 ± 0.6, 1.1 (0.9–1.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Initial effect-site target concentration of propofol (µg · mL⁻¹)</td>
<td>3.1 ± 1.2, 2.5 (2.5–3.0)</td>
<td>3.1 ± 0.5, 3.0 (2.8–3.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Maximal effect-site target concentration of propofol (µg · mL⁻¹)</td>
<td>4.1 ± 1.6, 4.0 (3.0–5.0)</td>
<td>4.0 ± 0.9, 4.0 (3.6–4.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>No. of propofol target modifications</td>
<td>2.5 ± 2.6, 2.0 (0.3–4.0)</td>
<td>4.0 ± 3.0, 4.0 (2.0–5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remifentanil dose (µg · kg⁻¹)</td>
<td>1.7 ± 0.8, 1.4 (1.1–1.9)</td>
<td>2.3 ± 1.2, 2.1 (1.5–2.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Initial effect-site target concentration of remifentanil (ng · mL⁻¹)</td>
<td>4.0 ± 1.8, 4.0 (2.5–5.5)</td>
<td>5.4 ± 1.2, 6.0 (5.5–6.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximal effect-site target concentration of remifentanil (ng · mL⁻¹)</td>
<td>5.3 ± 1.9, 5.0 (4.0–6.5)</td>
<td>7.5 ± 2.6, 7.0 (5.6–9.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of remifentanil target modifications</td>
<td>3.3 ± 2.7, 3.0 (1.0–5.0)</td>
<td>4.2 ± 3.2, 3.0 (2.0–6.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>NMBD</td>
<td>76 (90)</td>
<td>76 (90)</td>
<td>0.99</td>
</tr>
<tr>
<td>Treatment of hypotension or hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine bolus</td>
<td>36 (43)</td>
<td>33 (43)</td>
<td>0.66</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.99</td>
</tr>
<tr>
<td>BIS values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overshoot BIS &lt; 40 (s)</td>
<td>34 ± 48, 5 (0–60)</td>
<td>20 ± 29, 5 (0–30)</td>
<td>0.16</td>
</tr>
<tr>
<td>Undershoot BIS &gt; 70 (s)</td>
<td>8 ± 21, 0 (0–0)</td>
<td>2 ± 7, 0 (0–0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Occurrence of SR</td>
<td>16 (19)</td>
<td>7 (8)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are mean ± SD, median (interquartile range); and number (%). Duration = duration of induction defined as the time elapsed from the start of propofol administration to the moment when the BIS value decreased to and remained < 60 for 30 s; NMBD = use of neuromuscular blocking drug; overshoot BIS < 40 = duration of Bispectral Index (BIS) < 40 in a period of 3 min after the BIS value decreased and remained < 60; undershoot BIS > 70 = duration of BIS > 70 in a period of 3 min after the BIS value decreased and remained < 60; SR = burst suppression ratio.
than in the manual group, and the adjustments were smaller and remifentanil modifications were made in the dual-loop group (Table 4). More propofol mean calculated effect-site concentration of propofol were frequent in the dual-loop group (Table 4). The dose and the mean calculated effect-site concentration of propofol were similar in both groups whereas both values were larger for remifentanil in the dual-loop group (Table 4). More propofol and remifentanil modifications were made in the dual-loop than in the manual group, and the adjustments were smaller.

Table 4. Comparison of Anesthetic Procedures During the Maintenance Phase

<table>
<thead>
<tr>
<th></th>
<th>Manual group (n = 84)</th>
<th>Dual-loop group (n = 83)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (min)</td>
<td>150 ± 81, 131 (89–188)</td>
<td>140 ± 78, 117 (89–176)</td>
<td>0.38</td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose (mg · kg⁻¹ · h⁻¹)</td>
<td>5.0 ± 1.6, 4.7 (3.8–6.3)</td>
<td>4.7 ± 1.6, 4.5 (3.7–5.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Increment value (µg · mL⁻¹)</td>
<td>0.58 ± 0.36, 0.50 (0.33–0.73)</td>
<td>0.31 ± 0.09, 0.28 (0.25–0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean effect-site concentration (µg · mL⁻¹)</td>
<td>2.3 ± 0.6, 2.1 (1.9–2.6)</td>
<td>2.4 ± 0.7, 2.3 (1.8–2.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Modifications per hour</td>
<td>9 ± 6, 6 (5–13)</td>
<td>26 ± 5, 26 (22–28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose (µg · kg⁻¹ · min⁻¹)</td>
<td>0.16 ± 0.07, 0.16 (0.11–0.20)</td>
<td>0.22 ± 0.07, 0.20 (0.17–0.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Increment value (ng · mL⁻¹)</td>
<td>1.23 ± 0.60, 1.12 (0.80–1.57)</td>
<td>0.94 ± 0.28, 0.91 (0.78–1.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean effect-site concentration (ng · mL⁻¹)</td>
<td>4.8 ± 1.6, 4.5 (3.7–5.8)</td>
<td>6.1 ± 1.4, 6.3 (4.9–6.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Modifications per hour</td>
<td>8 ± 6, 7 (4–10)</td>
<td>32 ± 8, 33 (28–37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NMBD</td>
<td>42 (50)</td>
<td>46 (55)</td>
<td>0.48</td>
</tr>
<tr>
<td>MICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of hypotension or hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine bolus</td>
<td>29 (35)</td>
<td>30 (36)</td>
<td>0.92</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>12 (14)</td>
<td>14 (17)</td>
<td>0.40</td>
</tr>
<tr>
<td>Blood loss &gt;500 mL</td>
<td>14 (17)</td>
<td>7 (8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ringer lactate solution infusion (mL · kg⁻¹ · h⁻¹)</td>
<td>7 ± 4, 7 (4–10)</td>
<td>8 ± 5, 6 (5–10)</td>
<td>0.91</td>
</tr>
<tr>
<td>Somatic events</td>
<td>6 (7)</td>
<td>7 (8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Morphine dose (mg · kg⁻¹)</td>
<td>0.06 ± 0.04, 0.6 (0–0.1)</td>
<td>0.06 ± 0.04, 0.07 (0–0.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Time to tracheal extubation (min)</td>
<td>11 ± 5, 10 (6–14)</td>
<td>10 ± 4, 9 (7–12)</td>
<td>0.02</td>
</tr>
<tr>
<td>BIS values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS &lt;40 (%)</td>
<td>24 ± 21, 17 (7–39)</td>
<td>15 ± 11, 12 (6–22)</td>
<td>0.016</td>
</tr>
<tr>
<td>BIS &lt;45 (%)</td>
<td>51 ± 24, 53 (33–72)</td>
<td>41 ± 19, 38 (29–54)</td>
<td>0.005</td>
</tr>
<tr>
<td>BIS &lt;60 (%)</td>
<td>71 ± 19, 76 (59–85)</td>
<td>82 ± 12, 85 (73–91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BIS &gt;60 (%)</td>
<td>5 ± 7, 2 (0–6)</td>
<td>3 ± 4, 1 (0–3)</td>
<td>0.031</td>
</tr>
<tr>
<td>Mean BIS</td>
<td>46 ± 5, 46 (42–49)</td>
<td>47 ± 4, 47 (45–49)</td>
<td>0.142</td>
</tr>
<tr>
<td>Occurrence of SR</td>
<td>27 (32)</td>
<td>9 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PE</td>
<td>−8.0 ± 9.8, −8.3 (−15.2 to −2.0)</td>
<td>−6.4 ± 7.3, −5.7 (−10.3 to −2.7)</td>
<td>0.142</td>
</tr>
<tr>
<td>MDPE</td>
<td>−9.7 ± 9.6, −10.1 (−17.1 to −3.1)</td>
<td>−6.9 ± 6.4, −6 (−12 to −2.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>MDAPE</td>
<td>15.0 ± 5.5, 14.1 (11.5–18.0)</td>
<td>11.4 ± 4.3, 10.5 (9.0–14.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wobble</td>
<td>9.2 ± 3.5, 8.3 (7.0–11)</td>
<td>8.7 ± 3.3, 8.0 (7.0–10.0)</td>
<td>0.283</td>
</tr>
<tr>
<td>Global score</td>
<td>43 ± 40, 31 (24–49)</td>
<td>26 ± 11, 23 (19–30)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean ± SD, median (interquartile range); and number (%).

NMBD = use of neuromuscular blocking drug; time to tracheal extubation = time from discontinuation of propofol and remifentanil infusion until tracheal extubation; Bispectral Index (BIS) <40 = percentage of time in which the BIS value was <40; 40 < BIS < 60 = percentage of time in which the BIS value was between 40 and 60 during the maintenance; BIS >60 = percentage of time in which the BIS value was >60; mean BIS = average BIS value; SR = burst suppression ratio, occurrence of SR was defined as SR >10% lasting at least a minute; PE = performance error; MDPE = median of performance error or bias; MDAPE = median absolute performance error or inaccuracy; wobble = intraindividual variability in performance error; global score = overall performance of the system.

Figure 4. Histogram of global score. Normal distribution curve for dual-loop (dashed line) and manual (solid line) groups.

Figure 5. Histogram of percentage of time that the Bispectral Index value was between 40 and 60, which is defined as adequate maintenance control. Normal distribution curve for dual-loop (dashed line) and manual (solid line) groups.

(Table 4 and Fig. 3). The Feedforward term (Appendix) was triggered 2 ± 2, 2 (1–3) times per hour for propofol and 5 ± 2, 5 (4–6) times per hour for remifentanil (P < 0.0001).
Heart rate, systolic blood pressure, and BIS values were similar between groups before and after painful stimuli (Fig. 6). This analysis was based on 33 patients in the manual group and 31 in the dual-loop group for laryngoscopy, and on 44 patients in the manual group and 49 in the dual-loop group for surgical incision because electronic recording of hemodynamic data and notes of these events were available only for these patients. No patient received combined general/regional anesthesia.

The mean time to tracheal extubation was shorter in the dual-loop than the manual group (Table 4 and Fig. 7). This analysis was based on 70 patients in the manual group and 72 in the dual-loop group because the remaining patients remained intubated because of hypothermia ($n = 8$), residual neuromuscular block ($n = 5$), or planned extubation in the intensive care unit ($n = 12$).

A subgroup of patients corresponds to those who received combined general and regional anesthesia. Patients in the dual-loop group had a nonsignificant decrease in remifentanil consumption (0.22 ± 0.7, 0.20 [0.16–0.27] vs 0.19 ± 0.7, 0.20 [0.16–0.23] µg · kg$^{-1}$ · min$^{-1}$, general anesthesia versus combined general/regional anesthesia, $P = 0.52$). Patients in the manual group had a significant decrease in remifentanil consumption (0.17 ± 0.7, 0.16 [0.11–0.21] vs 0.12 ± 0.6, 0.10 [0.07–0.16] µg · kg$^{-1}$ · min$^{-1}$, general anesthesia versus combined general/regional anesthesia, $P = 0.003$).

Use of neuromuscular blocking drugs, ephedrine treatment, antihypertensive therapy, blood loss, Ringer solution...
infusion, somatic events, and morphine dose were similar in the 2 groups (Table 4). No cases of awareness with recall were reported.

**DISCUSSION**

Our results indicate that automated coadministration of propofol and remifentanil using BIS for the controller allows an improvement in GS: increase in time with BIS values within predetermined boundaries (i.e., the interval 40–60) and decrease of MDAPE without an improvement of wobble. It permits a decrease in the duration of the induction phase and the time to extubation.

Closed-loop administration of propofol using BIS as the controlled variable during general anesthesia is becoming a reality as demonstrated by the number of successful cases published.4–7,18–25 On the contrary, the choice of the controlled variable remains when discussing closed-loop administration of an opioid. Most investigators propose the use of heart rate and mean arterial blood pressure to control opioid administration. Most investigators propose the use of heart rate and mean arterial blood pressure to control opioid delivery.26–28 However, hemodynamics are not specific for the response to painful stimulation and may be affected by a number of covariates such as blood loss, heart failure, arrhythmia, manipulation of great blood vessels, and a variety of drugs. Schwilden and Stoeckel8 used the median EEG frequency to steer alfentanil administration. Morley et al.4 described closed-loop control of a propofol/alfentanil mixture using BIS, but showed no clinical advantage between closed-loop and manual control. The use of an isobole controller has been reported for the closed-loop coadministration of a hypnotic and an opioid drug29 and was tested in 1 dog. We have reported 2 cases using the propofol-remifentanil closed-loop controller in a 9-year-old boy requiring emergency lung volume reduction30 and in a patient with gigantism.31 The dual-loop controller successfully administered propofol and remifentanil. Because our controller continuously titrates drug effect against BIS, it compensates for the shortcomings of pharmacokinetic models.

Clinical hypotheses for the development of our controller were that closed-loop control of propofol maintains a continuous stable hypnotic level (BIS between 40 and 60) in the absence of noxious stimuli and that painful intraoperative stimuli provokes cortical activation with consequent increases in BIS.11,12 Description of the controller is detailed in Figure 1, the Appendix, and in Table 1. Briefly, the controller in the current study measures and calculates the error (BISerror), which is the difference between the set point (BIS = 50) and the measured BIS. If the BIS error is different from 0, the controller determines a new propofol and/or remifentanil concentration. The error size determines which drug will be modified: if the BIS error is small, only the remifentanil is changed; if the BIS error is higher, the 2 drug concentrations are changed (Table 1). The minimal interval between 2 consecutive controls is set equal to the time to peak effect of each drug with an additional delay of 60 seconds; this time interval is shorter for remifentanil14 than for propofol,13 thus remifentanil modifications are made more frequently.

The GS was chosen as the primary outcome for evaluation of controller performance. This score has previously been used5,6,22 but it has not been extensively validated, leaving our primary outcome consequently open to criticism. However, a particular goal of automated control is to keep the average value of the controlled variable within defined limits with low oscillations.32 These criteria are summarized by the GS, which weights the inaccuracy or MDAPE and the wobble16 against the percentage of time with BIS values between 40 and 60. The MDAPE represents the precision or the oscillation around the set point (BIS = 50). The wobble measures the intraindividual variability of PE, but the wobble can be low (or excellent) while the BIS values are outside of the range (40–60). Consequently, the wobble cannot alone assess the controller performance and the GS avoids a misinterpretation.5 Finally, GS, MDAPE, percentage of BIS in the range 40 to 60 (Fig. 4), <40, >60, or period of SR are in agreement and demonstrate a better control of the BIS using the closed-loop controller. The controller decreases the episodes of too deep anesthesia (BIS <40) associated with the occurrence of SR (Table 4). The occurrence of SR may be attributable to a variety of factors other than hypnotic drug overdosing such as changes in metabolism and/or perfusion pressure, hypothermia, or hypoxemia. However, the occurrence of an isoelectric EEG increases mortality in critically ill patients33,34 and SR is related to too deep anesthesia, which has been proposed as a cause of increased long-term mortality.35–38

Hemodynamic responses to painful stimuli (laryngoscopy or surgical incision), recorded in only a fraction of patients, were similar with closed-loop and manual control, which suggests that closed-loop control provides acceptable control of heart rate and arterial blood pressure. However, in the absence of specific or objective clinical signs or specific analgesia monitors, we cannot evaluate whether remifentanil administration was optimal.

Our study also shows some limits of our controller. The first limitation is the duration of the induction phase, which is mostly comprised between 3.4 and 6.1 minutes (interquartile range values). Such a duration, obviously too long for low-risk patients, is related to the delay between each new modification of propofol or remifentanil concentration (Appendix). An evolution of our controller could be the decrease of this delay in low-risk patients. The second limitation is remifentanil consumption. Whereas propofol consumption was similar in both groups, consumption of remifentanil was higher in the dual-loop group (Tables 3 and 4, and Fig. 3). Similarly, remifentanil effect-site concentrations were higher in the dual-loop group both during the induction phase and during maintenance. We plan to modify the controller, gain constant and limits of remifentanil, to decrease remifentanil consumption. Comparison of drug consumption or drug concentration with other studies is difficult because of different populations: one-third had major surgery, and 15% had combined general anesthesia and regional block. Finally, high remifentanil consumption can be considered harmful if it increases the occurrence of adverse events such as hemodynamic instability or awareness. Our trial lacks power to determine the incidence of awareness. The third limitation is the number of dropouts (Fig. 2). Some were attributable to errors in the conduct of the study by the investigators, i.e., patients

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with neurological disorders, dilution, or drug errors. Prolonged artifacts of BIS cannot be attributed to our system unlike recording system failures and computer failure. All of these cases are explained by the use of a prototype device in a conventional personal computer with Windows XP as the directory operating system.

Other points must be discussed. We defined an induction phase as the delay between the beginning of drug infusion and BIS value ≤60 for 30 seconds. We chose such a definition to avoid the risk of human error at the appearance of a clinical sign such as loss of verbal contact and the risk of a modification of the hypnotic state caused by repeated patient stimulation. The period of 30 seconds was arbitrary but it is usual to see the BIS value oscillating around 50 after an initial abrupt decrease. A shorter period would not have been enough. Second, our study was unblinded, multicentered, and had many investigators. The relatively high number of investigators is a strength showing that the controller works in other hands than those of the inventors. However, it is also a weakness because several points of patient care were left to the usual practice of the investigators, making the comparisons between the groups imprecise. This is particularly true when discussing hemodynamic profiles, requirement for fluid or vasoactive drugs, and extubation. Third, we compared our controller against an anesthesiologist-based control; this methodology has been used to study a single BIS-propofol closed-loop controller. Other approaches could be proposed in case of a dual controller to clarify the interaction between drugs: comparison of the propofol-remifentanil closed-loop controller to a single closed loop of propofol with a continuous and fixed infusion at different targets of remifentanil, or with a continuous fixed infusion of propofol at different targets associated with a single remifentanil closed-loop controller guided by BIS. Finally, our aim was to compare the current closed-loop controller as a new method for drug administration, with manual TCI of propofol and remifentanil, a present-day practice.

In conclusion, electrocortical activity given by the BIS monitor allows computerized control of simultaneous propofol and remifentanil administration. Several improvements of the controller are required before trials on large populations to demonstrate that automated control of anesthetic delivery is a useful tool.

**APPENDIX**

In both groups, patients received total IV anesthesia in target-controlled infusion (TCI) mode using the Infusion Toolbox 95® version 4.11 software. Infusion Toolbox 95 is programmed in Visual Smalltalk, an object-oriented language (VisualAge for Smalltalk® version 5.5; IBM, Armonk, NY). The software allows calculated plasma and effect-site concentrations (Ce) of propofol and remifentanil. The population pharmacokinetic sets of Schnider et al. and Minto et al. were selected for propofol and remifentanil, respectively. The software steers 2 Asena GH® infusion pumps (Alaris Medical UK Ltd., Basingstoke, Hampshire, UK). The Bispectral Index (BIS) electrodes were positioned on the forehead and connected to either an A-2000 XP (version 3.11) BIS monitor (Covidien, Mansfield, MA) or a BIS Module (Datecx-Ohmeda™ S/5TM, Helsinki, Finland). A standard personal computer running with Windows 98® or XP® (Microsoft, Redmond, WA) is used to provide a user interface, to store BIS, signal quality index, electromyographic (EMG) activity, and suppression ratio data every 5 seconds and to control communication via an RS232 serial port between the monitor and the 2 infusion pumps.

**1. Main Elements of the Controller**

The controller has a cascade structure including 2 proportional-integral-derivative (PID) controllers, each one having its own PID algorithm, and an interaction rule (Fig. 1). The controller includes 6 main elements:

- Calculation of the BISerror (difference between the set point of 50 and the actual unfiltered BIS value): it allows the titration until the target level of BIS = 50 is obtained. This parameter is calculated only if the signal quality index given by the monitor is >50%. New drug concentrations are calculated according to the “error” size and sign to actual concentrations. The controller increases or decreases the drug concentrations according to the “error” sign (positive or negative). The “error” size determines which drug will be modified. If the BISerror is small, only the remifentanil is changed; if the BISerror is higher than a threshold, the 2 drug concentrations are changed. Finally, the 2 agents are continuously modified by the controller. The delay between each modification is shorter and the trigger threshold lower for the remifentanil than for the propofol. Consequently, the controller is more reactive for remifentanil.

- Amplification of the feedback (AFB): a specific AFB has been determined for each drug and for each BIS “error.” A new target is determined by the following equation, which corresponds to an integral controller:

  \[ \text{New target} = \text{current target} \times \text{AFB_{BISerror}} \]

  with \[ \text{AFB_{BISerror}} = \left[ 1 + \left( \text{BIS}_{\text{error}} \right) / K \right] \].

  The controller continuously modifies the target concentration until a BISerror = 0 is obtained. The new target is calculated by using the current target, which was determined by the previous BISerror. In fact, the controller sums the instantaneous errors over time (integrating the error every 5 seconds throughout the maintenance phase), giving the accumulated offset that should have been corrected previously. The new target calculated by the use of this accumulated error provides the PID integral action.

  The values of the gain constants or K values for propofol and remifentanil are given in Table 1; these values were determined empirically using the simulator included in the Infusion Toolbox 95 software.

- Delay between each new modification of propofol or remifentanil concentration: it is determined by the time necessary for equilibration of the previous effect-site compartment given by the pharmacokinetic models (Fig. 1). For a given patient, the delay given by the pharmacokinetic model is constant. It depends especially on age. For propofol, the delay varies linearly between 96 seconds (20 years old) and 120 seconds (80 years old).
years old). For remifentanil, the delay varies nonlinearly between 80 seconds (20 years old) and 151 seconds (80 years old). Remifentanil delays were calculated using the simulator included in the Infusion Toolbox 95 software. An additional period of 60 seconds is added systematically during the maintenance phase.

- Feedforward, derivative term of PID algorithm: its 2 components, 1 for propofol and 1 for remifentanil, check the profile every 5 seconds and decide on a concentration correction proportionally to the BISerror. It is activated in 3 circumstances: (i) when the BIS is >62 (propofol component) or 60 (remifentanil component), (ii) when the slope of the BIS increases >15 (propofol component) or 10 (remifentanil component) in 10 seconds, and (iii) when the EMG activity is >37 dB (propofol component) or 35 dB (remifentanil component).

It is deactivated when the EMG is >42 dB for 1 minute, a figure related to an artifact. The derivative action has the priority for the decisions of concentration modifications. Furthermore, when the current propofol concentration is <1.3 μg·mL⁻¹ or the current remifentanil concentration is <4 ng·mL⁻¹, default corrections (1.8 μg·mL⁻¹ and 6 ng·mL⁻¹, propofol and remifentanil, respectively) are performed to avoid a too small or not clinically relevant correction. The derivative action is inhibited during induction. Finally, during the maintenance phase, when the BIS or EMG limits are exceeded, then the propofol and remifentanil target concentrations are updated according to AFB.

- Interaction rule between propofol and remifentanil: if the controller increases the remifentanil concentration successively >3 times, then the controller increases the propofol concentration.
- Safety feature: the system automatically maintains the calculated drug concentrations in the case of controller or BIS dysfunction or low signal quality index (SQI <50). Furthermore, minimum and maximum (default values) of concentrations are set at 1 and 5 μg·mL⁻¹ for propofol and at 3 and 12 ng·mL⁻¹ for remifentanil during maintenance. The user can modify these values without limits.

2. Clinical Use of the Controller

All investigators were clinically experienced in the use of BIS to titrate propofol and remifentanil, and all received 2 days’ training on the dual closed-loop controller at our center. The user enters the patient’s demographic data (sex, age, weight, and height) and the initial propofol target concentration for induction. The controller decides the first remifentanil concentration related to initial propofol concentration: if the initial propofol target is <2.5 μg·mL⁻¹, then the initial remifentanil target is 4 ng·mL⁻¹; if the initial propofol target is between 2.5 and 2.9 μg·mL⁻¹, then the initial remifentanil target is 5 ng·mL⁻¹; if the initial propofol concentration is >3 μg·mL⁻¹, then the initial remifentanil target is 6 ng·mL⁻¹. The derivative action or feedforward is inhibited during induction. After the induction phase (i.e., BIS ≤60 for 30 seconds), the controller switches automatically to the maintenance phase. Throughout the procedure, the user can adjust the targets if necessary or switch between closed-loop and manual control.

3. Summary of the Controller

When starting a procedure, the clinician enters an initial target value of Ce for the propofol Ceprop (I) and the controller sets an initial target value of Ce for the remifentanil Ceremi (I):

- if Ceprop (I) < 2.5 μg·mL⁻¹, then Ceremi (I) = 4.0 ng·mL⁻¹,
- if 2.5 μg·mL⁻¹ < Ceprop (I) < 2.9 μg·mL⁻¹, then Ceremi (I) = 5.0 ng·mL⁻¹,
- if Ceprop (I) > 3.0 μg·mL⁻¹, then Ceremi (I) = 6.0 ng·mL⁻¹

The following rules are used to update the new concentrations until BISerror = 0 is obtained:

Rule 1 Ceprop (k) = Ceprop (k - 1) (1 + [BISerror/Kprop])
Rule 2 Ceremi (m) = Ceremi (m - 1) (1 + [BISerror/Kremi])

where Ceprop (k) and Ceremi (m) are the new target of propofol or remifentanil, Ceprop (k - 1) and Ceremi (m - 1) are the current values of Ce, and BISerror is the difference between the current BIS value and 50. Table 1 gives the value for Kprop and Kremi as a function of the error BISerror.

A new target was updated after the time necessary for equilibration of the previous effect-site compartment given by the pharmacokinetic models. For a given patient, the delay given by the pharmacokinetic model is constant. It depends especially on age. The propofol delay varies linearly between 96 seconds (20 years old) and 120 seconds (80 years old). For remifentanil, the delay varies nonlinearly between 80 seconds (20 years old) and 151 seconds (80 years old). Remifentanil delays were calculated using the simulator included in the Infusion Toolbox 95 software. An additional period of 60 seconds is added systematically during the maintenance phase.

However, every 5 seconds a new correction is possible while the concentration between plasmatic and effect-site compartment is not in steady state, thanks to the derivative term if:

- BIS >62, then Ceprop (k) is updated.
- BIS >60, then Ceremi (m) is updated.
- BISerror >15, then Ceprop (k) is updated.
- BISerror >10, then Ceremi (m) is updated.
- EMG >37 dB and EMG <42 dB, then Ceprop (k) is updated.
- EMG >35 dB and EMG <42 dB, then Ceremi (m) is updated. If none of the 6 conditions listed above are met, the previous actions or rules 1 and 2 are invoked. During the maintenance phase, which is the period after the induction phase (defined as the time from the start of propofol and remifentanil administration to BIS <60 during 30 seconds) until the end of drug administration, we have added a supplementary delay of 60 seconds between each concentration modification. Moreover, if Ceremi is updated 3 times in a row, then Ceprop is automatically updated once.
DISCLOSURES

Conflict of Interest: Hôpital Foch, N. Liu, T. Chazot, and B. Trillat are patent holders in France for the gain constants and the control algorithm (No. BFF08P669, Institut National de la Propriété Industrielle, France).

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Conflicts of Interest: None

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Conflicts of Interest: None

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Conflicts of Interest: None

REFERENCES

30. Liu N, Bourgeois E, Chazot T, Murat I, Fischer M. Closed-loop administration of propofol and remifentanil guided by the bispectral index in patient requiring an emergency lung volume reduction. Paediatr Anaesth 2007;17:909–10
34. Seder DB, Fraser GL, Robbins T, Libby L, Riker RR. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med 2010;36:281–8