Feasibility of Closed-loop Titration of Propofol and Remifentanil Guided by the Bispectral Monitor in Pediatric and Adolescent Patients

A Prospective Randomized Study

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ABSTRACT

Background: This study was designed to assess the feasibility of dual closed-loop titration of propofol and remifentanil guided solely by the Bispectral Index (BIS) monitor in pediatric and adolescent patients during anesthesia.

Methods: Children undergoing elective surgery in this single-blind randomized study were allocated into the closed-loop (auto) or manual (manual) group. Primary outcome was the percentage of time with the BIS in the range 40 to 60 (BIS_{40-60}). Secondary outcomes were the percentage of deep ($BIS_{<40}$) anesthesia and drug consumption. Data are presented as median (interquartile range) or number (%).

Results: Twenty-three patients (12 [10 to 14] yr) were assigned to the auto group and 19 (14 [7 to 14] yr) to the manual group. The closed-loop controller was able to provide induction and maintenance for all patients. The percentage of time with BIS_{40-60} was greater in the auto group (87% [75 to 96] *vs.* 72% [48 to 79]; $P = 0.002$), with a decrease in the percentage of $BIS_{<40}$ (7% [2 to 17] *vs.* 21% [11 to 38]; $P = 0.002$). Propofol (2.4 [1.9 to 3.3] *vs.* 1.7 [1.2 to 2.8] mg/kg) and remifentanil (2.3 [2.0 to 3.0] *vs.* 2.5 [1.2 to 4.3] µg/kg) consumptions were similar in auto *versus* manual groups during induction, respectively. During maintenance, propofol consumption (8.2 [6.0 to 10.2] *vs.* 7.9 [7.2 to 9.1] mg kg^{-1} h^{-1}; $P = 0.89$) was similar between the two groups, but remifentanil consumption was greater in the auto group (0.39 [0.22 to 0.60] *vs.* 0.22 [0.17 to 0.32] µg kg^{-1} min^{-1}; $P = 0.003$). Perioperative adverse events and length of stay in the postanesthesia care unit were similar.

Conclusion: Intraoperative automated control of hypnosis and analgesia guided by the BIS is clinically feasible in pediatric and adolescent patients and outperformed skilled manual control. (**ANESTHESIOLOGY 2015; 122:759-67**)

S INCE the first description of closed-loop or automated administration of anesthetic drugs in 1950,[1] several adult studies have demonstrated that anesthesia delivered using the closed-loop system, with electroencephalogram activity as feedback controller, was feasible without increasing adverse events. In adult populations, randomized controlled studies have demonstrated that the automated administration of intravenous anesthetic drugs, guided by the Bispectral Index (BIS) monitor (Covidien, Dublin, Ireland), decreases propofol consumption during induction,[2] during maintenance of general anesthesia in patients undergoing cardiac surgery with cardiopulmonary bypass,[3] or during deep sedation in critically ill patients.[4] Moreover, the use of the automated controller improves hemodynamic stability during cardiac surgery or during deep sedation in critically ill patients by the decrease in vasopressor use,[3,4] outperforms manual control to maintain the BIS in the range 40 to 60 during maintenance of general

> ### What We Already Know about This Topic
>
> - Automated intravenous anesthetic drug administration guided by a Bispectral Index monitor decreases propofol consumption in adults and maintains the bispectral index in the range of 40 to 60 during maintenance of general anesthesia better than manual control
>
> ### What This Article Tells Us That Is New
>
> - Bispectral index–guided automated control of propofol hypnosis and remifentanil analgesia is feasible and maintains bispectral index in the range of 40 to 60 in 6- to 16-yr-old old patients better than skilled manual control
> - Propofol consumption during maintenance of anesthesia was similar in the two groups, but remifentanil consumption was higher in the automated control group

anesthesia,[2,5–9] decreases the workload during the induction period,[10] and enables faster recovery times.[2,8,9]

However, in children, the ability of BIS to accurately track volatile agent concentration change and evaluate depth of anesthesia is still controversial.[11–13] Moreover, only

a few pediatric studies have assessed BIS during total intravenous anesthesia with propofol in children.[14–22] In addition, the limited predictability of the majority of published pediatric pharmacokinetic models[23] and the wide interpatient variability observed in children[24] suggest a possible key role for closed-loop control in optimizing the administration of total intravenous anesthesia by continuous titration in the pediatric population. Currently, only a few studies have reported the use of closed-loop control of propofol anesthesia in children with varying degrees of success.[15,25] We have developed a closed-loop controller allowing automated titration of propofol and remifentanil guided solely by the BIS.[8,26–28] This dual closed-loop titration of hypnosis and analgesia guided by the BIS has already been used successfully in a 9-yr-old child requiring an emergency lung volume reduction.[29]

Therefore, we aimed at comparing manual *versus* dual closed-loop control during general anesthesia induction and maintenance in a pediatric population. Specifically, we tested the hypothesis that the dual-loop controller with the BIS as output increases the time spent within a predetermined target BIS range.

Materials and Methods

Our prospective randomized single-blind clinical trial was approved by the Ethics Committee of the University (Comité de Protection des Personnes, Hôpital A. Paré, N°080636, Boulogne Billancourt, France) and the relevant French regulatory office (Agence Française de Sécurité Sanitaire des Produits de Santé, N°2008-003216-35). It was registered with ClinicalTrials.gov (file number: NCT 00778505). The study was conducted in a single university hospital (Hôpital Necker-Enfants Malades, Paris, France). Both parents of each child were informed of the nature of the study and gave their written informed consent during the preoperative visit performed by the investigators. Inclusion criteria were patients aged between 6 and 16 yr and presenting for elective surgical procedures requiring general anesthesia expected to last at least 60 min. Exclusion criteria were a history of psychiatric and/or neurologic disorder, presence of a pacemaker, a surgical procedure with an evaluated risk of bleeding greater than 15% of the estimated blood volume, or planned intracranial surgery.

Procedure

Hydroxyzine (1 mg/kg) was given by the oral route to all patients, 30 min before starting anesthesia.

An intravenous cannula was introduced after EMLA® cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine; AstraZeneca Laboratories, Rueil-Malmaison, France) had been applied at the site of venipuncture for at least an hour.

A venous access, dedicated to propofol and remifentanil infusion pumps, was connected *via* a three-way Smartsite® Needle-Free System (Alaris Medical Systems, San Diego,

CA) with a priming volume of 0.3 ml to the pumps. Routine monitoring included core temperature and neuromuscular function at the adductor pollicis. Disposable pediatric or adult BIS sensors (Zippred; Bispectral Index; Covidien) were applied to the foreheads of the children and connected to the A2000XP monitor (version 3.11; Covidien) in accordance with the manufacturer's instructions. Just before induction of general anesthesia, patients were randomly assigned to the automated control or to skilled manual control based on the BIS index. The sequence of treatments was determined in blocks of 10 (5 auto and 5 manual group) using a random-number computer generator in a 1:1 ratio. Assignments were kept in sequentially numbered opaque envelopes until just before surgery. Investigators had considerable clinical experience titrating intravenous anesthesia using the BIS monitor and target-controlled infusion systems in a pediatric population.

All patients received total intravenous anesthesia in target-controlled infusion mode using the population pharmacokinetic sets of Schnider *et al.*[30] for propofol and Minto *et al.*[31] for remifentanil to target the effect-site concentration. Infusion Toolbox 95 version 4.11 software (Université Libre de Bruxelles, Brussels, Belgium)[32] implemented in a personal computer serving as a platform for: (1) calculating effect-site concentrations of propofol and remifentanil; (2) displaying effect-site concentration estimates in real time; (3) providing a user interface that permits entry of patients' demographic data (sex, age, weight, and height) and modifications to target concentrations; (4) controlling the propofol and remifentanil infusion pumps (Alaris Medical, Hampshire, United Kingdom); and (5) recording calculated effect-site drug concentrations, BIS data at 5-s intervals.

In the manual group, clinicians chose propofol and remifentanil effect-site concentrations for induction according to their clinical judgment. During maintenance, propofol and remifentanil were adjusted to maintain a BIS value as close to 50 as practical. As clinically necessary, anesthesiologists could modify the drug target concentration once 95% equilibration of the effect-site compartment was reached without the constraint of upper or lower limits for the two agents.

For the auto group, the controller has a cascade structure with a dual proportional-integral-derivative algorithm associated with a target-controlled infusion device. This controller was similar to one published in a randomized controlled trial[8] with the same gain constants, but the upper limits of targets were increased (5 to 7 µg/ml for propofol and 12 to 15 ng/ml for the remifentanil). Users entered the patient's sex, age, weight, and height. The investigator could modify the minimum or the maximum concentration of propofol or remifentanil targets or switch between auto and manual control. Clinicians chose the initial propofol effect-site concentrations for induction according to their clinical judgment. The controller decides the first remifentanil concentration related to initial propofol concentration. The controller includes several main elements:

- Calculation of the BIS_{error} 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.

- The "error" size determines which drug will be modified. If the BIS_{error} is small, only the remifentanil is changed, and if the BIS_{error} is higher than a threshold, the two drug concentrations are changed.

- A proportional correction has been determined for each drug and for each BIS_{error}. The controller continuously modifies the target concentration until a BIS_{error} = 0 is obtained. The new target is modulated by the use of this accumulated error and provides the integral action of the controller.

- 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.[30,31]

- A derivative term of the controller: check the profile every 5 s and decide on a rapid concentration correction.

- Interaction rule between propofol and remifentanil: if the controller increases the remifentanil concentration successively more than three 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 less than 50%.

In both groups, the induction phase was defined from the start of propofol and remifentanil administration to BIS less than 60 for 30 s, and BIS_{mini} is the minimum BIS value during a 10-min period after the induction phase; subsequent times until the end of surgery were considered to be the maintenance phase. Neuromuscular blockers were given to facilitate tracheal intubation followed by bolus administrations at the discretion of the anesthesiologist during the maintenance phase. Hemodynamic modifications were managed by administration of fluids and/or vasopressors.

Patients were ventilated with an air–oxygen mixture without nitrous oxide. Cardiovascular management, premedication, duration of anesthesia, blood loss, somatic events (movements, grimacing, and eye opening) were recorded. Approximately 45 min before the scheduled end of surgery, intravenous analgesics were given to provide postoperative pain relief: 0.05 to 0.15 mg/kg morphine, 15 mg/kg paracetamol, and nonsteroidal antiinflammatory drugs at the discretion of the clinician. A neuromuscular antagonist was given if indicated. At the end of surgery, propofol and remifentanil infusions were stopped. All patients were visited and interviewed about intraoperative recall on the second or third postoperative day using a specifically adapted questionnaire.[33]

The primary outcome was the percentage of time of BIS in the range 40 to 60 considered as adequate anesthesia (BIS_{40-60}). Secondary outcomes included the percentage overshoot ($BIS_{<40}$) and undershoot ($BIS_{>60}$) periods, occurrence of suppression ratio defined as suppression ratio greater than 10% lasting at least a minute.[34] The global score[2] gives the overall performance of a closed system and is calculated by the sum of median absolute performance error with the Wobble divided by the percentage of BIS_{40-60}. Excellent performance is characterized by low median absolute performance and Wobble values and a high percentage of BIS values between 40 and 60 and consequently a low value of global score.

The other secondary outcomes also included clinical data: drug consumption, number of somatic events (*i.e.*, movements and grimacing), length of stay in postanesthesia care unit, pain scores using the Face Legs Activity Cry and Consolability score[35] or pain visual analog score, morphine consumption in recovery room, and recall of intraoperative events as determined by a standardized interview performed on the second or third postoperative day using an interview adapted to the cognitive abilities of children.[33]

Data Analysis

A preliminary study indicated a percentage of BIS_{40-60} of approximately 70 ± 19% using manual propofol and remifentanil target-controlled infusion; in this superiority study, we expected an improvement of at least 25% with our automated controller. Based on these values, we estimated that a total of 36 patients (18 per group) would provide an 80% power at 5% two-sided type I error. We thus planned to recruit 46 patients to allow for dropouts. This trial was not overseen by an independent data safety monitoring board.

Data are presented as medians (interquartile ranges), percentages, or number of cases. Continuous data were compared by Mann–Whitney tests. Categorical data were compared with Fisher exact tests. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 20.0 (IBM-SPSS Science Inc., Chicago, IL).

Results

Seventy-two children were approached, 46 children were recruited between July 2009 and March 2012. Nineteen patients in the manual group and 23 in the auto group completed the study with usable data (fig. 1). Baseline characteristics were similar in the two groups (table 1).

The median BIS values and the calculated effect-site concentration of propofol and remifentanil from induction to discontinuation are presented in figure 2. Time course of heart rate and blood pressure, from induction to discontinuation, is shown in figure 3.

Anesthetic induction was similar with auto and manual induction, but there was a more pronounced overshoot in the manual group as indicated by the significantly lower
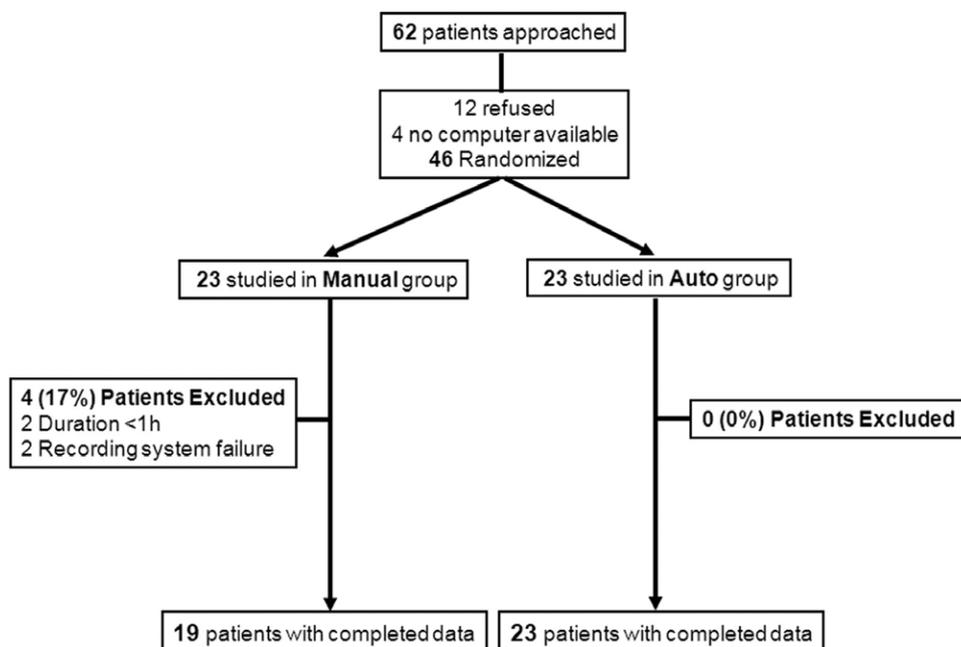
Fig. 1. Flow chart.

Table 1. Characteristics of Patients at Entry

	Manual (n = 19)	Auto (n = 23)	P Value
Age (yr)	14 (7–14)	12 (10–14)	0.79
Sex ratio (male/female)	11/8	13/10	1
Height (cm)	157 (135–168)	145 (130–160)	0.13
Weight (kg)	45 (27–57)	35 (30–51)	0.29
ASA physical status II	2 (6)	4 (13)	0.42
Type of surgery			
Otolaryngologic	7 (37)	11 (48)	0.47
Orthopedic	10 (52)	9 (39)	0.53
General	2 (11)	3 (13)	0.80

Results are expressed as median (interquartile range) or number (%).
ASA = American Society of Anesthesiologists; Auto = automated control of propofol and remifentanil guided by the bispectral index; Manual = manual control infusion group guided by the bispectral index.

BIS_{mini} (table 2). The automated system maintained anesthesia for a total of 58 h during which 3,906 target modifications were made automatically (1,141 for the propofol and 2,765 for the remifentanil). In the auto group, no manual modifications of propofol or remifentanil target were made. One patient in the auto group received an ephedrine bolus. Anesthetic procedures during the maintenance phase of anesthesia are presented in table 3. There was a significant increase ($P < 0.003$) in remifentanil consumption in the auto group (0.39 [0.22 to 0.60] $\mu g \ kg^{-1} \ min^{-1}$) as compared with the manual group (0.22 [0.17 to 0.32] $\mu g \ kg^{-1} \ min^{-1}$; table 3). There were no significant differences in the incidence of somatic events or the use of neuromuscular-blocking agent (table 3).

The fraction of time during which BIS was adequate, BIS_{40-60}, was significantly greater in the auto group (87%

[75 to 96]) than in the manual group (72% [48 to 79]). Periods of excessive anesthesia ($BIS_{<40}$) were shorter and the global score was better in the auto group (table 4). The occurrence of burst suppression ratio (table 4) was similar between the two groups.

In the recovery room, the length of stay, the number of patients in pain, the number of patients requiring morphine titration, and the total amount of morphine administered were similar between the two groups (table 5). No case of awareness with recall was recorded.

Discussion

The main result of this study is that intraoperative automated control of propofol hypnosis and remifentanil analgesia guided using BIS is clinically feasible and more precise than skilled manual control to maintain the BIS in the range 40 to 60 in pediatric patients. This is the first randomized controlled study of dual closed-loop anesthesia in children; only one case report describing the use of this closed-loop system in a child has been published to date.[29]

Studies concerning the use of a closed-loop controller in the pediatric population are still limited. One observational study reported a controller of propofol guided by the NeuroSense (NeuroWave Systems Inc., Cleveland Heights, OH) allowing the automated titration of propofol during induction and maintenance of sedation in 108 pediatric patients undergoing gastrointestinal endoscopy.[25] However, the NeuroSense monitor has only been compared to another electroencephalogram monitor such as the BIS monitor in 20 adult patients,[36] and the NeuroWave has never been evaluated in pediatric anesthesia. As acknowledged by the authors, the study was limited to sedation for endoscopic procedures
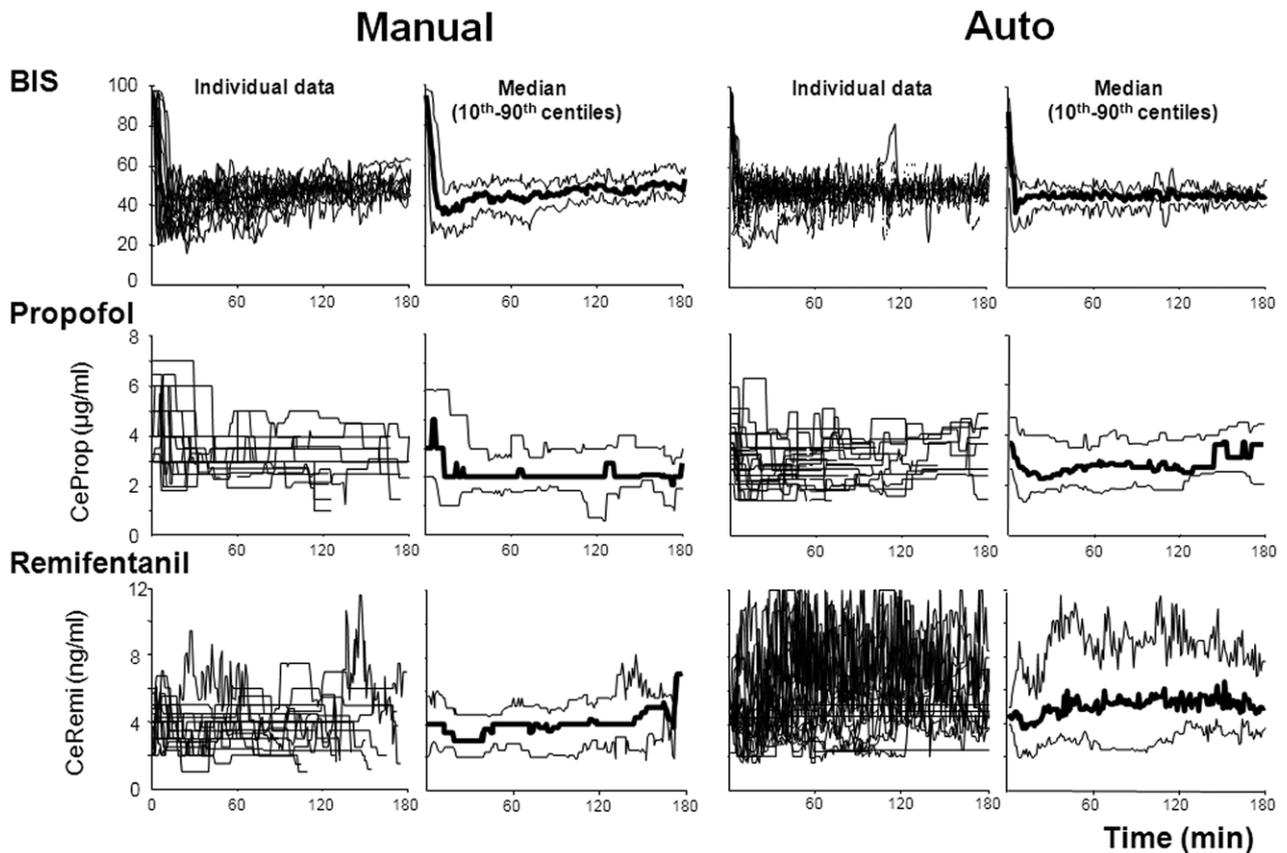
Fig. 2. Time course of bispectral index (BIS) values and calculated effect-site concentration of propofol (CeProp) and remifentanil (CeRem) from induction to discontinuation of these drugs. All individual values are shown; data are averaged for graphical representation with a moving average filter of 1-min duration. Median values (*thick line*) are presented with 10th and 90th percentiles (*fine line*). Auto: closed-loop control of propofol and remifentanil. Manual: manual group guided by the BIS.

which are associated with limited noxious stimulations as compared with conventional surgery. A prospective randomized study has compared manual titration of propofol and a closed-loop controller allowing the automated titration of propofol during induction and maintenance of general anesthesia in pediatric patients undergoing cardiac surgery with cardiopulmonary bypass.[15] This study demonstrated that the automated controller decreases propofol consumption during induction and off-cardiopulmonary bypass period and decreases the use of phenylephrine during the precardiopulmonary bypass. Moreover, the closed-loop controller outperforms manual titration to maintain the BIS in the range of 40 to 60. However, there were important differences between these studies and our study. First, in contrast to these two studies, where only propofol administration was automatically controlled, we used a dual closed-loop with automated control administration of both propofol and remifentanil, guided using BIS. Second, in the study performed in pediatric cardiac patients, the maintenance of BIS in the target interval was similar between closed-loop and manual groups. In addition, the authors noted a high incidence of propofol rate modifications per hour in the manual group, indicating an active and skilled titration. This situation, which has certainly played a key role in the maintenance of adequate

anesthetic depth in the manual group, represents a bias due to the Hawthorne effect.[37] In daily practice, the number of target modifications would probably be lower than during the study. We did not, however, observe any increase in the incidence of propofol rate modifications per hour in the manual group (table 3).

Whereas propofol consumption was similar in both groups, consumption of remifentanil was higher in the dual-loop group (table 3), as already noted in adult patients.[8] This increased use of remifentanil may be related to a real need in analgesia or to the controller algorithm. In brief, the controller includes a dual proportional-integral-derivative algorithm and a target-controlled infusion system for the administration of propofol and remifentanil. Every 5 s, the difference (BIS error) between the measured and the target BIS (BIS = 50) is calculated. If BIS error is different from 0, new propofol and/or remifentanil effect-site concentrations are calculated. The error size determines which drug will be modified; a small error leads to a change of remifentanil target only, and a large error leads to a change of both propofol and remifentanil. The minimal interval between two consecutive controls is set equal to the time to peak effect of each drug. Because this time interval is shorter for remifentanil than for propofol, remifentanil modifications are performed more
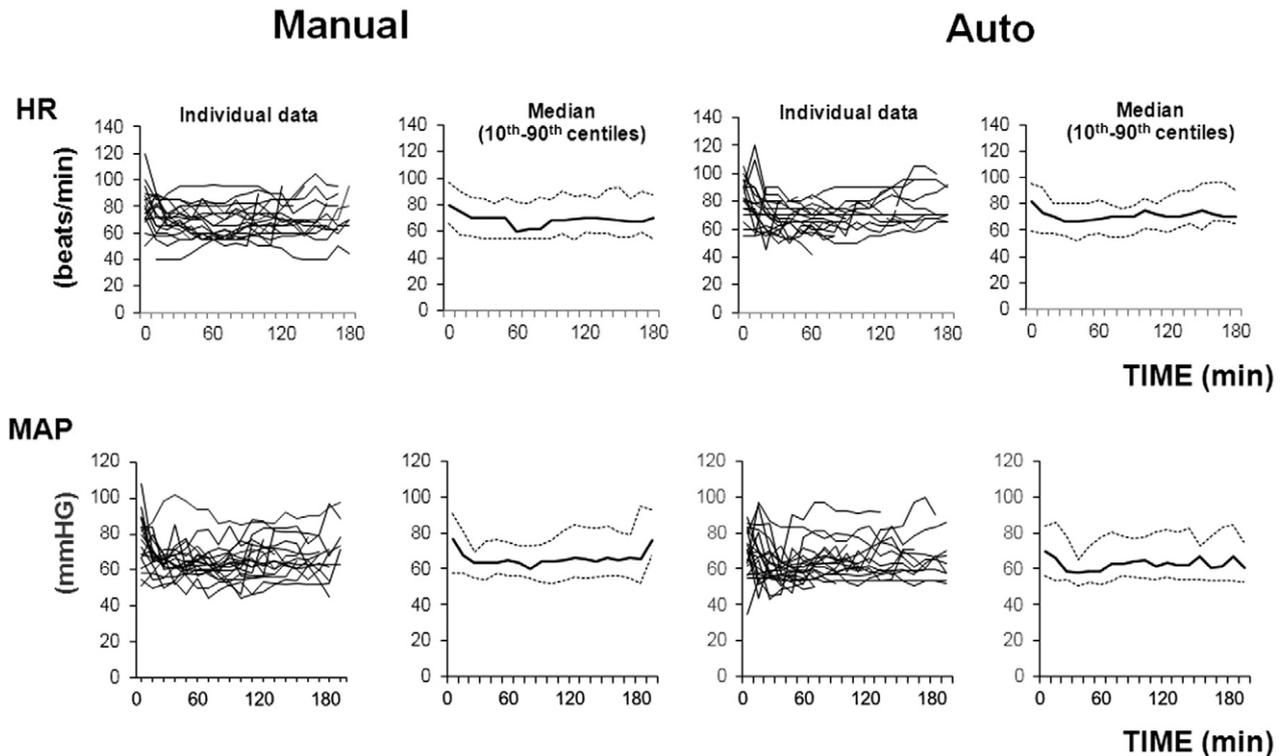
Fig. 3. Time course of heart rate (HR) and mean arterial pressure (MAP) from induction to discontinuation of anesthesia. All individual values are shown. Median values (*thick line*) are presented with 10th and 90th percentiles (*dotted line*). Auto: closed-loop control of propofol and remifentanil. Manual: manual group guided by the bispectral index.

Table 2. Comparison of Anesthetic Procedure during the Induction Phase

	Manual (n = 19)	Auto (n = 23)	P Value
Duration (s)	219 (135–352)	152 (114–292)	0.18
Propofol (mg/kg)	1.7 (1.2–2.8)	2.4 (1.9–3.3)	0.07
Remifentanil (µg/kg)	2.5 (1.2–4.3)	2.3 (2.0–3.0)	0.98
Occurrence of SR	2 (11)	1 (4)	0.58
BIS$_{mini}$	27 (23–35)	35 (29–44)	0.017

Data are presented as median (interquartile range) or number (%) of total patients of each group.

Auto = automated control of propofol and remifentanil guided by the bispectral index; BIS = bispectral index; BIS$_{mini}$ or overshoot after induction = minimum value of BIS during a 10-min period after the induction phase; Duration = time elapsed from the start of propofol administration to the moment when the BIS value fell below and remained under 60 for 30 s; Manual = manual control infusion group guided by the bispectral index; SR = burst suppression ratio.

frequently than propofol modifications. Clinical hypotheses for the development of our controller were that closed-loop control of propofol maintains a continuous stable hypnotic level (40 < BIS < 60) in the absence of noxious stimuli and that painful stimuli provokes cortical activation with consequent increases in BIS values.[38] In the current study, we used the earlier version of the controller algorithm (developed in 2006) for adult populations. Nevertheless, we plan to modify the controller gain constant, limiting the maximum target concentration of remifentanil, to decrease remifentanil consumption. However, high remifentanil consumption

can be considered harmful if it increases the incidence of adverse events such as hemodynamic instability, hyperalgesia, or awareness. All patients were interviewed about intraoperative recall using a specifically adapted questionnaire, and we did not observe any case of awareness; however, one should keep in mind that our trial lacks power to definitively eliminate a risk of awareness. Whereas we are not able to definitively exclude a risk of hyperalgesia because Von Frey hairs are not easily usable in children, no increase in pain scores, morphine requirements, or morphine consumption was observed in closed-loop patients in the postoperative period (table 5). Finally, no hemodynamic instability was noted, except in one patient in the closed-loop group who received an ephedrine bolus.

In our study, children received propofol and remifentanil using the models by Schnider *et al.*[30] and Minto *et al.*,[1] respectively, to target the effect-site concentration. Schnider's model, initially designed for adults, has been shown to adequately describe the predicted concentration–effect relation of propofol in children.[23] In contrast, the Kataria, Marsh, and Schüttler's models, for which pediatric versions are available, were less efficient in describing the predicted concentration–effect relation.[23] The pharmacokinetic model by Minto *et al.*[39] was developed in adult patients, but its use has also been reported in children. For example, target-controlled infusion using propofol with Kataria's pharmacokinetic model and remifentanil with Minto's model improves insertion of supraglottic devices suppressing airway reflexes.[40]

Table 3. Comparison of Anesthetic Procedure during the Maintenance Phase

	Manual (n = 19)	Auto (n = 23)	P Value
Duration of anesthesia (min)	173 (146–206)	150 (72–212)	0.23
Propofol			
Median dose (mg kg^{-1} h^{-1})	7.9 (7.2–9.1)	8.2 (6.0–10.2)	0.89
Increment value (μg/ml)	0.60 (0.53–0.72)	0.50 (0.39–0.64)	0.043
Modifications per hour (n)	6 (4–8)	19 (16–22)	<0.001
Median effect-site concentration (μg/ml)	3.0 (3.0–3.1)	2.8 (2.6–3.1)	<0.001
Remifentanil			
Median dose (μg kg^{-1} min^{-1})	0.22 (0.17–0.32)	0.39 (0.22–0.60)	0.003
Increment value (ng/ml)	0.67 (0.53–0.80)	0.48 (0.41–0.62)	0.003
Modifications per hour (n)	5 (4–8)	43 (37–54)	<0.001
Median effect-site concentration (ng/ml)	4.0 (3.8–4.0)	5.2 (4.9–5.5)	<0.001
Combined general/regional anesthesia	8 (42)	8 (36)	0.76
Somatic events	4 (13)	2 (6)	0.67
Neuromuscular blocker	2 (11)	4 (17)	0.67

Data are presented as median (interquartile range) or number (%) of total patients of each group.

Auto = automated control of propofol and remifentanil guided by the bispectral index; Increment value = median value of target concentration changes in propofol or remifentanil; Manual = manual control infusion group guided by the bispectral index.

Table 4. Efficiency of the Control System during Maintenance of Anesthesia

	Manual (n = 19)	Auto (n = 23)	P Value
BIS$_{40-60}$	72 (48–79)	87 (75–96)	0.002
BIS$_{<40}$	21 (11–38)	7 (2–17)	0.002
BIS$_{>60}$	6 (2–14)	2 (1–9)	0.16
Global score	31 (24–64)	16 (14–25)	0.001
SR	1 (5)	1 (4)	1

Data are presented as median (interquartile range) or number (%) of total patients of each group.

Auto = automated control of propofol and remifentanil guided by the bispectral index; BIS = bispectral index; BIS$_{40-60}$ = percentage of time in which the BIS value was between 40 and 60 during the maintenance; BIS$_{<40}$ = percentage of time in which the BIS value was less than a value of 40; BIS$_{>60}$ = percentage of time in which the BIS value was greater than a value of 60; Global score = Global score of BIS or overall performance; Manual = manual control infusion group guided by the bispectral index; SR = burst suppression ratio occurrence.

Table 5. Characteristics of the Patients of the Auto and Manual Groups during Their Stay in the Recovery Room

	Auto (n = 23)	Manual (n = 19)	P Value
Length of stay in the PACU (min)	120 (108–138)	120 (90–135)	0.88
Patients with an FLACC or VAS >3 (n)	13	16	0.09
Patients requiring morphine titration (n)	9	8	0.70
Total dose of morphine infused (mg/kg)	0.10 (0.10–0.17)	0.10 (0.10–0.16)	0.71

Data are presented as median (interquartile range) or number (%) of total patients of each group.

Auto = automated control of propofol and remifentanil guided by the bispectral index; FLACC = Face Legs Activity Cry and Consolability[35]; Manual = manual control infusion group guided by the bispectral index; PACU = postanesthesia care unit; VAS = visual analog score.

In another similar study, the authors, comparing propofol concentrations required for insertion of supraglottic devices with and without remifentanil (7.5 ng/ml), both drugs being administered in target-controlled infusion mode, observed that remifentanil halves the EC50 of propofol in children aged 2 to 12 yr.[41] The Minto model was successfully used in a study investigating the relation between BIS index and predicted plasma concentration of propofol delivered by target-controlled infusion during emergence in children.[42]

Our study presents some limitations. Regional anesthesia was used at the discretion of the anesthesiologist in charge of the patient. However, the proportion of patients with combined general and regional anesthesia was similar between the two groups. In addition, the main outcome and the secondary endpoints are not modified by regional anesthesia. Pediatric patients included in our study were 12 and 14 yr old in the closed-loop and manual groups, respectively. We had decided to include patients older than 6 yr (from 6 to 16 yr) because electroencephalogram monitoring of the depth of hypnosis may lack reliability in young children. Nevertheless, it was not a deliberate decision to include a majority of children older than 10 yr. However, obtaining a signed informed consent from the two parents was more difficult than anticipated in younger children, usually anesthetized using inhalation anesthesia in our institution. We cannot exclude that the anesthetists in the manual group considered also the hemodynamics when choosing the target concentrations, whereas the closed-loop system used only the BIS. To avoid such a bias would require blinding the hemodynamic data in the manual group. However, we consider this design to be unethical.

In conclusion, the use of a dual closed-loop controller that performs continuous monitoring of the drugs' effects, adjusting their administration to maintain BIS between 40 and 60, is clinically feasible and more precise than skilled manual control in pediatric and adolescent patients. Because the system is titrating automatically and continuously against BIS, it compensates for possible error when using adult pharmacokinetic models in children.

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