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Robust closed-loop control of induction and maintenance of propofol anesthesia in children

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Keywords
anesthetics; intravenous/administration & dosage; automation; drug delivery systems/methods; electroencephalography/drug effects; propofol/administration & dosage; software

Summary

Background: During closed-loop control, a drug infusion is continually adjusted according to a measure of clinical effect (e.g., an electroencephalographic depth of hypnosis (DoH) index). Inconsistency in population-derived pediatric pharmacokinetic/pharmacodynamic models and the large interpatient variability observed in children suggest a role for closed-loop control in optimizing the administration of intravenous anesthesia.
Objective: To clinically evaluate a robustly tuned system for closed-loop control of the induction and maintenance of propofol anesthesia in children undergoing gastrointestinal endoscopy.
Methods: One hundred and eight children, aged 6–17, ASA I-II, were enrolled. Prior to induction of anesthesia, NeuroSENSE™ sensors were applied to obtain the WAV_{CNS} DoH index. An intravenous cannula was inserted and lidocaine (0.5 $mg{\cdot}kg^{-1}$) administered. Remifentanil was administered as a bolus (0.5 $\mu g{\cdot}kg^{-1}$), followed by continuous infusion (0.03 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$). The propofol infusion was closed-loop controlled throughout induction and maintenance of anesthesia, using WAV_{CNS} as feedback.
Results: Anesthesia was closed-loop controlled in 102 cases. The system achieved and maintained an adequate DoH without manual adjustment in 87/102 (85%) cases. Induction of anesthesia (to $WAV_{CNS} \leq 60$) was completed in median 3.8 min (interquartile range (IQR) 3.1–5.0), culminating in a propofol effect-site concentration (C_e) of median 3.5 $\mu g{\cdot}ml^{-1}$ (IQR 2.7–4.5). During maintenance of anesthesia, WAV_{CNS} was measured within 10 units of the target for median 89% (IQR 79–96) of the time. Spontaneous breathing required no manual intervention in 91/102 (89%) cases.
Conclusions: A robust closed-loop system can provide effective propofol administration during induction and maintenance of anesthesia in children. Wide variation in the calculated C_e highlights the limitation of open-loop regimes based on pharmacokinetic/pharmacodynamic models.

Introduction

During closed-loop control of anesthesia, a drug infusion rate is continually adjusted according to feedback obtained from a measurement of clinical effect from the patient. Closed-loop anesthesia was first proposed in 1950 (1). While significant effort was devoted to its investigation in the 1980s and 1990s (2), recent developments in sensing the clinical effect, by measuring the depth of hypnosis (DoH) through effects on the electroencephalogram (EEG), have opened new opportunities for *closing the loop*. Studies with adult patients

have shown that closed-loop control of intravenous propofol administration is clinically feasible for the maintenance of anesthesia (3–9), and closed-loop induction of anesthesia has been demonstrated (7). We have previously reported the feasibility of automating both induction and maintenance of propofol anesthesia in adults using a simple robustly tuned proportional-integral-derivative (PID) controller (10).

Closed-loop control may offer advantages for pediatric anesthetic practice, such as improved and standardized control of the DoH, decreased consumption of drug, improved hemodynamic stability, and faster postoperative recovery (4,6–8). Closed-loop control can minimize individual operator variability in titration of anesthetic dose. Reduced variability has been suggested as a key goal in quality and safety improvement (11). These advantages, however, can only be realized if the safety of the system is demonstrated, and the performance is reproducible.

Closed-loop control relies on a real-time measured feedback variable. While processed EEG signals, such as the BIS and the NeuroSENSE™ WAV_{CNS}, do not necessarily reflect a direct clinical measure of level of anesthesia, they provide a means of quantification of the EEG that can be used to guide or control the administration of hypnotic agents (12,13). In this context, therefore, DoH refers to an EEG effect produced by hypnotic drugs, which is associated with loss of consciousness. By comparing the measured DoH against a target value (setpoint), a closed-loop system continually adjusts the administration of the hypnotic agent, optimizing it to the individual patient. With a PID controller, this adjustment is based on the current difference between the measured DoH and setpoint (proportional), the difference in the past (integral) and the anticipated future difference (derivative). Robust control design techniques have been used in the development of the controller used in this study. Robustness is an important concept in the design of control systems that aims to guarantee that the controller will preserve stability of the output (in this case, the measured DoH) and provide a minimum level of performance, irrespective of uncertainty or variations (within a defined range) in the characteristics of the system being controlled (in this case, the patient) (14,15).

Closed-loop systems represent a step beyond the use of target-controlled infusions (TCI), in which drug infusion rates are adjusted according to population-based pharmacokinetic (PK) and pharmacodynamic (PD) models. TCI for routine administration of propofol in children is limited by the lack of consistency in pediatric PKPD models related to the large interpatient PKPD variability observed in this population (16). Hence, closed-loop control may present an especially advantageous proposition in children: Optimizing the administration of propofol may reduce the effect of interpatient variability, while improving the stability of the DoH and safety of intravenous anesthesia. However, to date, the only published account of closed-loop anesthesia in children is a single case report (17).

The aim of this study was to evaluate the clinical feasibility of closed-loop control of propofol infusion for both induction and maintenance of anesthesia, based on feedback from the NeuroSENSE™ WAV_{CNS} index, in children undergoing gastrointestinal endoscopy and to collect pilot data to optimize the control parameters of the closed-loop system.

This article describes the application of the closed-loop controller in a clinical context, including a detailed description of the equipment and anesthetic protocol employed during the study, and presents the results with an emphasis on clinical outcomes. Details of the control algorithm and the identification data used in the design process are presented in a technical article by van Heusden *et al*. (18), which describes the development of the closed-loop controller and interprets the clinical results to evaluate whether engineering design objectives were met and to identify requirements for further technical development.

Methods

Devices

The device evaluated in this study (iControl) is a closed-loop anesthesia control system consisting of (a) the NeuroSENSE™ EEG monitor, (b) an embedded single-board computer with a controller (server), (c) a medical-grade personal computer with a touch-screen user interface (client), and (d) a syringe pump.

(a) The NeuroSENSE™ NS-701 Monitoring System (NeuroWave Systems Inc., Cleveland Heights, OH, USA) provides a bilateral DoH measure, WAV_{CNS} (Wavelet Analysis Value for Central Nervous System monitoring) by acquisition and processing of EEG data from sensors placed on the forehead (19). The WAV_{CNS} is a dimensionless index, ranging from 0 for an isoelectric EEG to 90–100 in fully awake subjects; values between 40 and 60 represent an appropriate range for anesthesia (20). The device has been optimized for closed-loop anesthesia with minimal time delay (21) and a linear response in the region of interest. The algorithm for deriving the WAV_{CNS} index has been published, and the index was validated in comparison with the BIS (13). NeuroSENSE™ output includes the electromyograph, signal quality, suppression ratio, and WAV_{CNS} from left and right hemispheres.

(b) The server software consists of a PID controller (described below) with integrated safety features such as automated hemisphere selection, automatic switching to fallback modes, and visual and audible alarms. These are based on real-time data that are collected (or calculated), evaluated, and then stored in an output file on the server every second. Values stored include: NeuroSENSE™ output data; heart rate, oxygen saturation and blood pressure from the patient monitor; infusion rate and error messages from the propofol pump; and predicted plasma (C_p) and effect-site (C_e) concentrations calculated by the PKPD model (22,23) based on the amount of drug infused.
(c) The client user interface displays current and trend values for propofol infusion rate, calculated C_e and the setpoint and measured WAV_{CNS}. The interface allows the anesthesiologist to input patient characteristics (gender, age, weight, and height), start/stop the infusion, modify the WAV_{CNS} setpoint, and administer additional manual bolus doses of propofol (0.25 $mg \cdot kg^{-1}$, 0.5 $mg \cdot kg^{-1}$, or 1 $mg \cdot kg^{-1}$) as required. The interface also displays a case log and safety messages.
(d) Once initiated by the anesthesiologist, an Alaris TIVA pump (CareFusion, San Diego, CA, USA), primed with propofol, is controlled automatically by the software on the server.

Following rigorous safety testing, risk analysis and usability evaluation, authorization for investigational testing (class III) of this system were received from Health Canada (application no. 168968).

Remifentanil was administered via a Graseby 3400 Anesthesia pump (Smiths Medical, Ashford, Kent, UK), which was not connected to the control system.

PID controller

The PID controller calculates the propofol infusion rate from the measured WAV_{CNS} value and setpoint defined by the anesthesiologist. The infusion rate is updated every 5 s. The controller settings used for the first 23 cases were based on models obtained from 14 manually dosed cases and were subsequently revised to be more responsive based on 14 models obtained from the initial closed-loop cases (18). In evaluating the controller performance, cases have been divided into two groups: Group 1 consists of the initial 23 cases, and a further eight cases, during which controller parameters were fine-tuned; Group 2 consists of 71 cases, in which a final set of control parameters were evaluated. Of the patient characteristics entered into the user interface, only weight was required for controller calculations; age and height were used only to calculate infusion safety boundaries, based on established PKPD models (22,23).

To reduce the pain observed with slow initial injection of propofol (24), the controller administered an initial rapid bolus of propofol. In the first 23 cases, this was achieved by initializing the derivative filter to a nonzero value. In the final controller design, a fixed dose of 25 mg was administered over 15 s. Thereafter, the infusion rate was determined by the controller, which was initially set to achieve and maintain a WAV_{CNS} setpoint of 50.

Further details of the controller design can be found in van Heusden *et al.* (18).

Study population

Ethical approval was obtained from the University of British Columbia Children's and Women's Research Ethics Board. The subject cohort comprised children aged 6–17 years, with an American Society of Anesthesiologists' physical status of I-II, within the 5th–95th percentile of weight-for-age, undergoing upper and/or lower gastrointestinal endoscopic investigations. Exclusion criteria included: any known or suspected EEG abnormality; any contraindication to the administration of lidocaine, propofol, or remifentanil; any chronic opioid analgesic or other sedative drug therapy; anticipated difficult airway, significant/uncontrolled reflux, delayed gastric emptying or other requirement for endotracheal intubation. Informed and written parental/guardian consent and assent (in subjects ≥ 7 years of age) were obtained for all subjects.

Anesthetic protocol

Upon arrival in the operating room, subject characteristics were entered into the iControl interface. NeuroSENSE™ sensors were applied to the forehead, followed by a preliminary determination of signal quality (impedance level <10 kΩ was considered acceptable) for each electrode. Standard patient monitoring devices (electrocardiogram, non-invasive blood pressure and pulse oximetry) were applied. An intravenous cannula was inserted, secured and flushed with lidocaine (0.5 $mg \cdot kg^{-1}$), with manual tourniquet application. A remifentanil bolus (0.5 $\mu g \cdot kg^{-1}$) was administered at 200 $ml \cdot h^{-1}$, followed by a continuous infusion (0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$) throughout the procedure. The closed-loop propofol infusion was initiated immediately following completion of the remifentanil bolus. Bolus doses of propofol could be administered and the setpoint adjusted at the discretion of the anesthesiologist, via the iControl user interface. Oxygen was delivered at 2 $l \cdot min^{-1}$ via nasal cannulae.

The initial 25 cases were performed by one of the authors (JMA) while subsequent cases were performed by 11 different pediatric anesthesiologists. No formal training was provided, but most users had had experience with the interface from a previous usability study.

A research assistant was present during every case to ensure the study protocol was followed, to document significant events and to record the anesthesiologist's clinical observations of the patient. Occurrence of an adverse effect was recorded if the anesthesiologist deemed it necessary to apply an airway intervention or to manually adjust the infusion.

Data analysis

Loss of eyelash reflex, insertion of mouth gag and endoscope, patient movement, and episodes of apnea were documented. Time from the end of the propofol infusion to response to verbal command and discharge from the postanesthetic care unit (PACU) were noted.

Induction of anesthesia was defined as the time between the start of the propofol infusion and the time the WAV_{CNS} first dropped below 60 and remained below 60 for at least 30 s (T_{ind}). Maintenance of anesthesia was defined as the time between T_{ind} and the end of the propofol infusion. The control system was evaluated based on various performance criteria, which included: time to complete induction of anesthesia, degree of WAV_{CNS} overshoot (percentage of time with $WAV_{CNS} < 40$) or undershoot (percentage of time with $WAV_{CNS} > 60$) in the 3 min following T_{ind}, and time during the maintenance of anesthesia with measured WAV_{CNS} within ± 10 units of the setpoint.

Furthermore, a standard set of performance measures, designed for TCI evaluation, but commonly reported for closed-loop control, were calculated for each case. The definitions and interpretations of these measures, which examine the offset of the measured WAV_{CNS} from the setpoint during the maintenance of anesthesia, can be found in Varvel *et al*. (25) and Liu *et al*. (6). Data from cases in Group 1 and Group 2 did not follow a normal distribution and have been compared using nonparametric Mann–Whitney *U* test; a Bonferroni correction was used to adjust the significance level and confidence interval (CI) limit.

Values for propofol C_p were calculated using the *Paedfusor* model (22) for children aged 6–16 years; values for propofol C_e were calculated using the *Paedfusor* PK model (22) and the corresponding PD model as identified in Coppens *et al*. (16). The *Schnider* model (23) was used to calculate both C_p and C_e for children aged 17 years.

Results

One hundred and eight patients undergoing upper and/or lower endoscopic investigations were enrolled in the study between August 2011 and September 2012. Three children were excluded prior to induction of anesthesia: in one case, failure to obtain intravenous access prompted an inhalational induction of anesthesia; in two cases, it was not possible to obtain adequate signal quality from the NeuroSENSE™ sensors. Three further cases were excluded during maintenance of anesthesia: the anesthesiologist switched the control system to TCI mode in two cases (one due to poor sensor signal quality and one due to persistent EEG artifacts); and, in one case, a pump error prompted a switch to manual infusion. Administration of propofol was closed-loop controlled during induction and maintenance of anesthesia in 102 cases (Table 1). Two representative cases are illustrated in Figure 1.

The system achieved and maintained an adequate DoH (Figure 2) with minimal intervention and tolerated manual adjustment when required. In 87/102 (85%) cases, adjustment of the propofol dose required no direct intervention from the anesthesiologist (i.e., apart from setpoint changes, see below). Bolus doses of propofol were manually administered in 6/102 (6%) cases during induction of anesthesia, totaling 0.5 $mg{\cdot}kg^{-1}$ ($n = 4$) and 1 $mg{\cdot}kg^{-1}$ ($n = 2$). Induction of anesthesia was completed in a median of 3.8 min (interquartile range (IQR) 3.1–5.0). During maintenance of anesthesia, the DoH was measured within 10 units of the WAV_{CNS} setpoint for a median of 89% (IQR 79–96) of the time. Bolus doses of propofol were manually administered in 10/102 (10%) cases during maintenance of anesthesia; these totaled 0.25 $mg{\cdot}kg^{-1}$ ($n = 1$), 0.5 $mg{\cdot}kg^{-1}$ ($n = 2$), 0.75 $mg{\cdot}kg^{-1}$ ($n = 1$), 1 $mg{\cdot}kg^{-1}$ ($n = 2$), 1.25 $mg{\cdot}kg^{-1}$ ($n = 3$), and 2 $mg{\cdot}kg^{-1}$ ($n = 1$).

Spontaneous breathing was maintained without manual intervention in 91/102 (89%) of cases; in 11 cases,

Table 1 Patient characteristics and procedures included in closed-loop controlled cases

Patient characteristics	
Gender (Female: Male)[a]	53 : 49
Age (years)[b]	12.5 (6–17)
Weight (kg)[b]	47.9 (19.3–75.0)
Height (cm)[b]	156.4 (112.0–184.8)
Endoscopic procedures	Duration (min)
Proctoscopy ($n = 1$)	5.2
Upper endoscopy ($n = 42$)[b]	14.2 (6.9–23.9)
Colonoscopy ($n = 12$)[b]	35.9 (23.7–76.7)
Upper endoscopy with colonoscopy ($n = 47$)[b]	49.3 (28.1–82.4)

[a]*n*; [b]median (range).

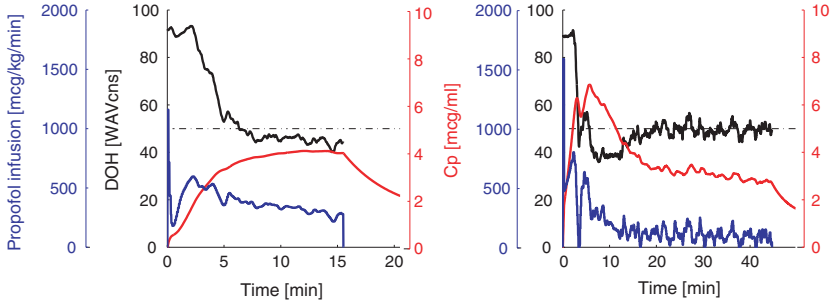

Figure 1 Two sample cases showing measured depth of hypnosis (DoH, WAV_{CNS}) (black solid line), setpoint (black-dashed line), predicted plasma concentration (C_p) (red line) and propofol infusion rate (blue line).

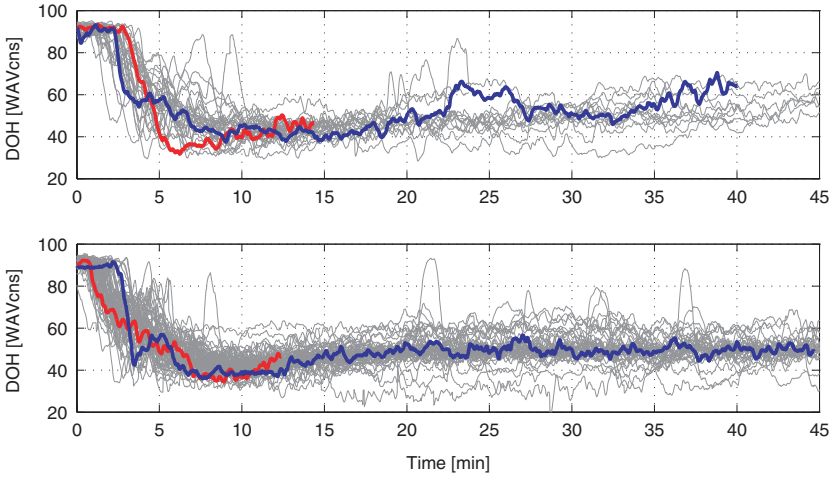

Figure 2 Depth of hypnosis (DoH, WAV_{CNS}): top graph shows Group 1 (first 23 cases with initial controller settings and eight cases during which settings were fine-tuned); bottom graph shows Group 2 (71 cases in which final control settings were evaluated); example cases have been highlighted in red (upper endoscopy) and blue (upper endoscopy with colonoscopy).

one or more interventions were required to resolve an apneic episode or airway obstruction, including application of an airway maneuver (jaw thrust or head-tilt chin-lift, $n = 9$), WAV_{CNS} setpoint increase ($n = 2$), reduction of remifentanil infusion dose (to 0.02 $\mu g \cdot kg^{-1} \cdot min$, $n = 1$), fitting of a face mask ($n = 1$), and suspending the propofol infusion (for <1 min, $n = 1$). No other adverse effects were observed.

The initial WAV_{CNS} target was set at 50 for all cases, but the setpoint was adjusted by the anesthesiologist in 42/102 (41%) cases. It was set for deeper anesthesia: to <50 but ≥ 40 in 8 cases; and to <40 in 2 cases. It was adjusted for lighter anesthesia during part of the maintenance phase (typically during colonoscopy once the ileum had been reached, and biopsies were being performed during withdrawal of the endoscope): to >50 but ≤ 60 in 29 cases; and to >60 in 5 cases. In two cases, WAV_{CNS} setpoint adjustments were made for both deeper anesthesia (to ≥ 40 but <50) and for lighter anesthesia (to >50 but ≤ 60) at different times during the procedure.

A wide variation was observed in predicted propofol C_p and C_e (Figure 3): C_p ranged from 1.8 to 8.0 $\mu g \cdot ml^{-1}$ and C_e ranged from 1.4 to 7.3 $\mu g \cdot ml^{-1}$ at T_{ind}; during maintenance of anesthesia, mean C_p ranged from 2.4 to 7.2 $\mu g \cdot ml^{-1}$ and mean C_e ranged from 2.4 to 7.1 $\mu g \cdot ml^{-1}$.

Response to verbal commands occurred at a median of 12 min (IQR 8–19) and discharge from PACU at a median of 30 min (IQR 25–38) following termination of the propofol infusion.

Controller fine-tuning resulted in a faster induction for Group 2 compared to Group 1, according to the clinical observation of eyelash reflex ($P < 0.001$, 97.5% CI 0.5–1.63 min); the defined T_{ind} showed a trend to a more rapid induction in Group 2 compared to Group 1 ($P = 0.02$, 97.5% CI −0.41–1.61 min) (Table 2).

Discussion

We have clinically evaluated a closed-loop control system, designed to administer propofol anesthesia in children undergoing endoscopic investigation. This is one of the first reported applications of closed-loop anesthesia in children. The system achieved and maintained an adequate DoH, with minimal intervention and minimal adverse effects, demonstrating that it is possible to control both induction and maintenance of anesthesia in children using a simple, fixed, robustly tuned controller.

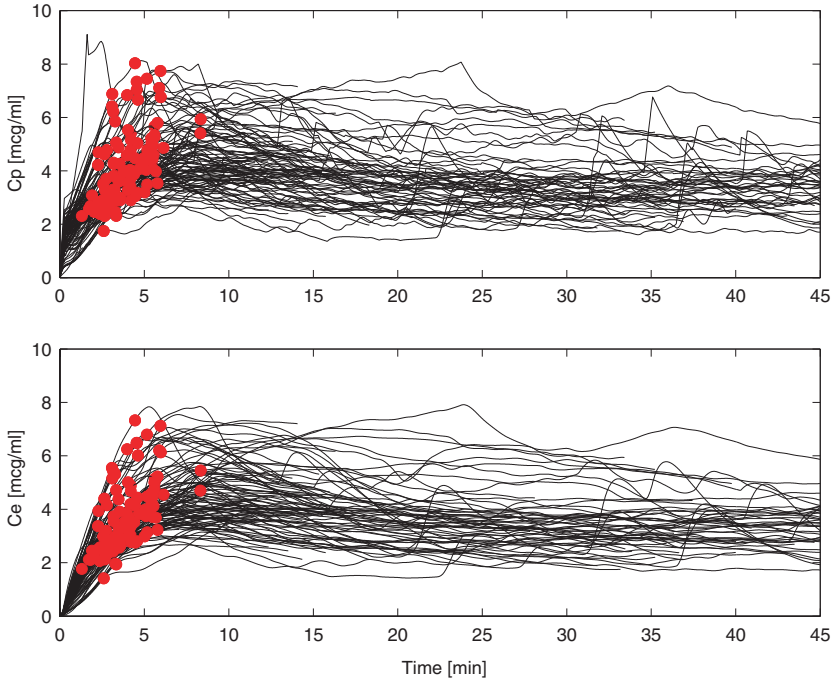

Figure 3 Variation of propofol predicted plasma concentration (C_p, top graph) and effect-site concentration (C_e, bottom graph) at T_{ind} (red dot) and throughout each case (black line); both graphs include all 102 cases.

Table 2 Achieved control performance

	Group 1 (n = 31)	Group 2 (n = 71)
Induction of anesthesia		
Time to loss of eyelash reflex (min)	3.0 (2.0–3.3)	1.9 (1.6–3.0)
Time to complete induction, T_{ind} (min)	4.2 (3.4–5.5)	3.6 (2.8–4.6)
Propofol, consumed prior to T_{ind} (mg·kg^{-1})	2.18 (1.79–2.80)	2.19 (1.77–2.98)
Propofol, predicted plasma concentration (C_p) at T_{ind} (μg·ml^{-1})	4.07 (3.12–4.83)	3.95 (3.03–4.91)
Propofol, effect-site concentration (C_e) at T_{ind} (μg·ml^{-1})	3.66 (2.78–4.28)	3.52 (2.70–4.49)
Setpoint overshoot, WAV_{CNS} <40 (%)[a]	1.7 (0–17.2)	0 (0–7.8)
Setpoint undershoot, WAV_{CNS} >60 (%)[a]	0 (0–0.6)	0 (0–6.7)
Maintenance of anesthesia		
Duration (min)	15.7 (10.3–36.5)	33.1 (10.5–48.6)
Propofol, mean utilization (μg·kg·min^{-1})	213 (169–309)	208 (164–296)
Propofol, mean predicted plasma concentration (C_p) (μg·ml^{-1})	3.80 (3.24–4.25)	3.76 (3.24–4.21)
Propofol, mean effect-site concentration (C_e) (μg·ml^{-1})	3.75 (3.20–4.28)	3.69 (3.20–4.21)
WAV_{CNS} within ±10 of setpoint (%)	85 (73–94)	89 (82–96)
Bias (MDPE)	−9.0 (−12.4 to −3.70)	−4.6 (−10.5 to −2.2)
Inaccuracy (MDAPE)	10.6 (6.2–14.0)	8.4 (5.1–12.1)
Intraindividual variability (Wobble)	5.6 (4.5–6.8)	5.2 (4.2–7.1)
Global score	20.4 (12.4–30.0)	17.0 (10.6–23.4)

Data are presented as median (interquartile range).
[a]% duration in which WAV_{CNS} exceeded stated limit during 3 min following T_{ind}.
T_{ind}, time at which WAV_{CNS} first drops below 60 and remains below 60 for at least 30 s.
MDPE (median performance error), MDAPE (median absolute performance error), Wobble and Global Score are performance measures, in which numbers closer to zero signify improved control (6,25).

Closed-loop control of intravenous anesthesia is in its infancy, partly because of concern about safety of automated systems in medical applications. Recent studies have reported improved outcomes of closed-loop control over manual control (4,6–8), but these comparisons are limited in scope and clinical applicability. Safety, robustness, and efficacy must be demonstrated before larger randomized controlled trials can evaluate impact on clinical outcomes.

The system used in this study was developed using robust control design techniques (14). Controller design must balance performance with robustness because

increased performance usually entails decreased robustness (i.e., a more aggressive controller tends to be less forgiving of uncertainty). Anesthesia contains inherent uncertainties because of inter- and intrapatient variability and unpredictable surgical stimulus. The control parameters were initially set with an emphasis on robustness (18). After evaluating performance during Group 1 cases, these parameters were optimized to improve speed of induction, minimize induction overshoot and improve response to stimulation without compromising patient safety.

The performance of the final redesigned controller (Table 2, Group 2) indicates what can be achieved with a simple robust PID controller using the same parameters for induction and maintenance of anesthesia. Previous studies have reported similar measures for closed-loop anesthesia systems that have relied on different control strategies (4–9). In most, only maintenance of anesthesia has been closed-loop controlled, while induction of anesthesia was open-loop controlled by TCI (4–6) or manually controlled (8,9). Closed-loop control for induction of anesthesia has been described with TCI as the basis for the closed-loop system (i.e., the controller adjusts the target C_e based on the measured clinical effect) (7).

Accuracy and reliability of the sensors, which should reflect the pharmacology and clinical observations of anesthetized patients, are crucial to the effective functioning of the control system. Time delays introduced by the sensor must be minimal and preferably known to provide reliable information for titration of anesthetic drugs (26). In contrast to the BIS and Entropy monitors, the NeuroSENSE™ was developed specifically for closed-loop control, providing undelayed bilateral measurements for control input (21). However, EEG monitoring of the depth of hypnosis in young children suffers from a lack of reliability (27) and NeuroSENSE™ has not yet been formally validated in children. Consequently, our study population did not include younger children (<6 years).

While the system delivered a fixed and stable measured hypnotic effect, both the predicted C_p and C_e of the infused propofol, based on population-based PKPD models (16,22,23), were widely dispersed (Table 2, Figure 3). These observations confirm the significant interpatient variability in the range of doses required for induction and maintenance of anesthesia in children. Open-loop control systems, such as TCI, rely on accurate PKPD models. The wide interpatient variability therefore makes development of universally accepted pediatric TCI systems challenging and suggests closed-loop control may be a safer and more reliable method of titrating drug doses in children. In closed-loop control, the use of feedback can overcome the limitations of an imperfect model and the unpredictable degree of surgical stimulation.

This study was limited to endoscopic investigations, which are not representative of stimulation during major surgery. Nonetheless, the selected cohort presented a challenging clinical setting. The airway was shared with the gastroenterologist without the insertion of an airway device, mandating the maintenance of spontaneous ventilation. While these procedures do not require a skin incision, the level of stimulation is highly variable, especially during initial insertion of the endoscope. The small number of subjects who required an intervention to support ventilation highlights the need to have skilled operators immediately available, despite the automation of drug administration. The risk of respiratory depression may have been reduced by slowing the speed of induction (28).

For closed-loop anesthesia during general surgery, automating the control of opioids will be essential. Feasibility studies have been reported for the dual control of propofol and remifentanil administration in adults, using either BIS (29) or Entropy (30) for DoH feedback. The clinical applicability of a control system requires that it can adjust to a range of anesthetic scenarios (e.g., inhalational induction and the administration of anesthetic drugs not controlled by the system) and is tolerant to the administration of bolus doses of drug.

In conclusion, we have developed and evaluated a robust closed-loop system for anesthesia, which controls propofol infusion based on feedback from the NeuroSENSE™ monitor. The system achieved and maintained an adequate DoH in children undergoing upper gastrointestinal endoscopy and/or colonoscopy and required minimal intervention from the anesthesiologist. We have demonstrated that closed-loop control can provide an effective mechanism for both induction and maintenance of propofol anesthesia in children and highlighted future research required before this technology can be adopted in routine clinical practice.

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References

1 Bickford RG. Automatic electroencephalographic control of general anesthesia. *Electroencephalogr Clin Neurophysiol* 1950; **2**: 93–96.

2 Linkens D. Intelligent Control in Biomedicine. London: Taylor and Francis, 1994.

3 Morley A, Derrick J, Mainland P *et al*. Closed loop control of anaesthesia: an assessment of the bispectral index as the target of control. *Anaesthesia* 2000; **55**: 953–959.

4 Struys M, De Smet T, Versichelen L *et al*. Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus 'standard practice' controlled administration. *Anesthesiology* 2001; **95**: 6–17.

5 Absalom A, Kenny G. Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery. *Br J Anaesth* 2003; **90**: 737–741.

6 Liu N, Chazot T, Genty A *et al*. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study. *Anesthesiology* 2006; **104**: 686–695.

7 De Smet T, Struys M, Neckebroek M *et al*. The accuracy and clinical feasibility of a new bayesian-based closed-loop control system for propofol administration using the bispectral index as a controlled variable. *Anesth Analg* 2008; **107**: 1200–1210.

8 Hemmerling TM, Charabati S, Zaouter C *et al*. A randomized controlled trial demonstrates that a novel closed-loop propofol system performs better hypnosis control than manual administration. *Can J Anaesth* 2010; **57**: 725–735.

9 Janda M, Simanski O, Bajorat J *et al*. Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade. *Anaesthesia* 2011; **66**: 1112–1120.

10 Dumont GA, Liu N, Petersen CL *et al*. Closed-loop administration of propofol guided by the NeuroSense: clinical evaluation using robust Proportional-Integral-Derivative design. American Anesthesiologists' Society Annual Meeting. Chicago, 2011.

11 Mackey DC. Can we finally conquer the problem of medical quality? The systems-based opportunities of data registries and medical teamwork. *Anesthesiology* 2012; **117**: 225–226.

12 Johansen JW, Sebel PS, Sigl JC. Clinical impact of hypnotic-titration guidelines based on EEG bispectral index (BIS) monitoring during routine anesthetic care. *J Clin Anesth* 2000; **12**: 433–443.

13 Zikov T, Bibian S, Dumont GA *et al*. Quantifying cortical activity during general anesthesia using wavelet analysis. *IEEE Trans Biomed Eng* 2006; **53**: 617–632.

14 Zhou K, Doyle J. Essentials of Robust Control. Upper Saddle River, NJ: Prentice Hall, 1997.

15 Dumont GA, Martinez A, Ansermino JM. Robust control of depth of anesthesia. *Int J Adapt Control Signal Process* 2009; **23**: 435–454.

16 Coppens MJ, Eleveld DJ, Proost JH *et al*. An evaluation of using population pharmacokinetic models to estimate pharmacodynamic parameters for propofol and bispectral index in children. *Anesthesiology* 2011; **115**: 83–93.

17 Liu N, Bourgeois E, Chazot T *et al*. Closed-loop administration of propofol and remifentanil guided by the Bispectral Index in patient requiring an emergency lung volume reduction. *Pediatr Anesth* 2007; **17**: 909–910.

18 van Heusden K, Dumont GA, Soltesz K *et al*. Clinical evaluation of robust PID control of propofol anesthesia in children. *IEEE Trans Control Syst Technol* 2013; in press.

19 Bibian S, Zikov T. NeuroSENSE® monitor with WAV_{CNS} cortical quantifier: a deterministic approach to EEG analysis. 2012. Available at: http://www.neurowavesystems.com/pdfs/NeuroSENSE_WhitePaper_Mar2012.pdf. Accessed 12 February, 2013.

20 Agrawal G, Bibian S, Zikov T. Recommended clinical range for WAVCNS index during general anesthesia. American Society of Anesthesiologists Annual Meeting. Atlanta, 2010.

21 Bibian S, Dumont GA, Zikov T. Dynamic behavior of BIS, M-entropy and NeuroSENSE brain function monitors. *J Clin Monit Comput* 2011; **25**: 81–87.

22 Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *Br J Anaesth* 2005; **95**: 110.

23 Absalom A, Mani V, De Smet T *et al*. Pharmacokinetic models for propofol – defining and illuminating the devil in the detail. *Br J Anaesth* 2009; **103**: 26–37.

24 Scott R, Saunders D, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–494.

25 Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinet Biopharm* 1992; **20**: 63–94.

26 Pilge S, Zanner R, Schneider G *et al*. Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices. *Anesthesiology* 2006; **104**: 488–494.

27 Constant I, Sabourdin N. The EEG signal: a window on the cortical brain activity. *Pediatr Anesth* 2012; **22**: 539–552.

28 Khosravi S, Hahn JO, Dosani M *et al*. Pharmacodynamic models of propofol in children: respiratory and EEG end-points compared. American Society of Anesthesiologists Annual Meeting, Atlanta, 2010.

29 Liu N, Chazot T, Hamada S *et al*. Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study. *Anesth Analg* 2011; **112**: 546–557.

30 Liu N, Le Guen M, Benabbes-Lambert F *et al*. Feasibility of closed-loop titration of propofol and remifentanil guided by the spectral M-Entropy monitor. *Anesthesiology* 2012; **116**: 286–295.