QUALITY AND PATIENT SAFETY

Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial

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Background. We have developed an automatic anaesthesia system for closed-loop administration of anaesthesia drugs. The control variables used were bispectral index (BIS) and Analgoscore for hypnosis and antinociception, respectively.

Methods. One hundred and eighty-six patients were randomly enrolled in two groups. Propofol, remifentanil, and rocuronium were administered using closed-loop feedback control (closed-loop, n = 93) or manually (control group, n = 93). The clinical performance of hypnosis control was determined by calculating the offset from a BIS of 45: ‘excellent’, ‘good’, ‘poor’, and ‘inadequate’ control was defined as BIS values within 10%, from 11% to 20%, from 21% to 30%, or >30% offset from the target. The clinical performance of analgesia was defined as the offset from Analgoscore values. Data presented as mean (standard deviation) (95% confidence interval).

Results. Excellent or good control of hypnosis was achieved significantly longer in the closed-loop group [47.0 (9.8%) (45.0/49.0), 34.4 (4.7%) (33.5/35.4)] than in the control group [37.3 (14.3%) (34.4/40.2) and 32.3 (7.6%) (30.7/33.7)], respectively (P = 0.0001 and 0.0085). Poor and inadequate control of hypnosis was significantly shorter in the closed-loop group [10.8 (5.0%) (9.8/11.8) and 7.7 (6.2%) (6.4/9.0)] than in the control group [14.7 (6.8%) (13.3/16.0) and 15.8 (14.7%) (12.8/18.8)], respectively (P < 0.0001). Excellent control of analgesia was achieved significantly longer in the closed-loop group [78.7 (16.2%) (75.4/82.0)] than in the control group [73.7 (17.8%) (70.1/77.3)] (P = 0.0456).

Conclusions. The closed-loop system was better at maintaining BIS and Analgoscore than manual administration.

Keywords: closed-loop systems; McSleepy

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The use of closed-loop systems in anaesthesia can improve the quality of drug delivery.1 Closed-loop systems consist of a ‘brain’—a central operating system with built-in algorithms—an ‘actuator’—a drug delivery system, such as a syringe pump. These three elements are connected by a feedback system, which allows the automated control of drug delivery in order to maintain a pre-set target value of the control variable without any manual input.2 By frequent sampling of the control variable and more frequent changes of drug delivery rates than with manually delivered anaesthesia, greater stability of the control variable may be achievable.2 The performance of a closed-loop system for anaesthesia depends on the reliability of the control variable;4 therefore, adequate target parameters must be used for each of the three components of general anaesthesia: hypnosis, analgesia, and neuromuscular block. The bispectral index (BIS) is a dimensionless number derived from processing the phase and frequency relations of the component frequencies of the EEG. It ranges from 0 (isoelectric brain activity) to 98 (consciousness). A value from 40 to 60 is considered as representing an adequate state of hypnosis.5 Numerous studies have used the BIS value as a control variable for a closed-loop system to deliver anaesthetic drugs, outperforming manual administration.3 6–8 The application of closed-loop control for opioids faces the problem of lack of
an optimal method to measure intraoperative pain when communication with the patient is impossible. A novel score (Analgoscore) using heart rate (HR) and arterial pressure was recently presented and successfully used to titrate closed-loop remifentanil administration. Monitoring neuromuscular block is easy to achieve using mechanomyography, acceleromyography, electromyography, or phonomyography; closed-loop systems for various neuromuscular blocking agents have shown good performance. The present study was designed to introduce an automated expert-based closed-loop delivery system (McSleepy) that monitors all three components of general anaesthesia throughout surgery and i.v. administers appropriate doses of the respective drugs based on the acquired data achieving a completely automated anaesthesia control of induction and maintenance. The aim of our study was to compare the performance of McSleepy in maintaining given levels of anaesthesia—hypnosis monitored via BIS, antinociception monitored via Analgoscore—with manual administration of total i.v. anaesthesia (TIVA).

**Methods**

This study was designed as a randomized controlled trial. After approval from the local Institutional Ethics Committee (McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada) and written informed consent, 186 patients age ≥18 yr undergoing elective surgery requiring general anaesthesia with an expected duration of ≥60 min were enrolled in the study (Fig. 1). Patients who had previous cranial neurosurgical procedures, neurological disorders, or who were allergic to anaesthetic study drugs were excluded. Inclusion criteria were patients undergoing elective surgery, aged 18–85 yr. Excluded were patients unable to provide informed consent, comatose patients, patients with dementia, or allergy to propofol.

McSleepy is an automated, expert-based closed-loop anaesthesia drug delivery system that integrates the three components of general anaesthesia: hypnosis, analgesia, and muscle relaxation. The BIS was used as the control variable for hypnosis in order to calculate propofol infusion rates to maintain a pre-determined target set-point. The target of BIS was set as 45. The Analgoscore, a pain score derived from HR and mean arterial pressure (MAP), was used as the control variable to titrate the effective dose of remifentanil. This score is calculated by measuring the offset percentage between the measured and target value of HR and MAP using expert-based rules. The Analgoscore scale ranges from -9 (very profound analgesia) to +9 (very superficial analgesia) in increments of 1. Neuromuscular monitoring was performed every 15 min at the adductor pollicis muscle; train-of-four (TOF) ratios were automatically computed and sent to the anaesthesia delivery system. Rocuronium was given by the system, if the type of surgery demanded surgical relaxation. In this study, the anaesthesia delivery system gave a bolus of 0.2 mg kg⁻¹ of rocuronium for every TOF ratio >25%. A lockout period of 20 min before the end of surgery was chosen, during which the system did not give any additional rocuronium but could be manually overridden; this was manually

Fig 1 Flowchart of the trial.
input into the system by the anaesthetist after feedback from the surgeon.

A BIS Vista monitor (BIS Vista™, Aspect Medical Systems, MA, USA) and a vital signs monitor (CASMED 740, CAS Medical Systems Inc., Branford, CT, USA) were used to obtain the control variables, while three standard infusion pumps (Graseby 3400, Graseby Medical, UK) served as the actuator. To close the loop, a personal computer (Gateway, 22 in, touch screen, USA) implemented the algorithm, provided the user interface, and controlled the communication between the BIS monitor, the vital signs monitor, and the syringe pumps.

McSleepy was designed with a graphical–numerical interface and was developed using LabVIEW 2010 (National Instruments, TX, USA). The graphical user interface contains colour-coded graphic and numeric elements, push buttons, charts, and a live video feed. The video feed can be placed either to show the surgical field or the patient according to different monitoring purposes. The interface requires patients' characteristics (sex, age, ASA, weight, height, type of surgery, type of anaesthesia) for set up (Fig. 2). Upon clicking the start button (Fig. 2), the system prompts the user with a popup menu to confirm the patients' input data. After confirmation, the system will proceed to the induction screen and automatically start the induction. A vertical countdown progress bar displays the elapsed time for each drug (remifentanil, propofol, rocuronium) and another, parallel, bar displays the total dose delivered. After induction, the system advances automatically to the maintenance phase.

During the maintenance period, BIS values, Analgoscore values, live video feed, and vital signs (systolic and diastolic arterial pressures, MAP, HR, peripheral oxygen saturation) are displayed in real time on the screen. The continuous infusion rates and average drug doses, and emergency bolus information are also displayed. By displaying trend charts of the drugs and monitoring variables, the system provides a detailed picture of the present and past clinical state of the patient. All variables were recorded continuously every 5 s and are written into a spreadsheet to facilitate documentation of anaesthetic records.

At the end of surgery, after discontinuation of the anaesthetic drugs, the system proceeds automatically to the emergence screen. This screen shows the extubation time and displays all the important clinical variables for extubation (total drug consumption, BIS value, and vital signs). Upon pressing the extubation button, the system automatically shuts down.

For propofol, a given dose is calculated on the basis of the following equation:

\[
\text{Dose}_{\text{prop}} = \text{previousDose}_{\text{prop}} \times K_m \times K_h
\]

where \(K_m\) is a coefficient proportional to the difference of the actual BIS to the target BIS and \(K_h\) a coefficient proportional to the difference of the mean BIS to the target BIS over the last time interval.
For remifentanil, the dose is calculated based on the following equation:

$$Dose_{remi} = \text{previousDose}_{remi} \times K_r \times K_{sr}$$

where $K_r$ is a coefficient proportional to the difference between the last and present Analgoscore values and $K_{sr}$ a coefficient that is dependent on the stage of surgery.

TIVA (propofol, remifentanil, rocuronium) was performed for all patients. Patients were randomly assigned to two groups: McSleepy group, in which the anaesthesia was induced and maintained via the automatic anaesthesia closed-loop delivery system (McSleepy, ITAG laboratory, McGill University, Montreal, Canada); or control group, in which TIVA using the same drugs was performed via standard practice by anaesthetists with significant experience of TIVA. Patients were first consented and then allocated by a research fellow (C.Z., E.A.) to one of the two groups in blocks of five using a computer-generated block randomization in pre-sealed envelopes.

After arriving in the operating theatre, two dedicated i.v. lines were inserted on all patients, one for TIVA and another for intraoperative emergency drug administration. Standard monitoring and BIS monitoring (BIS Vista™) started before anaesthesia induction until extubation. Neuromuscular monitoring started at induction and neuromuscular block was determined every 15 min (or on demand). Oxygen, 100%, was given by facial mask for pre-oxygenation before induction and oxygen 50% was provided during maintenance of anaesthesia.

The induction phase was defined as the period from the start of remifentanil administration to the end of the rocuronium induction bolus, for both groups. In both groups, the HR target and MAP target were defined based on the preoperative status of the patients by the attending anaesthetist.

In the McSleepy group, induction was performed following the flow chart (Fig. 3). Remifentanil was infused for 3 min, with a dose of 0.5 $\mu$g kg$^{-1}$ min$^{-1}$ for the first 2 min and with a dose of 0.2 $\mu$g kg$^{-1}$ min$^{-1}$ for the third minute. Remifentanil was then injected at a dose of 0.1 $\mu$g kg$^{-1}$ min$^{-1}$ for
the remainder of the induction phase. Propofol induction started 2 min after the beginning of the remifentanil infusion with a dose varying from 1.5 to 2 mg kg\(^{-1}\) depending on the patient’s ASA score and age. After the propofol induction bolus was given, the system waited for the patient’s BIS to decrease below 60 for a period of 60 s. If the BIS did not decrease below 60 in that period, the system gave a second propofol bolus of 0.5 mg kg\(^{-1}\). When the patient’s BIS decreased below 60, a rocuronium bolus of 0.6 mg kg\(^{-1}\) was given. In the McSleepy group, propofol was delivered to maintain a target BIS of 45, and remifentanil to maintain an Analgoscore target of 0 during the maintenance period. Infusion rates of propofol and remifentanil were adjusted automatically by the automated closed-loop anaesthesia system McSleepy, without giving a bolus. Rocuronium was administered automatically to maintain a TOF ratio of 0.25, if the type of surgery demanded surgical relaxation.

In the control group, drug doses during induction and induction time were manually controlled by the anaesthetist. During the maintenance period, the propofol infusion and remifentanil infusion rate were modified manually by the anaesthetist, without giving a bolus, to maintain the BIS at a target of 45, and an Analgoscore target of 0 (within the range of −3 and +3). Rocuronium was given manually to maintain a TOF ratio of 0.25, if the type of surgery demanded surgical relaxation.

In both groups, propofol and remifentanil were stopped simultaneously when the surgery was finished (immediately after skin closure). Reversal of neuromuscular block was given if necessary at the end of surgery. Fifteen minutes before the end of surgery, fentanyl 100–150 µg was given for analgesia. In patients who had had an epidural catheter inserted before operation, epidural analgesia was only used for analgesia 15 min before the completion of surgery.

The primary outcome was the clinical performance of the controller. The clinical performance of hypnosis was defined as the efficacy to maintain BIS as close to the target of 45 as possible.\(^3\) The clinical performance was defined in four categories: excellent, good, poor, and inadequate control, when the measured BIS values were within 10%, from 11% to 20%, from 21% to 30%, or >30% from the target BIS value, respectively.\(^3\) The clinical performance of analgesia was defined according to the Analgoscore values, −3 to +3 representing excellent pain control, −3 to −6 and +3 to +6 representing good pain control, and −6 to −9 and +6 to +9 representing insufficient pain control. ‘Other’ refers to periods where no score was determined since either ‘vagal-type reactions’ (decrease in HR solely, without significant change in MAP) or ‘hypovolaemia’ (increased HR solely) occurred.\(^1^1\)

As secondary outcome, the controller performance was determined using the methods of Varvel and colleagues.\(^1^6\) Performance error (PE) is defined as the difference between the real and the target values. The median PE (MDPE) is a measure of bias to describe whether the real values are either above or below the target values. The median absolute PE (MDAPE) indicates the size of errors.

Wobble measures the intra-individual variability in PE. Divergence reflects the evolution of the controller’s performance through time. In addition, we calculated the global performance index (GPI), to indicate the global performance of the controller.\(^3\)

Formulae are as follows:

\[
PE = \frac{BIS_{\text{measured}} - BIS_{\text{target}}}{BIS_{\text{target}}} \times 100
\]

\[
\text{MDPE}_i = \text{median}[\text{PE}_j, j = 1, \ldots, N_i]
\]

\[
\text{MDAPE}_i = \text{median}[[\text{PE}_j - \text{MDPE}_i], j = 1, \ldots, N_i]
\]

\[
\text{Wobble}_i = \text{median}[[\text{PE}_j - \text{MDPE}_i], j = 1, \ldots, N_i]
\]

\[
\text{GPI} = \ln(\text{excellent BIS control})^2 / (\text{MDAPE} + \text{wobble + inadequate BIS control})
\]

where \(i\) is the subject number, \(j\) the \(j\)th (a single) measurement of the observation period, and \(n\) the total number of measurements during the observation period.

Tertiary outcomes included the anaesthetic drug consumption, frequency of drug modifications, time to extubation (pre-defined as the time from discontinuation of anaesthetic drugs to tracheal extubation, initial attempt to wake up the patient by either verbal command or manual stimulation was only allowed once a BIS of 65 was reached in both groups), time of BIS values <40, <35, <30, and >60 (overshoot or undershoot of hypnosis control) during the maintenance period.

Sample size was estimated to find a difference of the mean predicted PE of 10% between the two groups, assuming a variability of 10% in each group and a power \((1 - b)\) of 90%.

Data were analysed using Excel 2007 (Microsoft Corp., Redmond, WA, USA) and XLSTAT 2011 (Addinsoft software, New York, NY, USA), presented as mean and standard deviation (95% confidence interval) for continuous data and value (proportions) for categorical data. Comparisons between the groups were performed using Student’s \(t\)-test or the Mann–Whitney \(U\)-test for continuous data and \(\chi^2\) test for categorical data. A \(P\)-value of \(<0.05\) was considered statistically significant.

**Results**

A total of 186 patients undergoing elective surgery were enrolled in the study and randomized in two groups of 93 patients each (Table 1). All of the patients completed the study.

In the McSleepy group, excellent and good control of hypnosis occurred significantly more often, while poor control and inadequate control occurred less often than in the control group (Fig. 4). In the McSleepy group, excellent
control of analgesia was achieved significantly more often
[47.0 (9.8%) (45.0/49.0), 34.4 (4.7%) (33.5/35.4)] than in the
control group [37.3 (14.3%) (34.4/40.2) and 32.3 (7.6%)
(30.7/33.7)], respectively (P, 0.0001 and 0.0085). Poor and
inadequate control of hypnosis was significantly shorter in
the closed-loop group [10.8 (5.0%) (9.8/11.8) and 7.7
(6.2%) (6.4/9.0)] than in the control group [14.7 (6.8%)
(13.3/16.0) and 15.8 (14.7%) (12.8/18.8)], respectively
(P<0.0001). Excellent control of analgesia was achieved sig-
ificantly longer in the closed-loop group [78.7 (16.2%) (75.4/
82.0)] than in the control group [73.7 (17.8%) (70.1/77.3)]
(P=0.0456). Similar clinical performance was achieved for
both groups for good and insufficient control of analgesia
(Fig. 5).

MDPE, MDAPE, and GPI of hypnosis were significantly
better in the McSleepy group. All other Varvel parameters
were similar in both groups (Table 2). A total dose of 1.1
(0.5) (1.0/1.2) mg kg⁻¹ of rocuronium was given in the
McSleepy group, similar to the rocuronium total dose of 1.1
(0.6) (1.0/1.2) mg kg⁻¹ in the control group. In the McSleepy
group, there were significantly more changes of propofol and
remifentanil infusion rates per hour than in the control group
(Table 3). Time to extubation was significantly shorter in the
McSleepy group (Table 3).

Overshoot and undershoot of the BIS target occurred sig-
nificantly more often in the control group (Table 4).

Discussion
Our study demonstrates that the automated administration
of propofol, remifentanil, and rocuronium is feasible and
capable of maintaining a target BIS value and target value
of Analgoscore. The McSleepy closed-loop system showed
better control of hypnosis and antinociception, shorter
periods of over- or undershoot of hypnosis, and also faster
extubation times than manually administered anaesthesia.
We defined four clinical performance attributes of hypnosis
control depending on the offset of the actual BIS value
from the target BIS.³ Previous studies¹⁵ ¹⁶ assessed the per-
formance of the controller as the percentage of time that the
BIS was in the 40–60 range, which is similar to the percent-
age of time when the BIS is within ±20% of the target value
of Analgoscore ranging from −9 to 6 or 6 to 9; ‘Other’ refers to periods where no score was determined.

Data are presented as mean (SD). *P<0.05, Mann–Whitney
U-test.
MDAPE, and GPI values in the McSleepy group for control of hypnosis. The MDPE is a signed value which represents the direction (undershoot or overshoot) of the PE. In the McSleepy group, we found an MDPE of \(-5.9\% (4.3\%)\) \((-6.8/5.0\) for the BIS controller indicating that the median BIS was 5.9\% below the target, and an MDAPE of \(11.0\% (2.6\%)\) (10.5/11.5), indicating that 50\% of the measured BIS were within 11.0\% of the target BIS. The performance parameters of our study are similar to those obtained in the study of Liu and colleagues: \(15\) (MDPE = \(-6.9\%\); MDAPE = 11.4\%, Wobble = 8.7\%). However, so far, no defined limits of these parameters exist for automated delivery systems. Liu and colleagues\(^6\) have demonstrated that MDPE, MDAPE, and wobble values may mislead the interpretation of the system evaluation, if taken alone. Therefore, we calculated a score that integrates performance parameters, the GPI, that is inversely proportional to the MDAPE, wobble, and the percentage of time of inadequate control, a high GPI indicating a better performance.\(^3\)

While the closed-loop administration of propofol to control BIS has been validated by several studies,\(^36-81\) the choice of the controlled variable for the closed-loop infusion of opioids is still debated. However, haemodynamic variables are most often studied to titrate opioid infusions.\(^9-11\)  

Table 2  Controller performance. *Significant difference at 0.05 level (two-tailed). Data are presented as mean (σ) (95% confidence interval), analysed with Student’s t-test and the Mann–Whitney U-test for parametric and non-parametric continuous data using XLSTAT 2011. MDPE, median performance error; MDAPE, median absolute performance error; GPI, global performance index

<table>
<thead>
<tr>
<th></th>
<th>McSleepy group (n=93)</th>
<th>Control group (n=93)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS MDPE (%)</td>
<td>(-5.9 (4.3) ((\pm)6.8/(\pm)5))</td>
<td>(-10.8 (11.9) ((\pm)13.3/(\pm)8.4))</td>
<td>(0.0003^*)</td>
</tr>
<tr>
<td>BIS MDAPE (%)</td>
<td>(11.0 (2.6) (10.5/11.5))</td>
<td>(15.4 (10.4) (13.3/17.5))</td>
<td>(0.0001^*)</td>
</tr>
<tr>
<td>BIS Wobble (%)</td>
<td>(9.0 (2.5) (8.5/9.5))</td>
<td>(9.4 (4.4) (8.5/10.3))</td>
<td>(0.4261)</td>
</tr>
<tr>
<td>BIS Divergence (% min(^{-1}))</td>
<td>(-0.06 (0.10) ((\pm)0.08/(\pm)0.04))</td>
<td>(-0.07 (0.17) ((\pm)0.11/(\pm)0.04))</td>
<td>(0.3658)</td>
</tr>
<tr>
<td>GPI</td>
<td>(4.4 (0.8) (4.2/4.6))</td>
<td>(3.5 (1.6) (3.2/3.8))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>Analgometer MDPE (%)</td>
<td>(0.3 (1.4) (0.0/0.6))</td>
<td>(0.4 (1.6) (0.0/0.7))</td>
<td>(0.5909)</td>
</tr>
<tr>
<td>Analgometer MDAPE (%)</td>
<td>(1.7 (0.9) (1.5/1.8))</td>
<td>(1.8 (1.0) (1.6/2.0))</td>
<td>(0.2088)</td>
</tr>
<tr>
<td>Analgometer Wobble (%)</td>
<td>(1.4 (0.6) (1.3/1.5))</td>
<td>(1.3 (0.6) (1.2/1.4))</td>
<td>(0.4536)</td>
</tr>
<tr>
<td>Analgometer Divergence (% min(^{-1}))</td>
<td>(-0.10 (0.20) ((\pm)0.14/(\pm)0.06))</td>
<td>(-0.98 (7.45) ((\pm)2.53/0.57))</td>
<td>(0.2810)</td>
</tr>
<tr>
<td>GPI</td>
<td>(7.2 (1.1) (6.9/7.4))</td>
<td>(7.2 (1.0) (7.0/7.4))</td>
<td>(0.2822)</td>
</tr>
</tbody>
</table>

Table 3  Dose and modifications of drugs and extubation time. *Significant difference at 0.05 level (two-tailed). Data are presented as mean (σ) (95% confidence interval), analysed using the Mann–Whitney U-test

<table>
<thead>
<tr>
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<th>Control group (n=93)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean propofol dose (μg kg(^{-1}) min(^{-1}))</td>
<td>(115 (30) (109/121))</td>
<td>(108 (25) (103/113))</td>
<td>(0.0801)</td>
</tr>
<tr>
<td>Modifications of propofol doses (times h(^{-1}))</td>
<td>(67 (18) (63/71))</td>
<td>(6 (8) (4/8))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>Mean remifentanil dose (μg kg(^{-1}) min(^{-1}))</td>
<td>(0.21 (0.11) (0.19/0.24))</td>
<td>(0.19 (0.09) (0.17/0.20))</td>
<td>(0.0742)</td>
</tr>
<tr>
<td>Modifications of remifentanil doses (times h(^{-1}))</td>
<td>(28 (8) (26/29))</td>
<td>(4 (5) (3/5))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>Total rocuronium dose (mg kg(^{-1}))</td>
<td>(1.1 (0.5) (1.0/1.2))</td>
<td>(1.1 (0.6) (1.0/1.2))</td>
<td>(0.6230)</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>(10.1 (4.7) (9.2/11.1))</td>
<td>(13.7 (8.8) (11.9/15.4))</td>
<td>(0.0013^*)</td>
</tr>
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Table 4  Overshoot or undershoot of BIS values (% time of maintenance period). *Significant difference at 0.05 level (two-tailed). Data are presented as mean (σ) (95% confidence interval), analysed using the Mann–Whitney U-test

<table>
<thead>
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<th>Control group (n=93)</th>
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<tbody>
<tr>
<td>BIS &lt; 40 (%)</td>
<td>(30.1 (12.1) (27.6/32.6))</td>
<td>(41.2 (17.8) (37.6/44.8))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>BIS &lt; 35 (%)</td>
<td>(10.6 (8.5) (8.9/12.3))</td>
<td>(20.5 (14.7) (17.5/23.5))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>BIS &lt; 30 (%)</td>
<td>(3.3 (4.8) (2.3/4.3))</td>
<td>(7.5 (8.2) (5.9/9.2))</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>BIS &gt; 60 (%)</td>
<td>(1.9 (2.1) (1.5/2.3))</td>
<td>(3.4 (4.5) (2.5/4.3))</td>
<td>(0.0051^*)</td>
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A study of three patients undergoing general surgery where the infusion rate of alfentanil was automatically controlled using MAP only did not show any controller performance results.\textsuperscript{9} A fuzzy logic controller study of MAP and HR adjusting alfentanil infusion rates during surgery in eight patients calculated that during 90% of the total anaesthesia time, MAP stayed within 15% of an individualized MAP target.\textsuperscript{10} There are no studies of a remifentanil closed-loop system based on haemodynamic parameters. We used a novel score as a control for remifentanil infusion. The Analgoscore is a measure of intraoperative nociception, which reflects a common practice of anaesthetists who interpret intraoperative arterial pressure and HR changes as variables indicating surgical pain\textsuperscript{17–19} and use them to titrate the infusion of remifentanil. In the McSleepy group, control of analgesia was better than in the control group. Our results are similar to those obtained in a previous study from our group\textsuperscript{11} (sum of excellent and good control time $\approx 98.7\%$), in which the Analgoscore was used to titrate remifentanil closed-loop infusion, while hypnotics and neuromuscular blocking agents were administered manually.

The extubation time in the McSleepy group was 10.1 min, $\sim 3.5\text{ min}$ faster than in the control group. This result is similar to what we found in a previous study using BIS to guide propofol closed-loop administration.\textsuperscript{3} However, even following strict extubation criteria, the assessment of readiness for extubation remains subjective and differences should not be overestimated.

There are several limitations of our study. This was not a strictly double-blind study since the anaesthetist in charge of the patient was aware of the group assignment. However, the data analysis was done by a research assistant unaware of the group assignment. It is possible that the performance of the manual group was better than normal by focusing more on maintaining the pre-set targets for Analgoscore and BIS than would be done in standard practice (Hawthorne effect). Although great care was taken to standardize the protocol for determining extubation times (initial attempt to establish a wake-up reaction depending on a given BIS target of 65), subjective factors cannot be excluded to have influenced the extubation times. Another limitation of the study—shared with other studies in the same field—is the fact that BIS is only an indirect measure of hypnotosis; although widely used in clinical practice and research, its significance as a parameter for hypnosis has its limits. Furthermore, there still is no reliable measure for intraoperative pain. However, most anaesthetists use haemodynamic values as surrogate variables for pain assessment when communication with the patient is not possible. Based on this clinical experience, the Analgoscore was created. It is important to note that the focus of this study was not the validity of either BIS or Analgoscore but the performance of the control of these parameters as targets in both groups. It is also important to assess the clinical significance of the results. From a pure control perspective, McSleepy achieves maintenance of BIS and Analgoscore at a given target for significantly longer periods. Most clinicians would agree that a BIS of 45 or 50 does not make any difference in the form of patient care. In addition, a difference of wake-up time of 4–5 min might not be clinically significant after a 2 h surgery. However, the significantly lower percentage of times in the McSleepy group when BIS is above 60 might help to reduce the risk of awareness and the significantly lower percentage of times when BIS is below 40 or 30 might even have an impact on morbidity or mortality after surgery,\textsuperscript{20–22} although we are well aware that there are not yet enough studies for a definite recommendation.

The authors believe that closed-loop systems, including McSleepy, should only be used in the presence of an anaesthetist. They are, in principal, not just advisory systems (as decision-support systems are) but automated systems whose correct functioning, however, should always be supervised by an anaesthetist. McSleepy has been designed with a conscious effort to allow manual overriding with the quick touch of a button and a user interface which provides the anaesthetist with as much information necessary—and in an easy-to-interpret manner—as to allow constant, but accessible, plausibility control of its functioning. As such, it is designed to aid the anaesthesiologist during general anaesthesia by allowing autonomous delivery of general anaesthesia, continuous communication between the delivery system and the user, and an extensive option for manual input and manual delivery via the system at the tip of a touch button.

In conclusion, we present, to the best of our knowledge, a first automated anaesthesia delivery system of all three anaesthetic components controlled using three different control parameters, which performs better than manual control.

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Declaration of interest

T.M.H. is the patent holder for McSleepy.

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