A Multicenter Evaluation of a Closed-Loop Anesthesia Delivery System: A Randomized Controlled Trial

Goverdhan D. Puri, MD, PhD,* Preethy J. Mathew, MD,* Indranil Biswas, MD,* Amitabh Dutta, MD,† Jayashree Sood, PGDHHM, FFRCS, MD, MBBS, FICA,† Satinder Gombar, MD,‡ Sanjeev Palta, MD,‡ Morup Tsering, MD,§ P. L. Gautam, MD,∥ Aveek Jayant, MD, DM,* Inderjeet Arora, MSc,* Vishal Bajaj, MD,¶ T. S. Punia, MD,¶ and Gurjit Singh, MSc#

BACKGROUND: Closed-loop systems for anesthesia delivery have been shown to outperform traditional manual control in different clinical settings. The present trial was aimed at evaluating the feasibility and efficacy of Bispectral Index (BIS™)-guided closed-loop anesthesia delivery system (CLADS) in comparison with manual control across multiple centers in India.

METHODS: Adult patients scheduled for major surgical procedures of an expected duration of 1 to 3 hours were randomized across 6 sites into 2 groups: a CLADS group and a manual group. In the manual control group, propofol infusion was titrated manually by the attending anesthesiologist to a BIS of 50 during induction and maintenance. Analgesia was maintained with fentanyl infusion and nitrous oxide in both groups. In the CLADS group, both induction and maintenance of anesthesia were performed automatically using CLADS. The primary outcome measure was the performance of the system as assessed by the percentage of total anesthesia time BIS remained ±10 of target BIS. The secondary outcome measures were a percentage of anesthetic-time heart rate and mean arterial pressure within 25% of the baseline, median absolute performance error, wobble, and global score. Wobble indicates intra-individual variability in the control of BIS, and global score reflects the overall performance; lower values indicate superior performance for both parameters. The performance parameters of the system also were compared among the participating sites.

RESULTS: Two hundred forty-two patients were randomized. BIS was maintained within ±10 of target for significantly longer time in the CLADS group (81.4% ± 8.9% of anesthesia duration) than in the manual group (55.34% ± 25%, P < 0.0001). The indices that assess performance were significantly better in the CLADS group than the manual group as follows: median absolute performance error was 10 (10, 12) (median [interquartile range]) in the CLADS group versus 18 (14, 24) in the manual group, P < 0.0001; wobble was 9 (8, 10) in CLADS group versus 10 (8, 14) in the manual group, P = 0.0009; and Global score, which reflects overall performance, was 24 (19, 30) in the CLADS group versus 51 (31, 99) in the manual group, P < 0.0001. The percentage of time heart rate was within 25% of the baseline was significantly greater in the CLADS group (heart rate of 95 [87, 99], median [interquartile range], in the CLADS group versus 90 [75, 98] in the manual group P = 0.0031). On comparison of data between the centers, the performance parameters did not differ significantly among the centers in the CLADS group (P = 0.94), but the parameters differed significantly among the centers in the manual group (P < 0.001).

CONCLUSIONS: Our study in a multicenter setting proves the consistently better performance of automated anesthesia drug delivery compared with conventional manual control. This highlights an important advantage of an automated system for delivering standardized anesthesia, thereby overcoming differences in practices among anesthesiologists. (Anesth Analg 2015;XXX:00–00)
the chosen target value specified by the user; (4) an actuator (the infusion pump driving drug administration); and (5) a controller to manage the actuator, which comprises an algorithm for translating a measured value of the controlled variable to a particular action in order for the actuator to steer the controlled variable closer to the target value.

The controlled variable of a closed-loop system depends upon the parameter it is intended to control. Closed-loop-guided hemodynamic controllers mainly use mean arterial pressure (MAP) as the controlled variable. However, the variable of interest for an anesthesiologist would be to control the depth of hypnosis. The most widely reported hypnotic depth entity used as a controlled variable in closed-loop systems is the Bispectral Index (BISM®; Covidien Ltd., Dublin, Ireland). The other electroencephalogram–derived variables, such as M-Entropy and NeuroSense monitors, also have been used successfully for the automated administration of propofol.

Closed-loop anesthesia delivery system (CLADS) is a locally developed BIS–guided, closed-loop anesthesia delivery system. It has been used successfully for automated administration of propofol in various situations, such as noncardiac surgery, cardiac surgery, postoperative sedation, and high-altitude surgery. However, all these previous investigations were single-center studies. CLADS has never been evaluated in a multicenter setting. Therefore, we realized the importance of testing this automated system in the setting of a controlled study involving multiple operators in their native/natural work environment.

The present trial was designed to evaluate the feasibility and efficacy of CLADS compared with manual control across multiple centers. We hypothesized that CLADS could maintain BIS within the target range during the intraoperative period for significantly longer than manual control, without adversely affecting hemodynamics or prolonging time of awakening and extubation.

METHODS
The study was conducted in 6 centers from January 2010 to September 2012. Five were tertiary care teaching hospitals, and 1 was a referral hospital in northern India. Approval was obtained from the respective ethics committees of the participating institutions (Appendix 1) before recruitment of participants in each site, and the trial was registered with Clinical Trial Registry of India (CTRI/2010/091/00041). The full trial protocol can be accessed at www.ctri.nic.in. Written, informed consent was obtained from each individual patient before enrolment.

This was a stratified randomized, patient-blinded, 2-arm parallel group, active-controlled trial. Adult patients of either sex ages 18 to 60 years without previous significant cardiorespiratory illness and scheduled for nonthoracic/nonsurgical/non-neurosurgical procedure of expected duration of 1 to 3 hours under general anesthesia without combined regional anesthesia were included for study. At least 40 patients were randomized from each site. Patients weighing <70% or >130% of ideal bodyweight, those with pacemakers, those with neurologic disorders, and those taking psychoactive drugs, including alcohol, were excluded from the study. Patients were allocated randomly to 1 of 2 groups—the manual group and the CLADS group—using computer-generated random numbers in sequentially numbered, sealed, opaque envelopes stratified by center. The random allocation sequence was generated centrally and handed over to the principal investigators of individual centers in sealed, opaque envelopes. These investigators enrolled and assigned participants to the allocated group.

Automated Controller
CLADS is a patented (502/DEL/2003) closed-loop propofol delivery system that uses BIS as the controlled variable and a standard infusion pump as the actuator. The basic control algorithm has been described in previous publications. The “control algorithm” is based on the relation between various rates of propofol infusion (producing different plasma concentrations) and BIS, taking into consideration the pharmacokinetic variables (distribution, clearance) established in the developmental stage of CLADS. The algorithm alters the rate of propofol infusion to steer and maintain BIS to the set target. It takes into account existing BIS, time elapsed since the initiation of infusion, pharmacokinetics, the time-delay factor between sensing and averaging of BIS data, the time-delay factor between the change in infusion rate and the actual change in the plasma concentration of propofol, and the peak effect of propofol. A personal computer was used to implement the control algorithm, provide a user interface, and control communication through serial ports (RS 232) with the infusion system (Pilot-C, Fresenius, Paris, France) and the vital sign monitor (AS5, Datex Ohmeda Division, GE Healthcare, Singapore).

CLADS can be operated in 2 different modes: manual and automatic. In the manual mode, the rate of propofol infusion is controlled manually to modify the weight-adjusted infusion through the keyboard. In the automatic mode, the algorithm regulates the rate of propofol infusion according to pharmacokinetic and pharmacodynamic model based on BIS feedback obtained continuously. The system updates the electroencephalographic data every 5 seconds and calculates the BIS error (Target BIS – Actual BIS). It uses a proportional integral differential algorithm based on this error to make the changes in propofol infusion rate every 30 seconds to achieve target BIS.

The automatic mode has 3 options: (1) induction, (2) maintenance, and (3) induction combined with maintenance. The algorithm fine-tunes the rate and duration of propofol delivery differently during induction and the maintenance phases of anesthesia delivery. During induction, the controller tries to achieve the target concentration in a stepwise fashion (while continuously receiving feedback of BIS every 5 seconds) and tries to achieve target BIS on the basis of the relation between plasma concentrations and BIS. During maintenance, 30 seconds is considered 1 epoch. The first and last 3 BIS values of each epoch are averaged and compared with determine the trend. When the trends indicate an increasing BIS, greater target concentrations, and thus greater rates of propofol, are set, and vice versa if the trends indicate a decreasing BIS. These trends are also cross-checked with larger epoch trends before making drug alterations.

The user can limit the maximal allowable rate of drug infusion and thereby the achievable calculated concentrations at induction and maintenance of anesthesia by
choosing the risk status of the patient as low-risk (ASA physical status I–III), high-risk (ASA III–IV, New York Heart Association class 2–3), and very high-risk (ASA IV–V, New York Heart Association III–IV). The algorithm alters the maximal plasma concentration targeted as well as the time period over which this concentration is achieved according to the risk status chosen by the user.

A safety feature incorporated in the current version stops the propofol infusion rate automatically whenever hemodynamics go below the safety limits set by the operator. The controller uses default values of heart rate 60/min and MAP 70 mmHg when the user does not set these safety limits. The propofol infusion would restart automatically when hemodynamics improve to values above the predefined lower limit. The time delay for this automatic cutoff is, at the most, 10 seconds—the interval at which the vitals are updated in the controller.

The system can also function in “Monitor” mode, where it only updates BIS and other patient data and provides a graphic display of current and trend values. The data recorded in the study were heart rate, noninvasive MAP, saturation of peripheral oxygen, end-tidal CO₂, BIS values, Signal Quality Index, electromyography activity, and suppression ratio. The sampling frequency of BIS was every 5 seconds.

Anesthesia Protocol

All patients received lorazepam 1 to 2 mg orally on the morning of surgery. Noninvasive arterial blood pressure, heart rate, and oxygen saturation were recorded every 1 minute during induction of anesthesia and every 5 minutes thereafter. In the manual control group, the propofol infusion was titrated manually by the attending anesthesiologist to a BIS of 50 during induction and also subsequently during maintenance. In the CLADS group, BIS was used as the controlled variable as well as the feedback for propofol administration rate. A BIS value of 50 was used as the set target point for induction and maintenance of anesthesia. Patients received 2 μg/kg IV fentanyl 3 minutes before induction, followed by infusion at 1 μg/kg/h until after skin closure. After induction, endotracheal intubation was facilitated with 0.1 mg/kg vecuronium and patients’ lungs were ventilated mechanically with nitrous oxide: oxygen mixture with 0.4 fraction of inspired oxygen throughout the procedure. A continuous infusion of the vecuronium at the rate of 50 μg/kg/h was initiated to maintain the neuromuscular block and titrated according to train-of-four response by the user in both groups.

During episodes when the MAP or heart rate exceeded 25% of the baseline, analgesia was supplemented with 0.5 μg/kg bolus of fentanyl after excluding hypovolemia and hypercarbia. If hypertension or tachycardia persisted with a BIS of <50, nitroglycerine infusion was administered to control blood pressure and esmolol to control heart rate, depending upon the clinical situation. In situations of hypotension (MAP <25% of baseline), inotropic support and/or vasopressor was initiated after ensuring normovolemia. Similarly, atropine sulfate was used to treat bradycardia (heart rate <45 bpm) after excluding other treatable causes.

At the end of procedure, propofol delivery was stopped 5 to 10 minutes before the expected end of surgery in the CLADS as well as the manual group. This was followed by reversal of neuromuscular blockade and extubation of the trachea. The patients were transferred to a postanesthesia care unit after regaining consciousness. Patients were asked about their recall of any events in the intraoperative period before discharge from the post anesthesia care unit.

The induction time (the time required to achieve target BIS after start of infusion), induction dose, minimal BIS within 1 minute of induction and total dose of propofol, mean duration of closed-loop or manual control, mean time interval between the end of closed-loop control (or the end of propofol infusion in manual control), ability to obey commands, and tracheal extubation were noted. Anesthesiologists involved in the study were conversant with the use of BIS monitor and had undergone pre-enrolment training at the host site in the use of CLADS.

Statistical Analysis

Physiologic data are presented as median (interquartile range). “CLADS time” is the total duration of time from induction to end of procedure during which the controller or anesthesiologist controlled the propofol delivery to achieve the target BIS. The time periods in which the closed-loop system (or BIS feedback in manual group) did not work properly, as the result of poor Signal Quality Index (<15) or interference from cautery, were subtracted from total control time required to obtain “valid CLADS time.” Invalid CLADS time was also computed by subtracting the valid CLADS time from the total CLADS time.

The primary outcome measure was the performance of the system as assessed by the percentage of total valid CLADS time (i.e., total anesthesia time) during which BIS remained within 10 of target BIS (50). Median absolute performance error (MDAPE), wobble,14 and global score (an overall performance assessment parameter that incorporates MDAPE) were secondary outcome measures (Appendix 2). The lower the global score, the better the control it indicates, meaning there was less absolute performance error and wandering and a longer maintenance of BIS value within the target range. The other secondary outcome measure studied was hemodynamic performance during anesthesia as assessed by the percentage of anesthesia time during which heart rate and MAP were within 25% of the baseline.

The data were coded for each site for analysis, and the data analyst blinded to the study groups as well as to site location. The analysis compared the CLADS group and the manual control group as well as the performances at each site. The normality of data for each variable of every group was checked visually by using Q–Q plot. Many were not normally distributed. Therefore, individual parameters were compared between the groups using Mann-Whitney U test. Parameters within a single group were compared between the sites using Kruskal-Wallis test followed by Mann-Whitney U test between individual sites. All the analyses were performed with SPSS v 16.0 for windows (SPSS Inc., Chicago, IL).

The previous study of CLADS in noncardiac surgery demonstrated that traditional manual control can maintain BIS within ±10 of target for an average of 70% of anesthesia.
time with a standard deviation of 14.3. To assess a 20% improvement of this parameter (BIS within ±10 of target) using CLADS over manual control with 80% power and α error of 5%, a sample size of 34 patients was calculated. An inadvertent data attrition of 20% was anticipated and, therefore, a minimum of 40 patients per center was estimated as sample size.

**RESULTS**

All the 242 patients completed the allocated interventions successfully (Fig. 1). Demographic characteristics and surgical factors were similar within the 2 groups (Table 1). All the randomized patients belonged to the “low-risk” group as categorized for CLADS.

On comparing the 2 groups based on data collected from all the centers, we found the following: (1) Induction was achieved with significantly smaller dose of propofol in the CLADS group than in the manual group (Table 2). (2) The overshoot of BIS during induction was significantly less in the CLADS group; however, induction time was significantly longer in the CLADS group (Table 2). (3) BIS was maintained within ±10 of target for significantly longer time in the CLADS group than in the manual group (Table 3). Other performance parameters, such as MDAPE, wobble, and global score were significantly lower in the CLADS group reflecting better performance (Table 3). (4) Hemodynamic stability, as indicated by percentage of time heart rate and MAP, within 25% of the baseline, was better in CLADS group (Table 3). (5) Recovery parameters were comparable between the 2 groups (Table 3). The median BIS at various time points during anesthesia in the 2 groups from all centers is depicted in Figure 2, A and B.

Fentanyl consumption was similar in both groups (Table 3). In the CLADS group, the controller stopped the propofol infusion a total of 54 times during 40 anesthetics for 121 patients. The median (interquartile range) duration of interruption was 120 seconds (60–180 seconds). These interruptions occurred mostly during the peri-induction period. Most of the hemodynamic disturbances were transient and resolved either spontaneously or in response to a fluid bolus. A vasopressor bolus was used in one patient, and an injection of atropine was administered in another. In the manual group, nitroglycerine infusion was used in 1 patient for hypertension. The manual group required a median of 10.5 alterations per hour (interquartile range 6.7–17.8) in propofol delivery by the attending anesthesiologist, compared with none in the CLADS group. One patient from the manual group reported awareness after the procedure. The wobble was high (16) for this patient, and duration of BIS >60 was 72.85% of the CLADS time.

On comparison of the performance between centers, the CLADS group showed similar values over the percentage of time BIS was maintained within ±10 of target, MDAPE, and global score (Table 4). However, there was significant
difference between centers regarding the induction dose of propofol required to achieve a BIS of 50 and the induction time ($P < 0.001$ for induction dose and $P = 0.03$ for induction time). Post hoc analysis revealed that the induction dose and time were significantly different at site V, which was the high-altitude center, compared with all other centers. On analyzing the data after excluding the high-altitude center, there was no significant difference between the remaining 5 participating centers ($P = 0.20$ for induction dose and $P = 0.25$ for induction time). In manual group, significant variability was noted between the centers regarding all these performance parameters and induction dose and time of propofol (Table 4, all $P < 0.027$, Kruskal-Wallis test). There was variability between the centers in BIS overshoot during induction, as well as in time from reversal to tracheal extubation in the manual group, whereas, in the CLADS group, there was no significant variability (Table 4). Post hoc analysis did not reveal any particular pattern of center performance.

**DISCUSSION**

This trial was undertaken to establish the efficacy of an automated propofol system for induction and maintenance of anesthesia when used by multiple operators across different centers and to compare its performance with manual control during fentanyl-nitrous oxide analgesia. The findings prove the superior performance of CLADS compared with the conventional manual control of anesthesia in the various settings included in this multicenter, randomized, controlled trial. The wide variability of the performance parameters, such as BIS within ±10 of target, MDAPE, and global score in the manual group between sites was an unexpected finding.

It is well known that pharmacokinetics and pharmacodynamics, including the response to propofol, differ among individual patients. Conventionally, the anesthesiologist blends his/her understanding of these factors, along with clinical cues from the patient, to decide which anesthetic to deliver. The human factors involved in this decision-making process are also subject to interindividual variations. In contrast, closed-loop control responds to every minute changes in BIS and trends in changes of BIS with fine and accurate patient-individualized titration of drug dosages. Thus, controlling the depth of hypnosis based on pharmacodynamic feedback helps to overcome interindividual differences and results in a more consistent attainment and maintenance of

---

**Table 1. Demographic and Surgical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CLADS group ($N = 121$)</th>
<th>Manual group ($N = 121$)</th>
<th>$P$</th>
<th>WMWodds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41 ± 13</td>
<td>42 ± 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>38:83</td>
<td>41:80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 ± 8</td>
<td>158 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 ± 14</td>
<td>62 ± 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLADS time (min)</td>
<td>75 (56, 106)</td>
<td>80 (56, 106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid CLADS time (min)</td>
<td>69 (49,92)</td>
<td>65 (49, 95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invalid CLADS time (min)</td>
<td>8 (4, 12.5)</td>
<td>7 (4, 10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of surgery: abdominal/otolaryngology/peripheral</td>
<td>93/5/23</td>
<td>86/7/28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as (mean ± SD) except for CLADS time and valid CLADS time expressed as median (interquartile range) and type of surgery as absolute numbers.

CLADS = closed-loop anesthesia delivery system.

---

**Table 2. Induction Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CLADS group ($N = 121$)</th>
<th>Manual group ($N = 121$)</th>
<th>$P$</th>
<th>WMWodds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol induction dose (mg/kg)</td>
<td>1.4 (1.2, 1.8)</td>
<td>1.8 (1.6, 2.2)</td>
<td>&lt;0.0001*</td>
<td>2.71</td>
</tr>
<tr>
<td>Induction time (seconds)</td>
<td>160 (125, 213)</td>
<td>105 (55, 150)</td>
<td>&lt;0.0001*</td>
<td>2.39</td>
</tr>
<tr>
<td>Minimal BIS at induction</td>
<td>42 (37, 47)</td>
<td>37 (30, 43)</td>
<td>0.0003*</td>
<td>1.74</td>
</tr>
<tr>
<td>Maximal BIS after intubation</td>
<td>62 (57, 68)</td>
<td>62 (51, 70)</td>
<td>0.5577</td>
<td>1.51</td>
</tr>
<tr>
<td>Minimal MAP during induction</td>
<td>90 (76, 96)</td>
<td>89 (78, 100)</td>
<td>0.6059</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Values in median (interquartile range).

CLADS = closed-loop anesthesia delivery system; WMWodds = Wilcoxon Mann-Whitney odds measure; BIS = Bispectral Index; MAP = mean arterial pressure.

* $P < 0.05$, Mann-Whitney $U$ test.

---

**Table 3. Performance Characteristics, Recovery Parameters, and Hemodynamic Stability**

<table>
<thead>
<tr>
<th></th>
<th>CLADS group ($N = 121$)</th>
<th>Manual group ($N = 121$)</th>
<th>$P$</th>
<th>WMWodds</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time BIS within ±10 of target BIS</td>
<td>82 (76, 89)</td>
<td>61 (41, 74)</td>
<td>&lt;0.0001*</td>
<td>5.15</td>
</tr>
<tr>
<td>% of time BIS &gt;60</td>
<td>10.28 (6.17, 16.536)</td>
<td>15.66 (4.589, 33.685)</td>
<td>0.0049*</td>
<td>1.53</td>
</tr>
<tr>
<td>% of time BIS &lt;30</td>
<td>0 (0.0)</td>
<td>0.33 (0.0, 3.875)</td>
<td>&lt;0.0001*</td>
<td>2.97</td>
</tr>
<tr>
<td>Median absolute performance error (MDAPE)</td>
<td>10 (10, 12)</td>
<td>18 (14, 24)</td>
<td>&lt;0.0001*</td>
<td>6.48</td>
</tr>
<tr>
<td>Wobble</td>
<td>9 (8, 10)</td>
<td>10 (8, 14)</td>
<td>0.0009*</td>
<td>1.64</td>
</tr>
<tr>
<td>Global score</td>
<td>24 (19,30)</td>
<td>51 (31, 99)</td>
<td>&lt;0.0001*</td>
<td>6.04</td>
</tr>
<tr>
<td>% time heart rate ±25% of baseline</td>
<td>95 (87, 99)</td>
<td>90 (75, 98)</td>
<td>0.0031*</td>
<td>1.56</td>
</tr>
<tr>
<td>% time mean arterial pressure ±25% baseline</td>
<td>92 (86, 96)</td>
<td>89 (79, 97)</td>
<td>0.0411*</td>
<td>1.36</td>
</tr>
<tr>
<td>Total propofol consumption (mg/kg/h)</td>
<td>5.4 (4.5, 6.7)</td>
<td>5.3 (4.3, 6.9)</td>
<td>0.5698</td>
<td>1.09</td>
</tr>
<tr>
<td>Fentanyl Consumption (μg/kg)</td>
<td>3 (2.8, 3.7)</td>
<td>3 (2.7, 3.5)</td>
<td>0.3367</td>
<td>1.15</td>
</tr>
<tr>
<td>Oxybene time from propofol stop(min)</td>
<td>8.0 (6, 10.5)</td>
<td>8.0 (6, 12)</td>
<td>0.2108</td>
<td>1.20</td>
</tr>
<tr>
<td>Extubation time from stopping propofol (min)</td>
<td>8.0 (7, 11)</td>
<td>9.0 (7, 12)</td>
<td>0.3579</td>
<td>1.15</td>
</tr>
</tbody>
</table>

The values are median (1st quartile, 3rd quartile).

CLADS = closed-loop anesthesia delivery system; WMWodds = Wilcoxon Mann-Whitney odds measure; BIS = Bispectral Index.

* $P < 0.05$, Mann-Whitney $U$ test.
adequate depth of hypnosis.\textsuperscript{8,9,15–17} We contend that this ability to maintain a standard and uniform performance across different centers is an important advantage of automated anesthesia systems.

CLADS achieved induction using comparatively smaller doses of propofol within an acceptable period of time and without causing any major change in hemodynamics. There was also less overshoot of BIS during induction compared with manual control. This may be because of the more frequent and smaller dose adjustments made by CLADS based on more frequent feedback updates of BIS data from the patient. Similar induction performances (less propofol, less overshoot, and longer times) have been reported earlier with automated propofol anesthesia.\textsuperscript{7} The hemodynamic fluctuations during induction and endotracheal intubation were similar in the automated control. However, the automated system was able to respond to any hemodynamic deterioration by stopping the infusion, thus limiting the undesirable contribution of propofol to hemodynamic instability. The comparatively longer time needed for induction in the CLADS group can also be due to the more frequent and finer dose adjustments made by the automated system. This also prevented overdosing of propofol during induction.

After induction, CLADS maintained adequate depth of anesthesia for considerably longer than manual control. The lower MDAPE in the CLADS group indicates that closed-loop controlled anesthesia had a better and more precise control of BIS than the conventional manual control of propofol dose delivery. Wobble depicts the intra-individual variability, which reflects the yo-yo effect in the performance of a system. This outcome was greater in the manual group and not unexpected, as it results from dose adjustments made by different anesthesiologists—some repeatedly overdosing and some others repeatedly underdosing. In contrast, the dose adjustments in the CLADS group was more gentle and frequent, resulting in less tendency to wobble around the target. The global score was lower in the CLADS group, indicating a better overall performance. Therefore, the current results reiterate the results of previous single-center studies\textsuperscript{7,10–12} and confirm the superiority of automated control over traditional manual control in maintaining a consistent depth of anesthesia.

Similarly, the wide variation seen in the manual group between the sites regarding induction dose of propofol and induction time reflects differences in the approach of different anesthesiologists. This is probably due to the use of high doses of propofol and a subsequent large overshoot of BIS. CLADS, in contrast, controlled induction more precisely, as evidenced by a similarity in the induction dose and induction time between the sites when high-altitude site was excluded. This may be explained by the fact that high-altitude patients require larger doses of propofol and longer induction times as compared to low landers.\textsuperscript{38}

The more frequent and smaller dose adjustments made by the CLADS, together with the stoppage of propofol infusion during periods when hemodynamic parameters were outside the user-defined limits, probably accounted for the better hemodynamic stability achieved in the CLADS group over the manual group.

The variations in BIS fluctuations around various points of surgery, resulting in significantly high variability of performance in the manual group, probably reflect the difference in practice among individual anesthesiologists. The demography of recruited patients, type, and duration of surgical procedures; use of nitrous oxide; intraoperative analgesic protocol; and fentanyl consumption were similar across the studied centers. It would have been ideal to explore the influence of these and other factors, such as hemodynamic perturbations and number of operators in each center that could affect the performance of manually controlled anesthesia. It is a limitation that such an exploratory analysis is missing from our current report. The anesthesiologist is also susceptible to distractions that are clinically relevant, such as monitoring and controlling of hemodynamics, management of airway and ventilation, assessment of surgical field/blood loss, etc. The contribution of such distractions to variable performance of manually controlled anesthesia also cannot be ignored. In contrast, closed-loop control of anesthesia is not susceptible to such distractions or differences in anesthesia practice. This enabled the automated controller to maintain consistent levels of anesthetic depth, as well as hemodynamics, across all the centers.

The superior performance of automated anesthesia to maintain consistent anesthetic depth may account for the absence of awareness among the patients in the CLADS group. In the single patient who reported awareness in the manual group, median performance error, MDAPE, and

![Figure 2. A, BIS values during anesthesia in CLADS group. B, BIS values during anesthesia in manual group. Data are represented as median values (red line) with 10th (green line) and 90th percentiles (blue line). BIS = Bispectral Index; CLADS = closed-loop anesthesia delivery system.](image-url)
Table 4. Variability of BIS Control Performance Variables Among Different Sites in 2 Groups

<table>
<thead>
<tr>
<th>Site</th>
<th>Site II (n = 20)</th>
<th>Site III (n = 21)</th>
<th>Site IV (n = 20)</th>
<th>Site V (n = 20)</th>
<th>Site VI (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS within ±10 of target BIS</td>
<td>85 (76, 90)</td>
<td>85 (73, 90.5)</td>
<td>80 (75, 88)</td>
<td>83 (80, 87)</td>
<td>83 (75, 91)</td>
<td>80 (72, 89)</td>
</tr>
<tr>
<td>MDAPE</td>
<td>10 (9, 12)</td>
<td>11 (10, 14)</td>
<td>10 (10, 14)</td>
<td>10 (8, 12)</td>
<td>12 (10, 14)</td>
<td>10 (9, 12)</td>
</tr>
<tr>
<td>Wobble</td>
<td>10 (8, 12)</td>
<td>8 (7, 10)</td>
<td>10 (7, 10)</td>
<td>8 (6, 9)</td>
<td>10 (8, 12)</td>
<td>10 (8, 10)</td>
</tr>
<tr>
<td>Global score</td>
<td>24 (19, 32)</td>
<td>24 (18, 35)</td>
<td>25 (19, 30)</td>
<td>22 (16, 24)</td>
<td>27 (20, 32)</td>
<td>26 (19, 30)</td>
</tr>
<tr>
<td>Minimal BIS (in 1 min after target BIS)</td>
<td>40 (36, 42)</td>
<td>41 (34, 47)</td>
<td>45 (41, 50)</td>
<td>41 (35, 49)</td>
<td>42 (39, 47)</td>
<td>40 (34, 44)</td>
</tr>
<tr>
<td>Extubation from reversal (min)</td>
<td>4 (3, 6)</td>
<td>3 (2, 4)</td>
<td>4 (3, 8)</td>
<td>3 (2, 5)</td>
<td>3 (2, 6)</td>
<td>3 (2, 5)</td>
</tr>
<tr>
<td>Induction dose (mg/kg)</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.3 (1.1, 1.4)</td>
<td>1.3 (1.0, 1.4)</td>
<td>1.5 (1.2, 1.7)</td>
<td>1.9 (1.6, 2.4)</td>
<td>1.3 (1.2, 1.9)</td>
</tr>
<tr>
<td>Induction time (s)</td>
<td>148 (115, 195)</td>
<td>125 (106, 165)</td>
<td>150 (110, 215)</td>
<td>160 (141, 213)</td>
<td>193 (151, 268)</td>
<td>163 (135, 240)</td>
</tr>
<tr>
<td>Total propofol (mg/kg/h)</td>
<td>4.7 (3.7, 6.6)</td>
<td>4.8 (4.1, 6.2)</td>
<td>5.3 (4.6, 7.9)</td>
<td>5.2 (4.5, 6)</td>
<td>7.4 (6.3, 9.2)</td>
<td>5.2 (4.8, 6.2)</td>
</tr>
</tbody>
</table>

Comparison of performance in the CLADS group (N = 121) across various centers

Comparison of performance in the Manual group (N = 121) across various centers

Significant variability amongst different sites in control group (P < 0.05, Kruskal-Wallis test).

BIS = Bispectral Index; CLADS = closed-loop anesthesia delivery system; MDAPE = median absolute performance error; TB = target BIS.
Wobble (of 16) values were very high, reflecting wide fluctuations in the depth of hypnosis, which may have resulted in the recall of intraoperative events.

In previously published single-center studies,7,10–12 the Hawthorne effect19 was one of the limitations wherein dosage adjustments of propofol might have been done more actively than usual by the anesthesiologist in the experimental study setting, thus precluding the real comparison between CLADS and routine manual control. Likewise, in the current multicenter study, we cannot rule out the confounding contribution of the Hawthorne effect, even though multiple anesthesiologists were involved. Frequent adjustments of the propofol delivery rate by anesthesiologist in the manual group (median of 10.5 times per hour) indicate a significant amount of human resource utilization for anesthetic depth control, which was not the case for the CLADS group. The decrease of workload by a closed-loop controller has been reported previously.10,11,13,20

CONCLUSIONS
The present multicenter study established the ability of CLADS, an automated anesthesia control, to perform consistently better than conventional, manually controlled anesthesia. The manual control of anesthesia is probably prone to variations resulting from differences in anesthetic practices among different anesthesiologists. The closed-loop systems bear the promise of becoming a useful tool for anesthesiologists by standardizing anesthetic delivery to maintain a consistent depth of hypnosis. CLADS achieved this in various surgical settings without causing major hemodynamic deterioration. ■

APPENDIX 1
Participating institutions:
1. Department of Anesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
2. Department of Anesthesia, Government Medical College and Hospital, Chandigarh, India.
3. Department of Anesthesia, Sir Ganga Ram Hospital, New Delhi, India.
4. Department of Anesthesia, Dayanand Medical College, Ludhiana, India.
5. Department of Anesthesia, Government Medical College and Hospital, Patiala, India.
6. Department of Anesthesia, Sonam Norbu M Hospital, Leh, Jammu & Kashmir, India.

APPENDIX 2
1. Performance error (PE) = \((\text{measured BIS} - \text{target BIS})/\text{target BIS}\)*100
2. Median performance error (MDPE) = \{\text{median PE}_{ij}, j = 1, \ldots, N\}
It is a measure of bias and describes whether the measured values are systematically either above or below the target value.
3. Median absolute performance error (MDAPE) = \text{median} \{|\text{PE}_{ij}, j = 1, \ldots, N|\}
It is a measure of inaccuracy of the control method.

4. Wobble = median \{|\text{PE}_{ij} - \text{MDPE}_i|, j = 1, \ldots, N\|\}
where \(i\) is the subject number, \(j\) the \(j\)th (one) measurement of the observation period, and \(N\) the total number of measurements during the observation period.

It is an index of time-related changes in performance and measures the intrasubject variability in the performance errors.

5. Global score = |MDAPE + wobble|/% of the time BIS value between 40 and 60)*100

DISCLOSURES
Name: Goverdhan D. Puri, MD, PhD.
Contribution: This author helped design the study, conduct of the study, collect, analyze, and interpret the data, and manuscript preparation.
Attestation: Goverdhan D. Puri approved the final manuscript, attests to the integrity of the original data and analysis in the manuscript, and is the archival author.
Name: Preethy J. Mathew, MD.
Contribution: This author helped design the study, analyze and interpret the data, and prepare the manuscript.
Attestation: Preethy J. Mathew approved the final manuscript.
Name: Indranil Biswas
Contribution: This author helped collect the data, and prepare the manuscript.
Attestation: Indranil Biswas approved the final manuscript.
Name: Amitabh Dutta, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Amitabh Dutta approved the final manuscript.
Name: Jayashree Sood, PGDHHM, FFARCS, MD, MBBS, FICA.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Jayashree Sood approved the final manuscript.
Name: Satinder Gombar, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Satinder Gombar approved the final manuscript.
Name: Sanjeev Palta, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Sanjeev Palta approved the final manuscript.
Name: Morup Tsering, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Morup Tsering approved the final manuscript.
Name: P. L. Gautam, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: P. L. Gautam approved the final manuscript.
Name: Aveek Jayant, MD, DM.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Aveek Jayant approved the final manuscript.
Name: Inderjeet Arora, MSc.
Contribution: This author helped analyze the data.
Attestation: Inderjeet Arora approved the final manuscript, and attests to the integrity of the original data and analysis in this manuscript.
Name: Vishal Bajaj, MD.
Contribution: This author helped conduct the study, and collect the data.
Attestation: Vishal Bajaj approved the final manuscript.
REFERENCES