Multicentre evaluation of Closed loop anesthesia delivery system

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Introduction:

Automated anesthesia was first conceptualized by Bickford[1,2] in 1950. Tremendous advance in the realm of computer and microprocessor technology, together with better understanding of drug pharmacokinetics-pharmacodynamics and availability of novel monitoring equipments has subsequently lead to development of various state-of-the-art automated anesthetic drug delivery systems in the recent years. Among these systems, the pharmacodynamic feedback guided systems, also known as closed loop systems, have been shown to perform better[3,4] than the pharmacokinetically targeted open loop systems as the former are able to cope with the interindividual variations in drug effects. Closed loop systems have outperformed manual control in various surgical settings as well as procedural sedations, both during induction[5], as well as maintenance[6].

Closed loop guided anesthesia delivery systems:

The basic components of closed loop guided anesthesia delivery systems are: (1) A system under control, which is the patient; (2) A controlled variable that measures the relevant drug effect; (3) A set point for this variable, which is the chosen target value specified by the user; (4) An actuator, the infusion pump driving the administration of drug; and (5) A controller to control the actuator, which comprises an algorithm to translate a measured value of the controlled variable to a particular action for the actuator to steer the controlled variable closer to the target value.

The performance of a closed loop system is assessed by the time the controlled variable is kept within the target range and the entities described by Varvel et al[7]- Median performance error (MDPE), Median absolute performance error (MDAPE), Wobble, Divergence and Global score. Performance error is measured as the ratio of the difference between target value and measured

value of the variable to the target value of the variable. MDPE is a measure of bias of the system; a negative/positive bias indicates that the median measured controlled variable is less/more than the target. MDAPE is the measure of precision- an MDAPE of x% indicates that 50% of the variable values were within x% of the target value. Wobble measures the total intra-individual variability in performance error. Another commonly used index Global score takes into account MDAPE, wobble and the time the controlled variable is kept within the target range and gives an overall idea of the performance of the system. The less the values of MDAPE, wobble and global score, the better is the performance of the system. Divergence is the slope of the linear regression equation of the performance error over time. A negative slope indicates that the system decreases the performance error over time, whereas the absolute value indicates the velocity with which it increases or decreases the performance error.

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[8-11]. However, to an anesthesiologist control of depth of anesthesia with closed loop system is of most importance. The most widely reported anesthetic depth entity used as a controlled variable in closed loop systems is Bispectral index(BIS)[3-6,12]. The accuracy of BIS in predicting depth of anesthesia is more than that of other EEG based monitors, such as Entropy, Spectral edge frequency, etc, in non-cardiac surgeries[13,14]. Use of BIS has been associated with decrease in anesthetic agent consumption, earlier awakening and decreased incidence of intraoperative awareness[15-20].

Puri et al[21] developed a pharmacodynamic feedback guided closed loop system- Closed loop anesthesia delivery system (CLADS). The system uses BIS as the controlled variable. CLADS (Closed loop anesthesia delivery system) is Bispectral Index (BIS™) - guided closed loop anaesthesia delivery system and has been used successfully for automated administration of propofol in various situations, like non-cardiac surgery[21], cardiac surgery[22], post-operative sedation[23] and high altitude[24]. However, all of these were single centre studies. The investigators realized that it is important to test this automated system in a controlled study setting that involves multiple operators in their native/ natural work environment.

A trial was designed to evaluate the feasibility and efficacy of CLADS in comparison to manual control across multiple centers in India. We hypothesized that CLADS will be able to maintain BIS within target range during the intra-operative period for a significantly longer time than

manual control, without adversely affecting hemodynamics or prolongation of time of awakening and extubation.

The study was conducted in a total of six centres- five were tertiary care teaching hospitals and the remaining one was a referral hospital- of northern India from January 2010 to September 2012. Approval was obtained from the respective Ethics Committees of the participating institutions (Appendix 1) prior to recruitment of participants in each site and the trial was registered with Clinical Trial Registry of India (CTRI/2010/091/000041).

Adult patients of either sex belonging to age group of 18 to 60 years without prior significant cardiorespiratory illness and scheduled to undergo non-thoracic/ non-vascular/ non-neurosurgical procedure of expected duration of 1-3 hours under general anaesthesia without combined regional anaesthesia were included for study in this stratified randomized, patient-blinded, two arm parallel group, active controlled trial. At least forty patients were randomized from each site.

Patients weighing <70% or >130% ideal bodyweight, those on pacemakers, those with neurological disorders and those on psychoactive drugs including alcohol were excluded from the study. Patients were randomly allocated to one of two groups– the manual group and the CLADS group using computer-generated random numbers in sequentially numbered, sealed, opaque envelopes stratified by centre.

Automated Controller

CLADS is a patented 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 earlier publications [21,25]. 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) that were 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, time-delay factor between sensing and averaging of BIS™ data, time-delay factor between the change in infusion rate and the actual change in the plasma concentration of propofol as well as the peak effect of propofol. A personal computer is used to implement the control algorithm, provide a user interface and to 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 two 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 s and calculates the BIS error (Target BIS — Actual BIS) and makes changes in the propofol infusion rate every 30 secs based on this trying always to correct the BIS towards target range.

The automatic mode has three options: a) induction, b) maintenance and c) induction combined with maintenance. The algorithm fine-tunes the rate and duration of propofol delivery differently during induction and maintenance phases of anaesthesia 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 deemed as one epoch. The initial three as well as the last three BIS values of each epoch are averaged and compared to assess the trend. When the trends indicate an increasing BIS, higher target concentrations and so higher propofol rates 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 maximum allowable rate of drug infusion and thereby the achievable calculated concentrations at induction and maintenance of anaesthesia by choosing the risk status of the patient as- low-risk (ASA I-III, NYHA I–II), high-risk (ASA III-IV, NYHA class 2-3), very high-risk (ASA IV-V, NYHA 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 system stops the propofol infusion rate automatically whenever haemodynamics go below the safety limits set by the operator. The controller uses default values of heart rate 60/ minute and mean arterial pressure 70 mmHg in case the user does not set these safety limits. The propofol infusion would restart automatically when

haemodynamics improve to values above the predefined lower limit. The time delay for this automatic cut-off is at the most 10secs which is 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. Heart rate, non-invasive mean arterial pressure, SpO_2, End-tidal CO_2 were continuously recorded on to computer at 10 secs intervals while BIS values, SQI, EMG activity, and suppression ratio were every 5 seconds.

It was a challenge to teach anaesthetist who were not using BIS regularly. So we gave BIS monitor facility to each centre to let them use it for six to 12 months before we showed them the functioning of CLADS at the parent institute. Subsequently they used the CLADS for one month before the patient recruitment started.

In 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 anaesthesia. Patients received 2 µg/kg fentanyl three minutes prior to induction, followed by infusion at 1µg/kg/hr till the end of skin closure. After induction, endotracheal intubation was facilitated with 0.1 mg/kg of vecuronium and patients’ lungs were mechanically ventilated with nitrous oxide: oxygen mixture with 0.4 fraction of inspired oxygen (FiO_2) throughout the procedure. A continuous infusion of the vecuronium at the rate of 50 µg/kg/hr was initiated to maintain the neuromuscular blockade and titrated according to train of four response by the user in both the groups.

During episodes when the mean arterial pressure 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 less than or equal to 50, nitroglycerine infusion was administered to control the blood pressure and esmolol to control the heart rate depending upon the clinical situation. In situations of hypotension (MAP less than 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 infusion was stopped 5-10 minutes prior to 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 trachea. The patients were shifted to PACU after they regained their consciousness. The presence of recall of any events of intra-operative period was enquired before discharging the patient from PACU.

The induction time (the time required to achieve target BIS™ after start of infusion), induction dose, minimum BIS™ within one minute of induction and total dose of propofol, mean duration of closed loop control or manual control, and mean time interval between end of closed-loop control (or end of propofol infusion in manual control) and obeying of commands by patients as well as extubation were noted. Anesthesiologists involved in the study were conversant with the use of bispectral index monitor and had undergone pre-enrolment training at the host site to use CLADS.

Statistical analysis

Physiologic data are presented as median (IQR). "CLADS time" is the total duration of time from induction to end of procedure during which the controller or anaesthesiologist controlled the propofol delivery to achieve the target BIS™. The total periods of time closed loop system or BIS™ feedback in manual group did not work properly due to poor SQI (<15) or interference from cautery were subtracted from total control time to get '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 (ie total anaesthesia time) BIS™ remained within 10 of target BIS™ (50). Median absolute performance error (MDAPE), wobble[14] and and global score- an overall performance assessment parameter which incorporates MDAPE, wobble and percentage of time BIS™ remains within target range were secondary outcome measures. The lesser the value of the global score, the better control it indicates, constituting of lesser absolute performance error and less wandering along with longer maintenance of BIS™ value within the target range. The other secondary outcome measure studied was the hemodynamic performance during anesthesia as assessed by: percentage of anesthesia time the heart rate as well as mean arterial pressure were within 25% of the baseline.

In this multicentre study BIS was maintained within ±10 of target for significantly longer duration of time in the CLADS group (81.4±8.9 % of anaesthesia duration)than in the Manual

group (55.34±25 %, p=0.000). MDAPE and Global score were also significantly better ($p < 0.05$) in CLADS group. The percentage of time HR and MAP were within 25% of the baseline was significantly better in CLADS group. On comparison of data between the centers, CLADS group performed consistently in all the centres, whereas significant variation was observed between the contres in manual group. Induction was achieved with significantly less dose of propofol in the CLADS group than in the manual group (1.51 ± 0.46 mg/kg vs 1.96±0.65 mg/kg p = 0.000, Table 2). The overshoot of BIS™ during induction was significantly less in the CLADS group. However, induction time was significantly more in the CLADS group (Table 2). Haemodynamic stability as indicated by percentage of time HR and MAP were within 25% of the baseline was better in CLADS group (Table 3). Recovery parameters were comparable between the two groups. (Table 3).

The fentanyl consumption was similar in both the groups. In the CLADS group, the controller stopped the propofol infusion a total of 54 times during 40 anaesthetics out of the total 121 patients. The median (IQR) duration of interruption of propofol infusion in this manner was 120 sec (60-180 sec). These interruptions were mostly during the peri-induction period. The majority of the haemodynamic disturbances were transient that 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 patient. In the manual group, nitroglycerine infusion was used in one patient for hypertension. The manual group required a median of 10.5 alterations per hour (IQR 6.7-17.8) in propofol delivery by the attending anaesthesiologist as compared to none in the CLADS group. One patient from the manual group had 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 comparing the performance between centers, the CLADS group showed similar values regarding percentage of time BIS™ was maintained within ±10 of target, MDAPE and Global score (Table 4A). However, there was significant difference between centres regarding induction dose of propofol required to achieve BIS™ of 50 and the induction time ($p < 0.001$). Post-hoc analysis revealed that the induction dose and time were significantly different at site V which was the high altitude centre as compared to all other centres. On analysing the data after excluding the high altitude centre, there was no significant difference between the remaining five

participating centres (p=0.25). In manual group, significant variability was noted between the centers regarding all these performance parameters and induction dose and time of propofol. There was variability between the centers in BIS™ overshoot during induction as well as in time from reversal to extubation in the manual group, whereas, in the CLADS group, there was no significant variability. Post-hoc analysis did not reveal any particular pattern of centre performance.

Discussion

The current trial was undertaken to establish the efficacy and feasibility of automated anaesthesia system for induction as well as maintenance of anesthesia and compare its performance with manual control across different centres. CLADS was able to achieve induction using comparatively less dose of propofol within acceptable period of time and without causing any major change in hemodynamics. The overshoot of BIS during induction was also less compared to manual control. This may be because of more frequent and smaller dose adjustments made by CLADS based on more frequent feedback updates of BIS data from the patient. Absence of any major hemodynamic fluctuations in the patients during induction is explained by fine tuning of propofol dose by the automated anaesthesia system. The comparatively longer time needed for induction in the CLADS group can also be due to more frequent and finer dose adjustments made by the automated system. This also avoided overdosing of propofol during induction.

Following induction, CLADS was able to maintain adequate depth of anesthesia for considerably longer period of time than manual control. The lower MDAPE in the CLADS group indicates that closed loop controlled anaesthesia had a better and 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. Wobble was higher in the manual group and not unexpected as it is contributed by dose adjustments made by different anesthesiologists - some repeatedly overdosing and some others repeatedly under-dosing in contrast to the more gentle and frequent dose adjustments in the CLADS group and therefore, less tendency to wobble around the target. The global score was better in the CLADS group indicating a better overall performance. Therefore, the current results reiterates the results of

previous single centre studies[21,26-28] and confirms the superiority of automated control in maintaining a consistent depth of anesthesia over traditional manual control.

Propofol pharmacokinetics as well as pharmacodynamics differs among individuals. The sensitivity of central nervous system and cardiovascular system to propofol is different in each individual. So, control of depth of anaesthesia based on pharmacodynamic feedback helps in overcoming inter-individual differences and results in more consistent attainment as well as maintenance of adequate depth of anaesthesia[29-33]. The wide variability of the performance parameters, like BIS within ±10 of target, MDAPE, global score- in the manual group between the sites indicates the difference in practice of different anesthesiologists regarding control of anesthetic depth. On the other hand, closed loop control responds to every minute changes in BIS as well as trends in changes of BIS with fine and accurate patient-individualized titration of drug dosages. These features of automated anaesthesia system made it feasible to maintain consistent and uniform performance across all the centers.

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 may probably be due to the use of either high doses or sometimes low doses of propofol and subsequent large overshoot of BIS. CLADS, on the other hand, was able to control the induction more precisely, as evidenced by similarity in the induction dose and induction time between the sites when high altitude site was excluded. This may be explained as the high altitude patients are reported to require larger doses of propofol requiring longer induction time as compared to low landers[34].

The wide variations in the fluctuations of BIS and hemodynamics around various points of surgery in the manual group reflects the difference of practice among the individual anesthesiologists and also their being susceptible to distractions owing to paying attention to various aspects like monitoring and controlling of hemodynamics, management of airway and ventilation, assessment of surgical field/blood loss etc. In contrast, closed loop control was not susceptible to such distractions or differences in anaesthesia practice and thus was able to maintain consistent levels of anesthetic depth as well as hemodynamics across all the centers.

The superior performance of automated anaesthesia to maintain consistent anesthetic depth may account for the absence of awareness in any of the patients in the CLADS group. In the case of the patient reporting awareness in the manual group, the MDPE as well as MDAPE values were

very high, depicting wide fluctuations in the depth of anesthesia, which may have resulted in the recall of intra-operative events.

Comparison of performance across different separate centres with different anesthesiologists possibly made this study overcome this drawback of the previous single-centre studies. Frequent adjustments of propofol delivery rate by anesthesiologist in manual group (mean of 18 times) indicate a significant amount of human resource utilization for anesthetic depth control which was saved in CLADS group.

Use of CLADS did not lead to any prolongation in the time to extubation or recovery of patients from anaesthesia, when compared to manual control. This further adds to the efficiency of automated anaesthesia in anesthetic practice.

Conclusions

This study established the efficacy and feasibility of CLADS, an automated anaesthesia control, over conventional manual control and also its ability to perform more consistently despite variations in patient and surgical variables as well as differences in anaesthetic practices among different anaesthesiologists. The closed loop systems bear the promise of becoming a useful tool to anaesthesiologists in delivering a consistent depth of anaesthesia, without causing major hemodynamic deterioration in various surgical settings in various patient population and at the same time, take a significant burden off the anaesthesiologists' shoulder and thus allowing them to devote attention to other demanding tasks in the operating room.

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Table 1: Demographic and surgical characteristics (mean ± SD).

	CLADS group	Manual group	p value
Age (Years)	40.9±13.2	41.5±12.9	0.751
Sex (M:F)	38:83	41:80	0.473
Height (cm)	157.5+ 8.4	158.4 +7.6	0.439
Weight	61.1±13.6	61.8±12.8	0.912
CLADS Time(min)	82.9±37.7	87.4±48.3	0.801
Valid CLADS Time (min)	74±36.9	78.5±47.6	0.748
BSA(m^2)	1.63±0.21	1.64±0.196	0.791
BMI(Kg/m^2)	24.08±4.89	24.53±4.15	0.572

No Significant difference between the groups ($p>0.05$, Mann-Whitney U test)

Table 2: Performance characteristics and heamodynamic stability.

	CLADS group	Manual group	p value
% time BIS within ± 10 of target BIS	81.4±8.9	55.34±25	0.000*
MDPE	3.93±6.82	4.33±18.7	0.424
MDAPE	11.03±3.04	20.04±9.1	0.000*
Wobble	8.94±2.5	11.26±5.6	0.004*
Global score	25.2±8.2	195.25±565.5	0.000*
Divergence	0.071±0.276	0.064±0.39	0.998
% time HR ± 25% of baseline	90.64 ± 11	81.6 ± 22.8	0.003*
% time MAP ± 25% baseline	89.8 ± 9.8	83.2 ± 19.2	0.04*

The values are mean ± SD. (* indicates $p<0.05$, Mann Whitney U test)

Table 3: Induction characteristics, drug usage and recovery parameters.

	CLADS group	Manual group	p value
Propofol induction dose(mg/kg)	1.51 ± 0.46	1.96±0.65	0.000*
Induction time (seconds)	172.23±71.99	142.02±137.8	0.000*
Minimum BIS at induction	41.86±8.14	39.07±15.02	0.000*
Total propofol (mg/kg/hr)	5.78 ± 1.73	5.66 ± 2.39	0.558
Maximum BIS after intubation	63.2±9.2	59.6±14.3	0.219
Minimum MAP during induction	87.9±15.1	88±13.8	0.894
Obeying time from propofol stop (min)	8.8±4.3	9.2±3.7	0.279
Extubation time from stopping propofol (min)	9.1±4.1	9.4±3.5	0.358