

# Closed loop anaesthesia at high altitude (3505 m above sea level): Performance characteristics of an indigenously developed closed loop anaesthesia delivery system

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## ABSTRACT

**Background:** Closed loop anaesthesia delivery systems (CLADSs) are a recent advancement in accurate titration of anaesthetic drugs. They have been shown to be superior in maintaining adequate depth of anaesthesia with few fluctuations as compared with target-controlled infusion or manual titration of drug delivery. **Methods:** Twenty patients scheduled to undergo general abdominal or orthopaedic procedures under general anaesthesia at Leh (3505 m above sea level) were recruited as subjects. Anaesthesia was delivered by a patented closed loop system that uses the Bispectral Index (BIS™) as a feedback parameter to titrate the rate of propofol infusion. All vital parameters, drug infusion rate and the BIS™ values were continuously recorded and stored online by the system. The data generated was analysed for the adequacy of anaesthetic depth, haemodynamic stability and post-operative recovery parameters. **Results:** The CLADS was able to maintain a BIS™ within  $\pm 10$  of the target of 50 for 85.0 $\pm$ 7.8% of the time. Haemodynamics were appropriately maintained (heart rate and mean arterial blood pressure were within 25% of baseline values for 91.2 $\pm$ 2.2% and 94.1 $\pm$ 3% of the total anaesthesia time, respectively). Subjects were awake within a median of 3 min from cessation of drug infusion and achieved fitness to recovery room discharge within a median of 15 min. There were no adverse events or report of awareness under anaesthesia. **Conclusions:** The study demonstrates the safety of our CLADS at high altitude. It seeks to extend the use of our system in challenging anaesthesia environments. The system performance was also adequate and no adverse events were recorded.

**Key words:** Bispectral index, closed loop anaesthesia, high altitude, propofol

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## INTRODUCTION

Closed loop anaesthesia delivery systems (CLADSs) are a recent advancement in accurate titration of anaesthetic drugs. They have been shown to be superior in maintaining adequate depth of anaesthesia with few fluctuations as compared with target-controlled infusion or manual titration of drug delivery.<sup>[1]</sup> We have described an indigenous CLADS.<sup>[2]</sup> In further attempts at validation, we present below a description of its performance at high altitude (Leh, 3505 m above sea level).

## METHODS

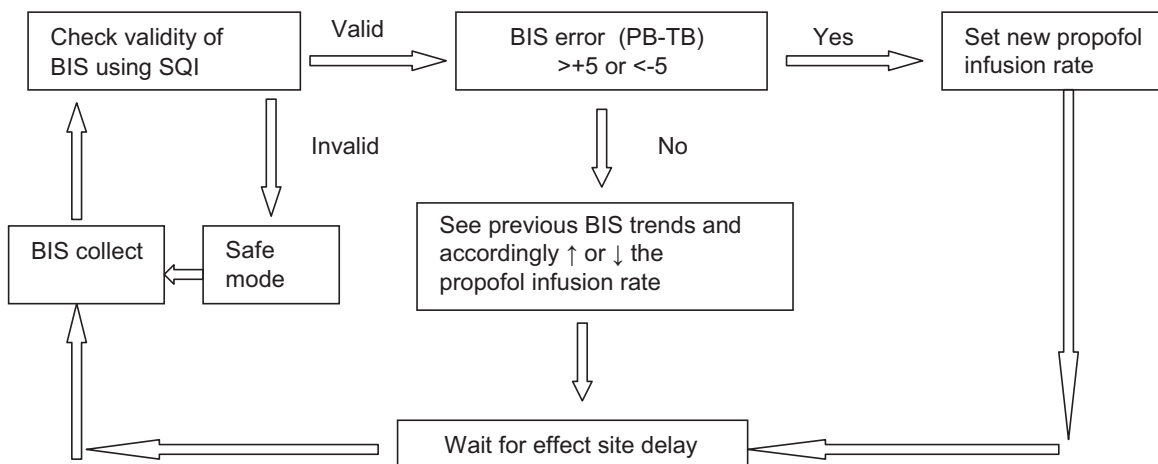
After clearance from the Institutional Ethics Committee, 20 consenting adult patients (ASA I–II) scheduled to undergo elective general or orthopaedic surgery were recruited in the study. Patients with a known hypersensitivity to propofol or fentanyl and those with a record of previous adverse events to general anaesthesia were excluded. Intravenous access was secured and standard intraoperative monitoring instituted (Five-lead continuous electrocardiography, pulse oximetry, non-invasive blood pressure

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measurement and side stream capnometry) using the Datex-Ohmeda S/5™ anaesthesia monitor (Datex-Ohmeda Inc., Madison, WI, USA). Baseline room air oximetry and capnometry readings were obtained. Patients received 0.5 mg intravenous midazolam and 2  $\mu\text{g}/\text{kg}$  of fentanyl before induction of anaesthesia. A Bispectral Index monitor (BIS™; Aspect Medical Systems Inc., Newton, MA, USA) was used to monitor the depth of anaesthesia and titrate the anaesthetic delivery to a target BIS of 50 both at the time of induction as well as during the maintenance of anaesthesia. CLADS is a patented (502/DEL/2003) drug delivery system for induction and maintenance of total intravenous anaesthesia. BIS™, version 3.0 rev 0.5, is the control variable with an averaging interval set at 15 s. A standard syringe infusion pump (Pilot-C; Fresenius, France) serves as the control actuator. An IBM-compatible Pentium 4 (2 GHz) personal computer (PC) is used to implement the algorithm, to provide a user interface (RS-232) and to control communication with the A-2000 monitor and infusion pump. The system can be used for both induction as well as maintenance of anaesthesia. The system requests an update of the electroencephalographic data every 5 s and calculates the BIS error (difference between the target and actual BIS value). This value is passed to the control algorithm, which uses the error to calculate an adjustment in rate of infusion needed to achieve target BIS. The decisions regarding the change in propofol rate are affected by the effect of previous decisions on the change in BIS, keeping an eye on the difference of current BIS from target BIS. This is actually a simplified expression of the proportional integral derivative control algorithm. In this, the “proportional” bit of the algorithm suggests

that decisions on increasing and decreasing infusion rates is based on how far one is from the target – the larger the difference between actual and target, the larger the difference in the change in infusion rate. The “integral” component of the model is by which the controller can achieve, in a quick single step, what it might take several small steps in adjusting the rate of the infusion to reach a target. Derivative action is, in simple terms, a guess that the system makes as to where the actual BIS is headed (towards or away from the target); this guess making is based on the behaviour of the BIS variable when previous increase or decrease in rates has occurred; this guess is then used to adjust the rate of infusion. These principles are outlined in a diagram [Figure 1].

Vital signs and the BIS were continuously recorded and stored online on the same personal computer (PC) used as the controller. The time interval after attainment of BIS of 50 to cessation of drug delivery is taken as the closed loop anaesthesia delivery time. A further refinement uses the signal quality index (SQI) data from the A-2000 monitor; here, the time duration for which the SQI <15 (and where the BIS monitor generates no values) is subtracted from the total CLADS time to yield a “valid CLADS time”. Vecuronium bromide (0.1 mg/kg) was used to facilitate endotracheal intubation and 1.5 mg/kg of preservative-free lignocaine was administered 90 s prior to laryngoscopy to blunt the haemodynamic responses to endotracheal intubation. Anaesthesia was maintained using propofol infusion (titrated to endpoint of BIS 50) and 66% nitrous oxide in oxygen. Intermittent positive-pressure ventilation was adjusted to keep the end tidal carbon dioxide values within  $\pm 10\%$  of



**Figure 1:** Basic algorithm of ‘CLADS’. Signal quality index is checked before accepting the BIS numbers as valid for taking action on these. Effect site delay is based on the time needed for the Propofol to produce effect on BIS. PB = present or current BIS at any given time point, TB = target BIS set by the user, BIS error is the difference between the PB and TB

baseline. Fentanyl infusions were continued at 1 µg/kg/hr for the duration of surgery. At the end of the procedure, patients received 30 mg of intramuscular ketorolac and 50 mg of intravenous tramadol for post-operative analgesia.

Propofol and fentanyl infusions were stopped at skin closure and neuromuscular blockade was reversed. The time to obeying command from cessation of propofol infusion was noted. Patients received supplemental oxygen till such time that room air oximetry readings were comparable to those present pre-operatively. Any adverse events were noted.

**Statistical analysis**

Physiologic data are presented as mean (SD) and time intervals are presented as median (interquartile range (IQR)). Performance of the system was assessed by calculating median performance error (MDPE), median absolute performance error (MDAPE), wobble, divergence (time-related trends) and mean offset (measured BIS – target BIS) using the methods of Varvel et al.<sup>[3]</sup>

The performance error is given by the formula:

$$PE = (BIS_{\text{measured}} - BIS_{\text{target}}) * 100 / BIS_{\text{target}}$$

The median performance error, which reflects the bias of CLADS in the *i*th subject, is determined as:

MDPE = median {PE<sub>ij</sub> j = 1.....N<sub>i</sub>}, where N<sub>i</sub> is the number of (PE) values obtained in the *i*th subject.

Median absolute performance error (MDAPE) = median {I PE<sub>ij</sub> j = 1.....N<sub>i</sub> I}

Wobble is determined from the equation:

$$\text{Wobble} = \text{median} \{I PE_{ij} - MDPE_i, j = 1.....N_i\}$$

MDPE and MDAPE are measures of bias and precision, respectively, and wobble measures the intraindividual variability in the performance errors. The percent of time when BIS remained Within ±10 of target BIS was also calculated. Adequacy of haemodynamic control was adjudged by the percentage of anaesthesia time the mean arterial blood pressure and heart rate were ±25% of baseline. All analyses were performed using SPSS v11.0 for Windows (SPSS Inc., Chicago, IL, USA). Awareness under anaesthesia was determined using standardised questionnaires.<sup>[4,5]</sup>

**RESULTS**

Baseline characteristics of the study population are shown in Table 1.

The subjects required 2.2±0.64 mg/kg (mean±SD) of propofol to achieve a BIS value of 50. The total CLADS time was 58.28±20 (mean±SD) min, of which the valid CLADS time was 55.2±21 (mean±SD) min. The performance of CLADS at the time of induction of anaesthesia is shown in Table 2.

Average propofol infusion rate required for maintaining target BIS of 50 with CLADS was 7.5±2.4 mg/kg/hr. The heart rate and blood pressure were maintained within 25% of baseline for 91.1±2.2% and 94.1±3% of time during that period. The BIS was maintained within limits of 50±10 for 85.0±7.8% of the time. Further descriptive variables of performance are shown in Table 3.

The median time to obeying command was low (3, interquartile range (IQR) 6 min). All patients achieved baseline pulse oximetry values without supplemental oxygen within 15 (IQR of 25) min. There were no adverse events and no reports of awareness determined using standardized proforma.

**Table 1: Baseline characteristics**

Age (years)	37.69±15.25
Sex (M:F)	9:11
Body mass index (kg/m <sup>2</sup> )	17.2±3.5
Room air pulse oximetry (%)	89±1.0
Pre-induction end tidal CO <sub>2</sub> (mmHg)	25.5±3.48

All data except count datum expressed as mean ± SD

**Table 2: Performance of closed loop anaesthesia delivery at induction of anaesthesia**

Induction dose of propofol*	2.2±0.6 mg/kg
Time to achieve target BIS at induction*	221.7±93 s
Minimum BIS at induction (median IQR)@	46 (10)
Change in heart rate from baseline@	8 (8) beats
%change in MAP from baseline*	18.1±12.1 mmHg
Pulse oximetry values (intraoperative)@	98 (2)

\*Data expressed as mean ± SD; @Data expressed as median (IQR)

**Table 3: Performance characteristics of CLADS**

Mean offset*	3.3±2.8
MDPE@	6 (8)
MDAPE@	12 (4)
Mean PE*	6.4±4.2
Wobble@	10 (8)
Divergence*	0.12±0.2

\*Data expressed as mean ± SD; @Data expressed as median (IQR)

## DISCUSSION

We sought to validate our indigenous CLADS in a challenging anaesthesia environment such as exists at a high altitude. The system was used for both induction and maintenance of anaesthesia. The BIS remained well within defined limits and therefore the dose used seemed to have been appropriate for this population

The system maintained adequate depth of anaesthesia during the maintenance phase about 85% of the time. This was similar to our experience with the system at low altitude.<sup>[2]</sup> The MDPE, which is a signed value, was +6, which means the median BIS during the study was around 6% higher than the target. Overall, 50% of the BIS values were within 11% of the target BIS of 50 as suggested by the MDAPE. The divergence of 0.12 indicates that the system had a small tendency to increase the performance error with time. Short durations of anaesthesia limit further comment on how the system performance would improve as drug levels built up within the body. The MDPE and MDAPE values we obtained were however higher than those described in our earlier report<sup>[2]</sup> and in the literature.<sup>[4,6]</sup> This may have been due to the relatively short duration of anaesthesia at high altitude in the present study and due to the nature of the BIS algorithm itself. The BIS algorithm may be such that it can detect extremes of consciousness – between alertness and deep anaesthesia, but is less discriminatory between these two opposites.<sup>[7]</sup> The clinical significance of these small oscillations in the BIS values can also be questioned – although they are important in determining satisfactory system performance, a BIS value maintained oscillating around a target may not significantly compromise the anaesthetic depth or cause too deep anaesthesia.

Nitrous oxide was a part of the anaesthetic protocol. Nitrous oxide has been shown to modestly increase pulmonary artery pressures (PAP),<sup>[8]</sup> and this might argue against its use at high altitudes. However, the resident anaesthesia team at Leh has always been using nitrous oxide as a part of its anaesthetic protocol. The team there provides anaesthetics to over 1000 cases a year using nitrous oxide and, although they do not have published data, their anaesthesia-related morbidity and mortality figures appear to be comparable to anaesthesia delivery practice at lower altitudes and better-equipped centres. Because we did not monitor PAP, we cannot comment on the exact interaction of nitrous oxide with PAP in this population. However, from a perusal of the intraoperative pulse oximetry

values during the study (values are median (IQR) of recorded intraoperative values after induction of anaesthesia, Table 2) nitrous oxide did not cause any hypoxaemia. Also, PAP at high altitude seem to have modest correlation with baseline pulse oximetry (the baseline SpO<sub>2</sub> in our study was around 89%, which in most papers does not usually correspond to significant PAH).<sup>[9]</sup> On the other hand, raised PAP has also been described independent of the level of hypoxaemia, and this has been attributed to ethnic differences.<sup>[9]</sup>

From our previously published observations, we noted that high-altitude dwellers needed significantly higher doses of propofol to achieve a particular BIS<sup>TM</sup>.<sup>[10]</sup> This paper was to extend the use of our CLADS in different anaesthesia settings and different populations. We also chose not to compare CLADS with manual delivery at high altitude for this reason – we believe that CLADS performing better than manual anaesthesia is a given fact from our earlier work<sup>[2]</sup>. Although our current data did not systematically study the variability in haemodynamics, there seems to be less heart rate response to noxious stimuli in this population. This should further reinforce the idea of titrating anaesthetic depth on the basis of objective monitors rather than on haemodynamics alone. The overall stability of haemodynamic parameters supports the idea of closed loop anaesthesia. The quick awakening time may also be an index of the good performance of the system. Even though the system tended to overdose slightly (MDPE of 6 as detailed above), there was absolutely no effect on quick recovery from anaesthesia and recovery discharge. This might be especially important at high altitude, where the attendant hypoxaemia<sup>[11]</sup> can be further aggravated by anaesthetic-induced respiratory depression. We believe that the present study evaluating for the first time the BIS-controlled anaesthesia at high altitude demonstrates the safety of our CLADS even in these extreme situations.

## CONCLUSIONS

The study demonstrates the safety of our CLADS at high altitude. It seeks to extend the use of our system in challenging anaesthesia environments. The system performance was also adequate and no adverse events were recorded.

## ACKNOWLEDGMENTS

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## REFERENCES

- Liu N, Chazot T, Genty A, Landais A, Restoux A, McGee K. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: Closed loop versus manual control: A prospective, randomised, multicenter study. *Anesthesiology* 2006;104:686-95.
- Puri GD, Kumar B, Aveek J. Closed loop anaesthesia delivery system (CLADS) using bispectral index: A performance assessment study. *Anaesth Intensive Care* 2007;35:357-62.
- Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinet Biopharm* 1992;20:63-94.
- Struys MM, De Smet T, Versichelen LF, Mortier EP, De Velde SV, Van Den Broecke R. Comparison of closed-loop controlled administration of propofol using bispectral index as the controlled variable versus standard practice controlled administration. *Anesthesiology* 2001;95:6-17.
- Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during general anaesthesia. *Br J Anaesth* 1970;42:535-42.
- Absalom AR, Sutcliffe N, Kenny GN. Closed-loop control of anesthesia using bispectral index, performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. *Anesthesiology* 2002;96:67-73.
- Leslie K. Current depth of anaesthesia monitors: Jacks of all trades and masters of none. *Anaesth Intensive Care* 2007;35:333-4.
- Pagel PS, Farber NE, Pratt PF Jr, Warltier DC. Cardiovascular Pharmacology. In: Miller RD, editor. *Miller's Anesthesia* 7<sup>th</sup> ed. Philadelphia PA: Churchill Livingstone; 2009.
- Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitude. *Healthy Highlanders and Chronic Mountain Sickness. Circulation* 2007;115:1132-46.
- Puri GD, Jayant A, Dorje M, Tashi M. Propofol fentanyl anaesthesia at high altitude: Anaesthetic requirements and hemodynamic variations when compared with anaesthesia at low altitude. *Acta Anaesthesiol Scand* 2008;52:427-31.
- Safar P, Tenicela R. High altitude physiology in relation to anesthesia and inhalation therapy. *Anesthesiology* 1964;25:515-31.

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