Anaesthesia practice in operating room primarily involves giving anaesthetics drugs to patients to produce unconsciousness and ensuring safe surgery without any untoward incidence. Some of these processes and procedures are fixed and predetermined and some are based on the patients’ response to the interventions like altering anaesthetic drug infusions or inhaled concentrations, giving drugs and infusions to maintain hemodynamic etc. The processes which are repetitive and require constant attention of the anaesthetist are always prone for human errors. Putting an intravenous line, checking the machine and equipment, monitoring, giving anaesthetic drugs, titrating the drugs, securing an airway, maintaining the respiration and hemodynamic and giving intravenous fluids and blood products, keeping an eye on the surgical field and monitors, altering the dosages of potent drugs based on patients’ requirement and responses, are some of the activities which an anaesthesiologist is supposed to be doing routinely day in and day out while anaesthetizing the patients. Though the incidences of errors in these may be low, the risk involved is high. This has been shown and proven number of time in different industries and is the reason automation has been adopted as safety measures in these industries. One such example is airline industry. Induction, maintenance as well as recovery from anaesthesia can be compared to take off, flying and landing of the aero plane. In view of this there is need to automate some of the processes related to anaesthesia so that the human error can be minimized, distractions from routine repetitive activities can be minimized and anaesthetist can have more time for direct patient care. The Department of Anaesthesia and Intensive Care at Post Graduate Institute of Medical Education and Research Chandigarh has made great strides in developing automated anaesthesia system that is predicted to be the future of standard anaesthesia care.

Figure 1 Complex operating room environment and its interaction with human physiology

With the development of computers attempts at automating the delivery of anaesthetics and related drugs were made using the apparent relationship between the depth of anaesthesia and changes in the EEG to control the delivery of intravenous anaesthetic drugs. Investigators have used simple electronic circuits with analog systems for data acquisition and conversions to mechanical outputs for the delivery of a drug. With the advances in microprocessor technology and miniaturisation of electronic sensors the EEG signals picked from the head of the patients can be used for development of objective parameters of measurements of depth of anaesthesia. As anaesthetic requirement variability requires the titration of drugs based on patient’s response, these
Objective anaesthetic depth monitors have hugely opened the possibility of automation of anaesthetic delivery based on these parameters and probability of closing the loop of this drug delivery has increased recently.

Automated drug delivery consists of computer programs designed to maintain a targeted effect by adapting/ varying the administered amounts of drug based on the feedback of effect of the drugs on the specific body functions which it has been given to alter. A closed-loop system is the ideal means of automated drug delivery.

**CLOSED LOOP SYSTEM**

Fig 2 Broad framework of Closed loop systems in the clinical medicine

A closed-loop system senses the level of output, feedbacks this information, compares it to a set point that defines the desired output level and uses the difference to push the output towards the set point. Such systems are referred to as feedback control systems. Because of more frequent sampling of the control variable and more frequent changes to the rate of drug delivery than with manually delivered anaesthesia, the stability of the control variable may be greater. At the same time, the dose delivered is customized to meet the exact requirements of each patient, thereby overcoming the problems of inter-individual differences and differing levels of surgical stimulation. The advantage of closed-loop anaesthesia delivery system is that the control is continuous and responsive that may improve the quality of care as compared with intermittent control practiced routinely. Recovery times and the risk of inadvertent awareness may thereby be decreased. The advantages of closed loop systems are more apparent in complex situations like open heart surgery where not only a large number of drugs are being administered simultaneously but their requirements also change on a minute to minute basis.

The pharmacodynamic feedback guided automated anaesthesia delivery systems, also known as closed loop systems, have been shown to outperform the traditional manual drug delivery of anaesthetic agents. Such pharmacodynamic feedback to control anaesthesia may be superior in situations of altered pharmacokinetics such as those encountered during cardiopulmonary bypass (CPB) and hypothermia. CLADS (Closed Loop Anaesthesia Delivery System) is a BIS guided closed loop anaesthesia delivery system developed at PGIMER, Chandigarh and has been used successfully for administration of propofol, an intravenous anaesthetic, in various situations, like non-cardiac surgery, cardiac surgery, post-operative sedation and high altitude. CLADS had the uniqueness of using simple syringe pumps to control the intravenous anaesthetic drug delivery and for the first time using closed loop administration of anaesthetics both for induction as well as maintenance of anaesthesia. It has been in use since last more than 10 years and has been used on more than 6000 patients including patients with cardiac, liver and renal dysfunctions both for
cardiac surgery as well as non cardiac surgery and its usefulness and safety has been well proved in different groups of surgical patients. During last 10 years the system has been continuously refined and upgraded to incorporate a number of safety features including hemodynamic control as well as user friendly options of using both intravenously as well as inhalational anaesthetic agents depending upon user’s choice and interchange of these anaesthetic agents during active anaesthesia. IAADS (Improved Anaesthetic Agent Delivery System), an improved version of CLADS with a number of safety features of hemodynamic control and which can administer isoflurane and muscle relaxants besides propofol in adults and children not only encompasses the induction and maintenance of intravenous anaesthesia but also controls the muscle relaxant delivery based on the feedback from neuromuscular junction monitoring and analgesic delivery based on the preset rate of delivery along with as and when required based on the hemodynamic and EEG responses. The ultimate goal for closed-loop controllers is their general acceptance in clinical practice for which multicenter study has been completed successfully.

Fig 3 Line diagram of CLADS / IAADS showing interfacing of different monitors and drug infusing syringe pumps with algorithm in the computer to control the drug infusions based on the feedback from the patient monitors.

CLADS / IAADS system can operate in various modes. In “monitor” mode, it requests an update of the latest BIS and other vital sign data at user-defined intervals, provides a graphic display of current and trend values and records them on the hard disc of the computer (PC). In “manual” mode, the user can also control the propofol infusion rate manually, using the keyboard / mouse / screen of the PC. The PC displays a graph of the propofol delivery rate and trends the BIS and other vital signs values. When the system is in “automatic” mode, in addition to the functions already described, it also automatically controls the anaesthetic agent, muscle relaxant and narcotic infusion, according to mode selected as induction, maintenance or induction and maintenance combined. User need to enter a target BIS value, maximum allowable anaesthetic infusion rate, a starting infusion rate in case of maintenance mode and status of the patients - Low Risk (ASA I-III), High Risk (ASA IV, NYHA class 3), Very high risk (ASA IV-V, NYHA IV), Children.

The ‘control algorithm’ is based on the relationship between various rates of propofol infusion (producing different plasma concentrations) and BIS, taking into consideration the pharmacokinetic variables (distribution and clearance) that were established in the developmental stage of CLADS. The system also incorporates an algorithm for children, which takes into account the alteration in pharmacokinetics, mainly change in the distribution compartment and clearance (age-wise) of anaesthetic drugs in them. This allows the system to be used for induction and maintenance of anaesthesia in paediatric patients. The system also notifies the anaesthesiologist deviations in blood pressure, heart rate or changes in the end tidal CO₂ concentration. The system stops administering agents automatically if there is deterioration in vital parameters beyond the limits set by the anaesthesiologist. It uses voice clips in addition to visual display to notify the anaesthesiologist deviations in vital parameters, cut-off of anaesthetic agents, high EMG activity, etc and also provides possible suggestions, such as, “give atropine”, “give muscle relaxant”, “start inotropes”, etc. for managing haemodynamic disturbances.
Check Validity of BIS using SQI
  
  Valid
  
  BIS Error (PB-TB) > +5 or < -5
    
    Yes
    
    Set new Propofol infusion rate
      
      No
    
    See previous BIS trends and accordingly ↑ or ↓ the propofol infusion rate

  Invalid
    
    Safe Mode

Fig 3 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.

Calculate:
1. TC
2. FRC
3. IAA uptake

Check $\text{CO}_2 + \text{EIAA}$ Check BIS

BIS Error < -5 (PB-TB) Yes

Stop IAA injection

No

Maintain IAA Rate

BIS Error > +5

TC error $\text{positive} (\text{TC}-\text{PC})$

Yes

Reset TC

No

IAA injection Rate Based on:
1. TC error
2. PC
3. DOA
4. ROTCA

TC error $\text{negative} (\text{TC}-\text{PC})$

Yes

Reset TC

No

TC = target concentration; WT = weight of patient.

Fig 4 Broad algorithm of CLADS for inhalational anaesthetic delivery. CV = circuit volume; DOA = duration of anaesthesia; FRC = functional residual capacity; HT = height; IAA = Inhalational anaesthetic uptake; PB = present BIS; PC = present concentration; ROTCA = rapidity of target concentrations achievement; RB = Target BIS; TC = target concentration.
The success of the system to administer propofol and isoflurane anaesthesia has been demonstrated in both adults and children and both cardiac and non cardiac surgery. CLADS as well as IAADS are able to achieve induction in all patients without major hemodynamic instability and within acceptable period of time. The induction dose needed and the BIS overshoot during induction are both significantly less while using closed loop systems of anaesthesia. This is because of more frequent and smaller dose adjustments made by CLADS/IAADS 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 finer tuning of propofol dose by IAADS and automatic cutoff of propofol delivery in the event of a major drop in hemodynamic. Following a smooth induction, the CLADS/IAADS is able to maintain clinically adequate anaesthesia in all the patients during the period of automatic control.

CPB and hypothermia alters the pharmacokinetics and pharmacodynamics of propofol unpredictably. Moreover, propofol pharmacokinetics differs in children from that in adults. Therefore, controlling the pharmacodynamic effect of propofol may be superior to target-controlled infusions based on serum or effect-site concentrations. Various investigators have demonstrated good correlation between predicted plasma propofol concentration and BIS in children. Since BIS is the controlled parameter in our system, the variations in pharmacokinetics that affect propofol requirements during CPB may be overcome in this pharmacodynamic based closed loop control. CLADS/IAADS has been successfully evaluated even in open heart surgery for children.

Hemodynamic stability is better maintained using IAADS than manual control - which is very much desired in open heart surgery. This may probably be because the anaesthesiologist often gets distracted from the accuracy of anaesthetic delivery for want of paying attention to other aspects of anaesthetic management like coagulation/blood gas monitoring/ventilation, etc. This may have led to a late detection of increased propofol delivery rate and subsequent adjustments of hemodynamic. Also, the frequent dose adjustments that were required in the manual group to obtain good stability of anaesthetic depth involved substantial involvement of anaesthesia human resources. Use of IAADS could enable the anaesthesiologist to pay attention to other aspects of anaesthesia, e.g, hemodynamic control, performance of trans-esophageal echocardiography, etc.

Cost effectiveness is an important measure of efficiency in assessment of quality of health care services provided these days. Closed loop anaesthesia system CLADS / IAADS use significantly lesser amounts of propofol during induction and maintenance and also conserves isoflurane during inhalational anaesthesia delivery for maintenance of anaesthetic depth as compared to the manual control. This was achieved because of the frequent alterations done by the IAADS to maintain the optimal depth of anaesthesia judged by BIS and thus avoiding either very deep or light planes of anaesthesia. Although the difference in consumption of anaesthetic agent
appears small, the cumulative difference if used for long duration surgeries and multiple surgeries can result in cost effective anaesthetic administration. Moreover, the number of times isoflurane dial settings were changed manually translates to an involvement of anaesthesia human resource in maintaining appropriate depth of anaesthesia. Use of CLADS and IAADS has also better hemodynamic stability in critically ill cardiac surgery patients.

In conclusion closed loop systems have an important role in the future clinical management during anaesthesia and CLADS as an indigenous system of automated anaesthesia has a great potential.

References

Abstract
With the advancement in microprocessor technology and development of objective anaesthesia depth indicators, the use of automated anaesthesia delivery system using feedback from different EEG derived parameters has become a reality. The anaesthetic drugs can be delivered based on patients’ individual requirement using computer controlled syringe infusion pumps. CLADS is an indigenously developed closed loop anaesthesia delivery system which can control delivery of both intravenous as well as inhalational anaesthetics depending upon patient requirement with continuous feedback from the patient. The system has been developed at PGIMER Chandigarh and is in use for last more than 10 years and its performance has been successfully evaluated in patients undergoing both cardiac as well as non-cardiac surgery in adult as well as paediatric patients. It can control neuromuscular blocking agents in addition to anaesthetics as well as analgesic drugs. With this automated anaesthesia has become a reality with optimum anaesthetic drug control and improved hemodynamic stability intraoperatively.