Closed-loop delivery systems versus manually controlled administration of total intravenous anesthesia: a meta-analysis of randomized clinical trials.

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Supplemental Material

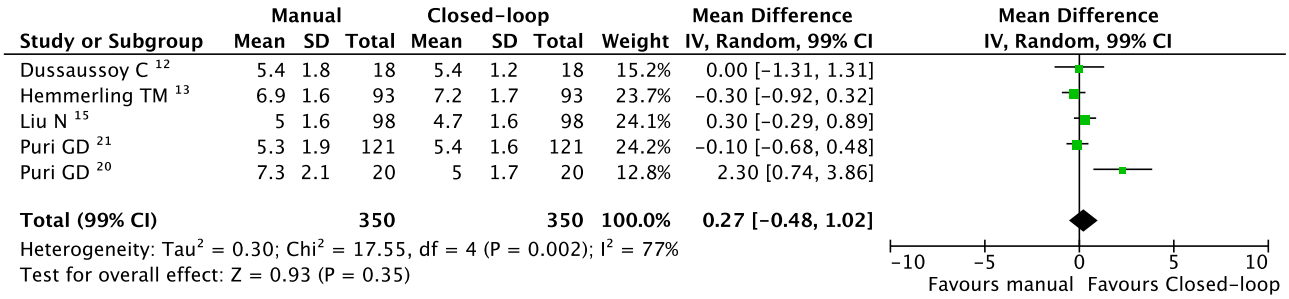
Table of contents:

Table 1. Results of assessment of risk of bias, based on Cochrane risk of bias tool.

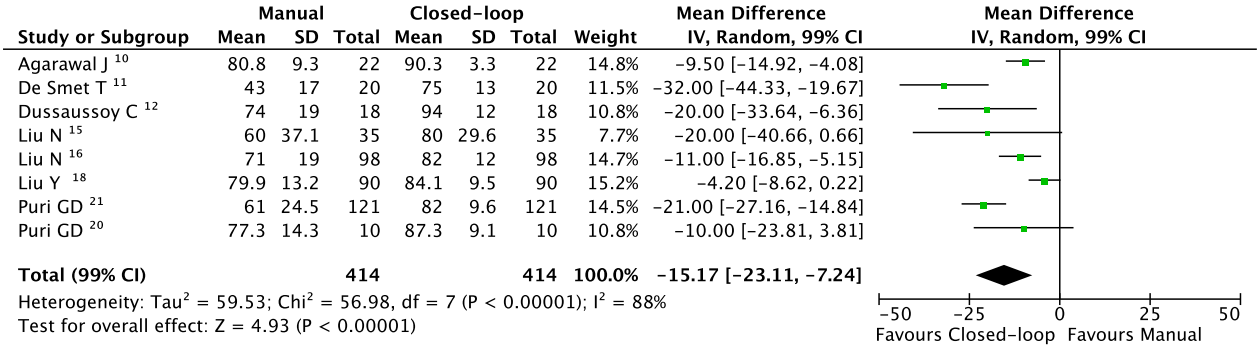
First author	Year	Random sequence generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data addressed	Free of selective reporting	Free of other bias	Score	Overall risk of bias
Agarawal J[10]	2009	Unclear	Yes	No	No	No	Yes	Yes	**7**	**Moderate**
De Smet T[11]	2008	Unclear	Unclear	No	No	Yes	Yes	Yes	**6**	**Low**
Dussaussoy C[12]	2014	Yes	Unclear	No	No	Yes	Yes	Unclear	**6**	**Low**
Hemmerling TM[13]	2010	Yes	Unclear	No	No	No	Yes	Yes	**7**	**Moderate**
Hemmerling TM[14]	2013	Unclear	Unclear	No	No	No	Yes	No	**10**	**High**
Liu N[15]	2011	Yes	Yes	No	No	No	Yes	No	**8**	**Moderate**
Liu N[16]	2012	Yes	Yes	No	No	No	Yes	Unclear	**7**	**Moderate**
Liu N[17]	2006	Yes	Unclear	No	No	No	Yes	Yes	**7**	**Moderate**
Liu N[18]	2006	Yes	Unclear	No	No	Yes	Yes	Yes	**5**	**Low**
Morley A[19]	2000	Unclear	Unclear	No	No	Yes	Yes	Unclear	**7**	**Moderate**
Puri GD[20]	2007	Yes	Unclear	No	No	Yes	Yes	Unclear	**5**	**Low**
Struys MM[21]	2001	Unclear	Unclear	No	No	Yes	Yes	Unclear	**7**	**Moderate**

Overall risk of bias was estimated with the following scoring chart: 2 points for each “No”, 1 point for each “Unclear”, 0 points for each “Yes”.
0-6 points: Low risk of bias; 7-8 points: Moderate risk of bias; 9-10 points: High risk of bias

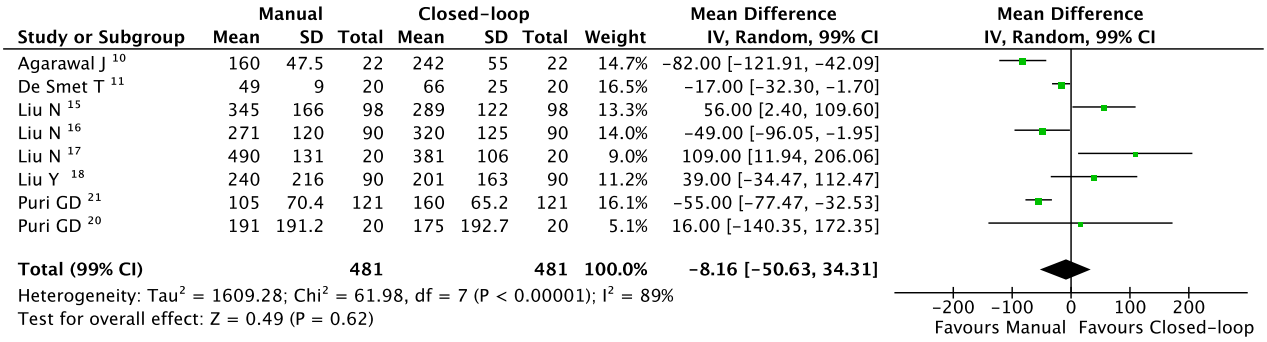
Supplemental Figure 1. Forest plot for dose (mg/kg/h) of administered propofol.



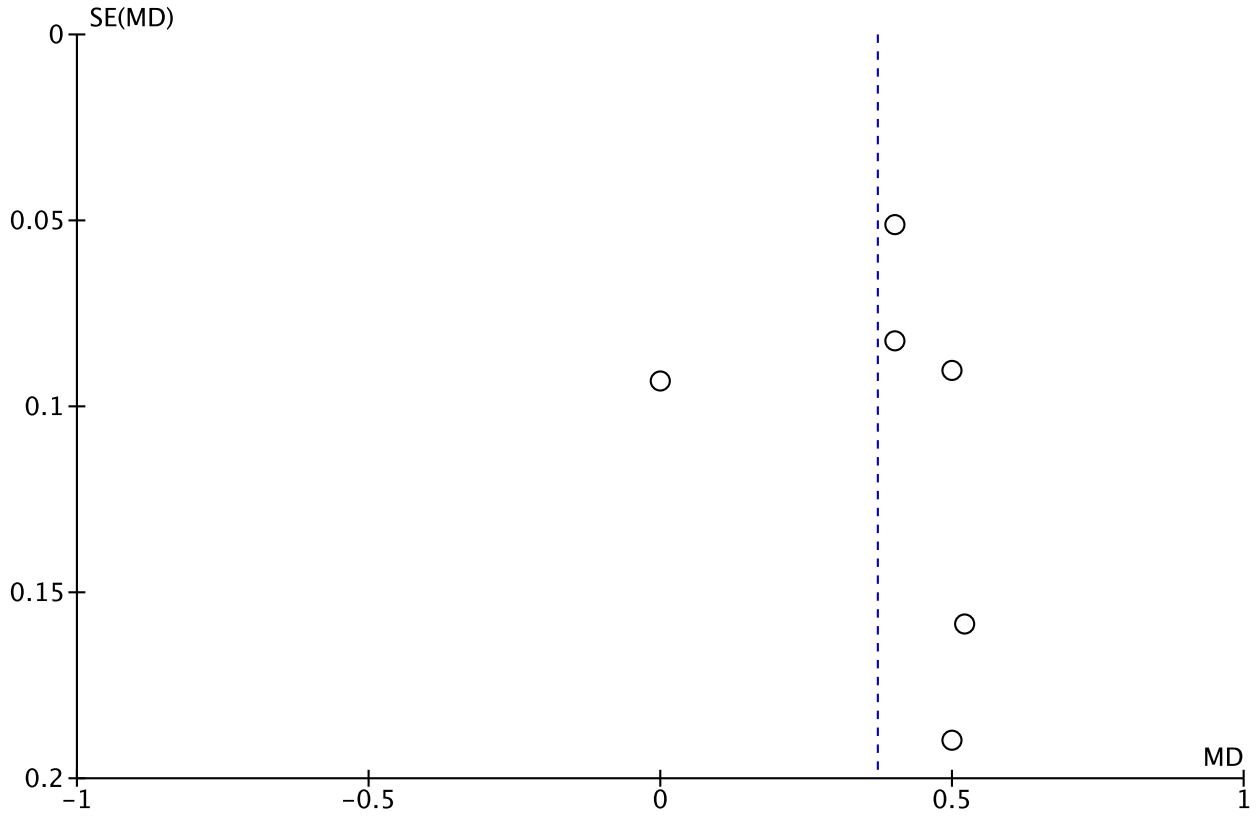
Supplemental Figure 2. Forest plot for BIS ± 10% of target



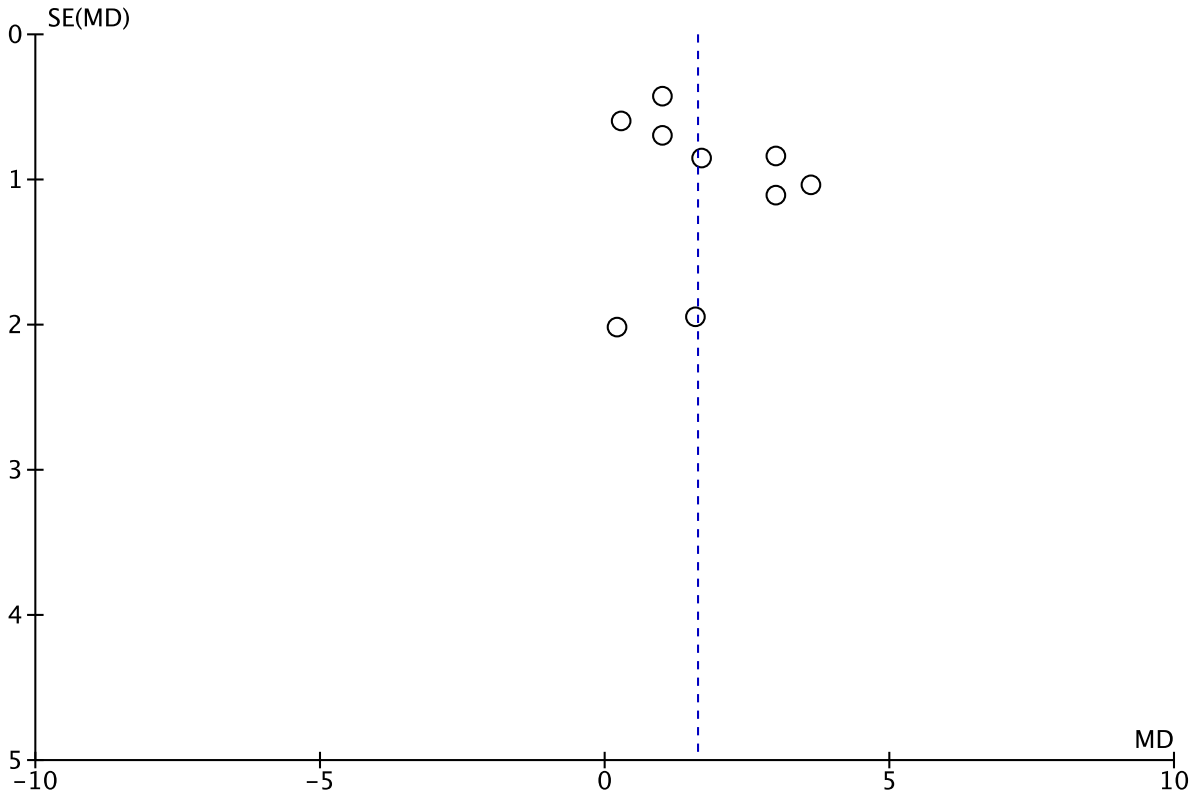
Supplemental Figure 3. Forest plot for time (seconds) to anesthesia induction



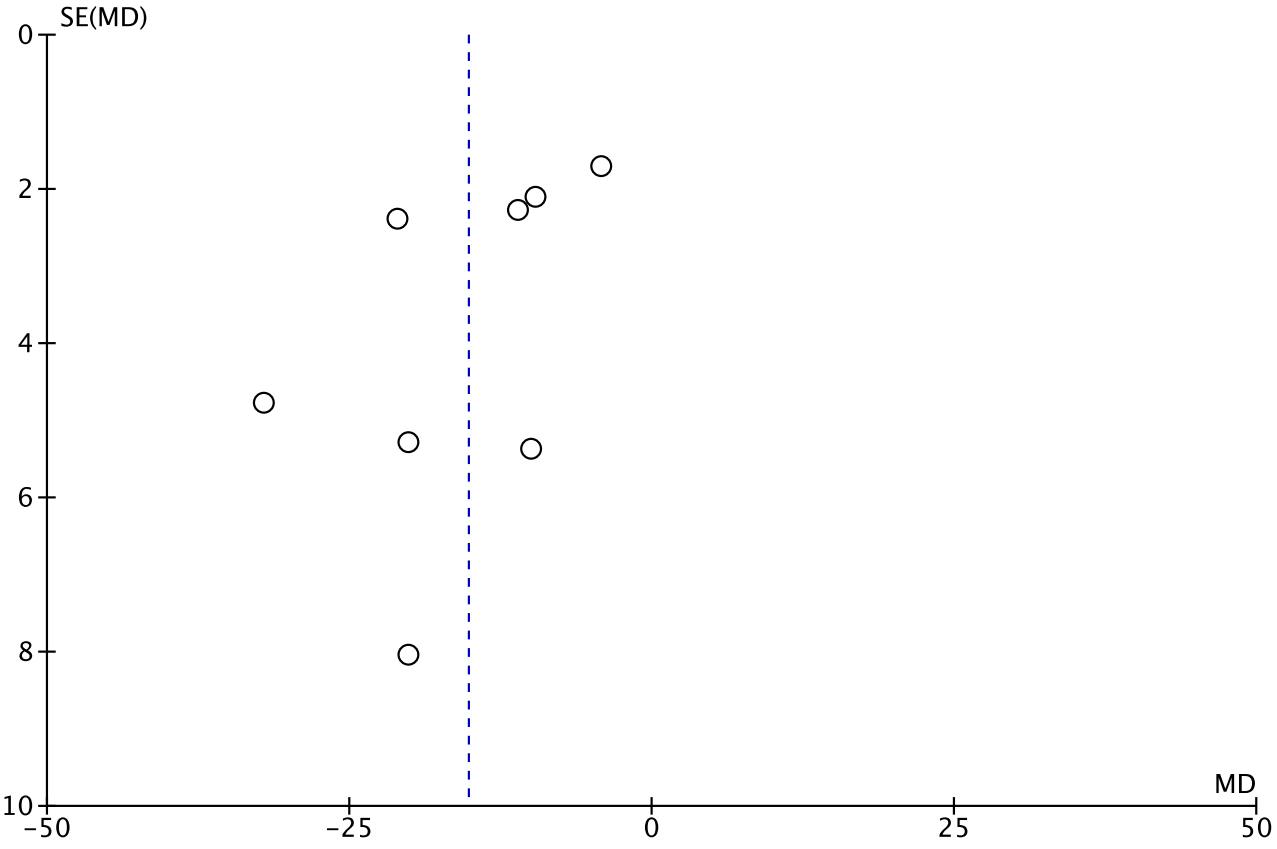
Supplemental Figure 4. Funnel plot for dose (mg/kg) of propofol administered for anesthesia induction



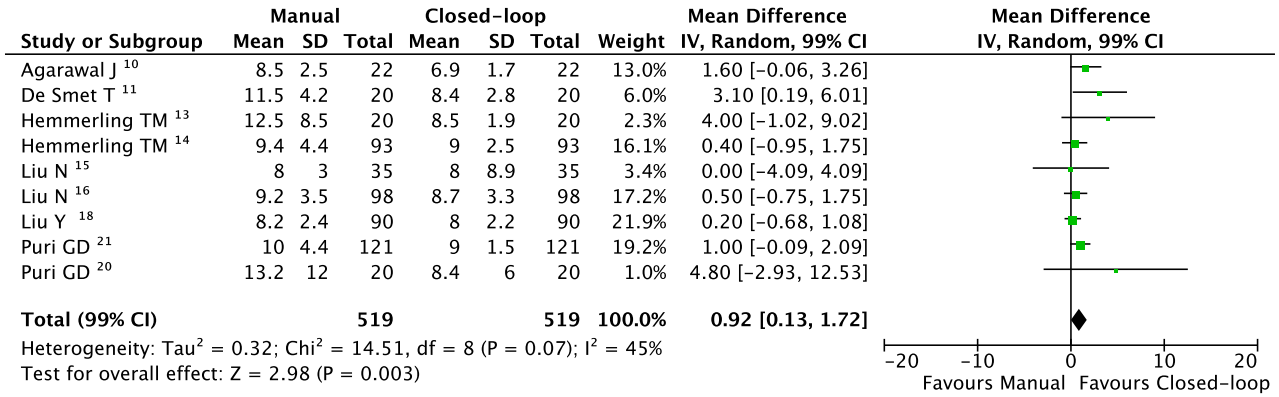
Supplemental Figure 5. Funnel plot for recovery time



Supplemental Figure 6. Funnel plot for BIS 10%



Supplemental Figure 7. Forest plot for Wobble Index



Details on the devices and algorithms

Agarwal J

CLADS is a patented (502/DEL/2003) propofol delivery system, that uses BIS as the 'controlled variable' and a standard infusion pump as the 'actuator'. 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 and clearance) that were established in the developmental stage of CLADS. The algorithm alters the rate of propofol infusion to steer BIS to the set target taking into account the existing BIS, the 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 as well as the peak effect of propofol. An IBM compatible PENTIUM 4 PC is used to implement the control algorithm, provide a user interface and to control communication through serial ports (RS 232) with the BIS monitor (A2000, version 3.0 rev 0.5, Aspect Medical System Inc., Norwood, MA), the infusion system (Pilot-C, Frasenius, Paris, France) and the Datex vital sign monitor (AS5, Datex Ohmeda Division, GE Health- care, Singapore).

CLADS can be operated in two different modes – manual and automatic. In the manual mode, the rate of propofol infusion is controlled manually through the keyboard of the personal computer (PC). In the automatic mode, the system automatically controls the rate of propofol infusion based on BIS feedback. The user can limit the maximum allowable rate of drug infusion and thereby the achievable plasma concentrations at induction and maintenance by choosing the risk status of the patient, in general, ASA IV or NYHA III or above as high risk and ASA I–III as low risk.

De Smet T

The BIS was applied as controlled variable to titrate
propofol administration. BIS (BIS-XP®, version 4) is derived from the frontal electroencephalogram as calculated by the A-2000 BIS® Monitor (Aspect Medical Systems, Inc., Norwood, MA) using four BIS-Sensor electrodes (Aspect Medical Systems).

In all patients, our setup used a laptop running RUGLOOPII1* to calculate the target controlled infu- sion (TCI) algorithms to steer the infusion pump, and to record all relevant physiologic data including the BIS signal. The target controlled infusion system used a three compartment model with an effect compart- ment, previously published by Schnider et al.16,17 As in a previous study of Struys et al.,18 for the calculation of the propofol effect-site concentration (CePROP) a fixed time-to-peak effect site concentra- tion19 of 1.6 min was used, as also published by Schnider et al.17

In the closed-loop control group, the RUGLOOPII platform also executed the closed-loop control, calcu- lating an adequate propofol effect-site concentration from the measured BIS, to serve as the input to the effect compartment controlled TCI system. In the control group, the anesthetist applied the TCI system directly to titrate the propofol administration.

Blood pressure, heart rate, end-tidal CO2, and Spo2 were acquired using the S5-monitor. (GE Healthcare, Helsinki, Finland.). All data were stored on hard disk at a 5-s interval.

More information available at http://www.anesthesia- uzgent.be

Dussaussoy C

A BIS electrode (Zipprep, ÒCovidien, Dublin, Ireland) was posi- tioned on the patient's forehead and connected to an A-2000 XP (version 3.11) BIS monitor.

All patients received total intravenous anesthesia in TCI mode using the population pharmacokinetic set of Schnider et al. [10] for propofol and Minto et al. [11] for remifen- tanil during induction and maintenance of general anaes- thesia. However, TCI was either manually adjusted by the anesthesiologist, according to BIS readings (TCI Manual) or TCI was automatically driven by the controller to which BIS monitor was interfaced (TCI Loop). Here, BIS signal was the input to the controller which automatically adjus- ted TCI target concentrations to maintain BIS in the range 40–60 %. The controller [9] was implemented using Infusion Toolbox 95Ò software (version 4.11) [12] which served as a platform. It allowed: (1) calculating effect-site concen- trations of propofol and remifentanil using the pharmaco- kinetic populations; (2) displaying these calculated effect- site concentration estimates in real time; (3) providing a user interface to enter patient's demographic data (sex, age, weight and height) and set modification of upper and lower limits of drug concentrations; (4) controlling the propofol and remifentanil infusion pumps (Alaris Medical, Hamp- shire, UK); and (5) recording BIS, and calculating effect- site concentrations. Hemodynamic data (heart rate and blood pressure) was manually recorded every 5 min. In the TCI Loop group, the investigator chose the initial propofol effect-site target concentration according to his/her clinical judgment and the controller set the first remifentanil effect- site target concentration by applying a fixed algorithm. Then, starting from these initial target concentrations, the controller automatically piloted changes in target concen- tration to reach a BIS endpoint of 50 % during induction and then to maintain it in the range 40–60 % during maintenance. A detailed description of the proportional- integral-derivative controller has been provided in a pre- vious controlled study [9]. Throughout anesthesia, the anesthesiologist could temporarily override the controller without restriction by manually adjusting target concen- tration of remifentanil, as judged necessary by BIS read- ings or for any clinical reason. At the end of surgery, the TCI Loop controller was switched off to allow emergence from anesthesia.

Hemmerling TM 2010

The BIS Vista monitor (BIS VistaTM) (Aspect Medical Systems, Inc., Newton, MA, USA) was used as the control variable, while a standard syringe pump, Graseby 3400, (Graseby Medical, Watford, UK) was the actuator. To close the loop, a notebook computer was used to imple- ment the algorithm, provide the graphical interface, and control communication between the BIS VistaTM monitor and the syringe pump via RS-232 ports. The user must insert the target BIS and the age and weight of the patient, and the system automatically con- trols the rate of propofol infusion in ''automatic'' mode. The target BIS can be changed according to clinical need during the course of the surgical procedure. The system acquires an update of the BIS, SQI, and EMG every five seconds and calculates a moving average of valid BIS every 20 sec. A valid BIS measurement is assumed when the SQI is[40% and the EMG is\40dB. It is important to note that an empty EMG bar on the BIS monitor corresponds to an EMG level \ 30 dB. If the resultant BIS average is 30 to 60, the algorithm calculates another average of valid BIS such that the resultant BIS is an average taken at each 40 sec interval, and a dose would be calculated at that time interval. If the first BIS average (20 sec) is 20 to 30, a minimal dose is administered, if \ 20, the infusion stops, and if [60, an automatic bolus is given (Fig. 1).

The system is self-adaptive in that the dose calculation is a function of the previous dose and the adjustment fac- tors are proportional to: 1) BIS error, i.e., the difference between the target and the actual BIS value; 2) BIS vari- ation, i.e., the difference between the actual and the previous BIS; and 3) BIS trend, i.e., the difference between the target and the average BIS values on a longer time interval. Patient characteristics (age and weight) determine the minimum and maximum allowable doses of propofol infusion and the bolus doses. These allowable doses are also a function of the BIS trend. For instance, measured BIS values above the target for the preceding five minutes will induce an increase of the maximal dose. During periods of artefacts (invalid BIS), the algorithm calculates and administers the average doses infused during the last period of time, and time is proportional to the duration of artefacts.

In ''manual'' mode, the anesthesiologist needs to change the propofol infusion dose to maintain the BIS as close as possible to a desired target. In both modes, the system records the input variable from the BIS monitor as well as output data at ten-second intervals for subsequent analysis.

The graphical user interface is designed using LabVIEW (National Instruments, Austin, TX, USA). It contains col- our-coded graphic and numeric elements, push buttons, and graphs (Fig. 2). As recommended by the BIS manufacturer, the SQI and EMG are displayed along with the BIS, and they turn red when they fall outside their accepted boundaries, indicating artefacts. The BIS blinks during that

period. The interface requires patient characteristics, which can be modified during start-up. It also displays the infu- sion dose, the corresponding rate, the average dose, and emergency bolus information.

Hemmerling TM 2013

McSleepy is an automated, expert-based closed-loop anaesthesia drug delivery system that integrates the three components of general anaesthesia: hypnosis, analgesia, and muscle relaxation.
http://www.medgadget.com/2008/05/mcsleepy_automated_anesthesia_system.html

Liu N Eur J Anesthesiol 2006, Liu N 2011, Liu N Anesthesiology 2006

The software Infusion Toolbox 95® version 4.8 [7] was used to implement our closed- loop algorithm. The software is programmed in Visual Smalltalk, an object oriented language (VisualAge for Smalltalk® version 5.5 IBM). The software calcu- lates plasma and effect-site propofol concentration (Ce) using several pharmacokinetics models. It controls two infusion pumps Asena GH® (Alaris Medical UK Ltd, Basingstoke, Hants UK) and records the Bispec- tral Index obtained from an A-2000 XP® (Aspect Medical System, version 3.11). A standard PC run- ning a Windows 98® was used to implement the control algorithm, to provide a user interface and to control communication with the A-2000 XP® mon- itor and the infusion pumps via an RS232 serial port. The user must enter the gender, age, height and weight of the patient.
The control algorithm was written by one of the authors (B.T.) and based on a proportional differential control algorithm allowing the titration of propofol until the target level of Bispectral Index of 50 was reached. The algorithm uses the pharmacokinetic model of propofol of Schnider [8]. The delay between each modification of target propofol was determined by the time necessary for the equilibration of the effect-site compartment. The gain constant used in the control algorithm was determined using the simula- tor included in Infusion Toolbox and tested in a pilot study.

Liu Y 2015

The CONCERT-CL closed-loop infusion system designed by VERYARK Technology Co., Ltd. (Guangxi, China) is an innovation using TCI combined with closed-loop controlled intra- venous anesthesia under the guide of BIS
http://www.veryark.com/plus/list.php?tid=21 nessuna informazione aggiuntiva

Morley A 2000

A modified proportional-integral- derivative (PID) controller algorithm for drug adminis- tration was developed. This was incorporated into an existing software program `Monitor', written by one of the authors (J.D.) for a Macintosh Power PC computer. `Monitor' enables the user to download data from several sources onto the same file using a multiple serial interface (SEQS, Creative Solutions Inc., USA). In this study we recorded data from the RS-232 port of the anaesthetic machine, a Narkomed 4E with attached Vitalert 2000 monitor (North American Drager, Telford, PA, USA). EEG data were acquired from bi-frontal electrodes via the `Processed EEG' port of an Aspect A-1000 EEG monitor (software v3.12 Aspect Medical Systems, Framingham, MA, USA). Electrode impedance was maintained below 5 kV. Incorporation of the PID algorithm into the program allowed the computer to control anaesthetic drug administration, according to the BIS, using a syringe pump (Graseby 3400, Graseby Medical, Watford, UK) from which infusion rate data were also recorded. Heart rate, end-tidal isoflurane concentration (FEÂ iso), median frequency, SEF and BIS, and drug infusion rates were recorded and processed at 5-s intervals, and noninvasive arterial blood pressure (NIBP) at 3-min intervals. In a pilot study, the system was tuned to a BIS of 50 using the method of Zeigler and Nichols [10]. Tuning was performed separately for the two different anaesthetic techniques.

Puri GD 2015 and Puri GD 2007

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.7,13 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 exist- ing BIS, time elapsed since the initiation of infusion, phar- macokinetics, 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 communi- cation 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 infu- sion 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 cal- culates the BIS error (Target BIS − Actual BIS). It uses a pro- portional integral differential algorithm based on this error to make the changes in propofol infusion rate every 30 sec- onds to achieve target BIS.

The automatic mode has 3 options: (1) induction, (2) maintenance, and (3) induction combined with mainte- nance. The algorithm ne-tunes the rate and duration of propofol delivery differently during induction and the maintenance phases of anesthesia delivery. During induc- tion, the controller tries to achieve the target concentration in a stepwise fashion (while continuously receiving feed- back 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 rst and last 3 BIS values of each epoch are aver- aged and compared with determine the trend. When the trends indicate an increasing BIS, greater target concentra- tions, 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 mak- ing drug alterations.

The user can limit the maximal allowable rate of drug infusion and thereby the achievable calculated concen- trations 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 hemo- dynamics 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 lim- its. The propofol infusion would restart automatically when hemodynamics improve to values above the prede ned 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 CO_2, BIS values, Signal Quality Index, electromyography activity, and sup- pression ratio. The sampling frequency of BIS was every 5 seconds.