DEVELOPMENT AND PERFORMANCE OF A CLOSED-LOOP PROPOFOL SYSTEM

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ABSTRACT

Objective: The purpose of this project is to develop a novel, expert-based closed-loop system for propofol administration using Bispectral Index (BIS).

Methods: The system is designed to process real-time BIS during general anesthesia, compare it with a target BIS and use the difference to adjust the infusion rate of propofol. A graphical user interface as well as remote control and monitoring are integrated in the system. After IRB approval and written consent, 50 patients are randomly assigned to 2 groups of equal size. After manual propofol induction, closed loop control is used to maintain anesthesia at a chosen target BIS of 45 (*Closed-loop group*); in the *Control group*, propofol is administered manually by an experienced anesthesiologist.

Results (preliminary results, n = 22): Closed-loop control was able to achieve maintenance of anesthesia for all patients. In the *Closed-loop group*, BIS was within ± 10% of the target significantly longer, and outside ± 30% of the target time than in the *Control group* (P=0.001, P=0.01, respectively).

Discussion: An expert-based closed-loop system for propofol was designed including a numeric-graphical interface. It seems to offer better control of anesthesia than manual control.

Index Terms — Closed-loop, anesthesia, BIS, propofol

INTRODUCTION

The use of closed-loop systems might improve the quality of drug administration [1]. Automated drug delivery systems use an input variable (e.g. anesthetic depth or blood pressure) to control the output (drug delivery rate) [2]. A number of basic components are required to develop a satisfactory closed-loop drug delivery system: (1) a system under control - the patient; (2) a controlled variable that measures the relevant drug effect; (3) a set point for this variable - the chosen target value; (4) an actuator - the infusion pump allowing continuous drug administration; and (5) a controller to control the actuator, which comprises algorithms to translate a measured value of the controlled variable to a particular action for the actuator in order to maintain the controlled variable close to the target [1].

The Bispectral Index (BIS) derives from processing the phase and frequency relations of the component frequencies of the electroencephalogram (EEG) [3]. BIS is a dimensionless number scaled from 0-100, with 100 representing an awake patient and 0 representing no EEG activity; a value between 40 and 60 is considered as representing an adequate state of hypnosis [4]. Previous studies proved that BIS was well suited as control variable for closed-loop control systems [1], [5-9]. Other concluded that closed-loop systems using BIS outperforms manual control [2-4].

The focus of the current project is to develop a new expert-based closed-loop system for propofol administration; to assess its performance and to integrate an easy-to-use graphical interface as well as a module for remote control and monitoring using a personal digital assistant (PDA).

METHODS

System specifications

Bispectral Index is recorded using the Vista monitor (BIS Vista™, Aspect Medical Systems, Inc, Newton, MA, USA); a standard syringe pump (Graseby 3400, Graseby Medical, Watford, UK) is the actuator. An IBM compatible Pentium 4 notebook computer running Windows XP (Microsoft, Redmond, WA, USA) is used to implement the algorithm, provide the graphical interface and control the communication with the Vista monitor and the pump via RS-232 ports. The system controls propofol infusion to achieve a target BIS to maintain anesthesia. The user must enter target BIS, age and weight of the patient.

A valid BIS measurement is assumed when the signal quality index (SQI) (used by the BIS monitor to indicate absence of artefacts) is greater than 40, and the EMG (indicator of high frequency activity, e.g. electrocautery) is less than 40. The system acquires an update of BIS, SQI and EMG every 5 s and calculates a moving average of valid BIS every 20 s, which is used for the control algorithm determining the

action accordingly: if the resultant BIS average is between 30 and 60, the algorithm calculates another average of valid BIS such that the resultant BIS is an average taken at a 40 s interval. A dose shall be calculated at that time interval. If the first BIS average (20 s) is between 20 and 30, a minimal dose is administered; if below 20, the infusion stops and if above 60, an automatic bolus is given. The system is *self-adaptive* as such that the dose calculation is a function of the previous dose and adjustment factors proportional to: (1) BIS error, i.e., difference between the target and the actual BIS value; (2) BIS variation, i.e., difference between the actual and the previous BIS; (3) BIS trend, i.e., difference between the target and the average BIS values of the last 5 minutes; (4) patient characteristics (age and weight). Patient characteristics also determine the minimum allowable dose of propofol infusion and the bolus doses. The maximum allowable dose is a function of the BIS trend. During periods of artefacts (invalid BIS), the average dose of the last 10 minutes is administered. The graphical user interface is designed using LabVIEW (National Instruments, Austin, TX, USA). A compact version of the display is designed for PDA, in a client-server environment where the computer acts as a server and the PDA connects to it via Wi-Fi using peer-to-peer connection.

Clinical trial

After IRB approval and written consent, 50 patients undergoing orthopedic or general surgery are randomly assigned to 2 groups of equal size. After manual propofol induction (1.5 mg/kg), closed loop control is used to maintain anesthesia at a *target BIS* of 45 (*Closed-loop group*); in the *Control group*, propofol is administered manually using a syringe pump by an experienced anaesthesiologist in order to maintain a target of 45 as closely as possible. Data are recorded every 10 s.

Precision of the system is assessed using the performance indices proposed by Varvel et al. [10]. Performance error (PE) is calculated as the difference between actual and target values. Bias or median performance error (MDPE) describes whether the measured values were either above or below the target ones and thus represented the direction (undershoot or overshoot) of the PE. Inaccuracy or median absolute performance error (MDAPE) describes the size of the errors. Wobble measured the intraindividual variability in PE. Formulas are provided below.

$$PE = \frac{BIS_{measured} - BIS_{target}}{BIS_{target}} \times 100 \quad (1)$$

$$MDPE_i = Median\{PE_{ij}, j = 1,..., N_i\} \quad (2)$$

$$MDAPE_i = Median\{|PE|_{ij}, j = 1,..., N_i\} \quad (3)$$

$$Wobble_i = Median\{|PE_{ij} - MDPE_i|, j = 1,..., N_i\} \quad (4)$$

The performance of the system is defined as excellent, good, poor or inadequate, when the BIS was within 10%, between 10 and 20%, between 20 and 30% or above 30% of the target BIS, respectively. Data are presented as mean ± SD. Parameters between the two groups are compared using the Mann-Whitney U test for continuous data and the Chi-square test for categorical data; P<0.05 considered statistically significant.

RESULTS

(Preliminary results, *Closed-loop group*, n = 11; *Control group*, n = 11):

Figure 1 depicts the user interface and PDA interface. Mean patient data were similar with age was 50 ± 16 yrs versus 60 ± 16 yrs, weight 80 ± 9 kg versus 70 ± 15 kg, with 9 men, 2 women versus 7 men, 4 women, in the *Closed-loop* versus *Control group*, respectively (Table 1).

(a)

(b)

Figure 1: (a) Graphical user interface of the closed-loop system

(b) Interface on PDA

TABLE 1: Patient characteristic data

	Closed-loop Group	Control Group	P value
Age (y)	50 ± 16	60 ± 16	0.13
Weight (Kg)	80 ± 9	70 ± 15	0.05
Sex (M/F)	9/2	7/4	0.63

Duration of anesthesia, time to extubation and median infusion dose were 178 ± 68 min versus 115 ± 68 min, 9 ± 2 min versus 11 ± 4 min, and 102 ± 47 µg/kg/min versus 97 ± 20 µg/kg/min, *Closed-loop* versus *Control group*, respectively (Table2).

The performance indices were significantly better in the Closed-loop group (Table 3).

In the *Closed-loop group,* excellent control of anesthesia occurred significantly more often (P=0.0006) and inadequate control less often than in the *Control group* (P=0.005) (Figure 2).

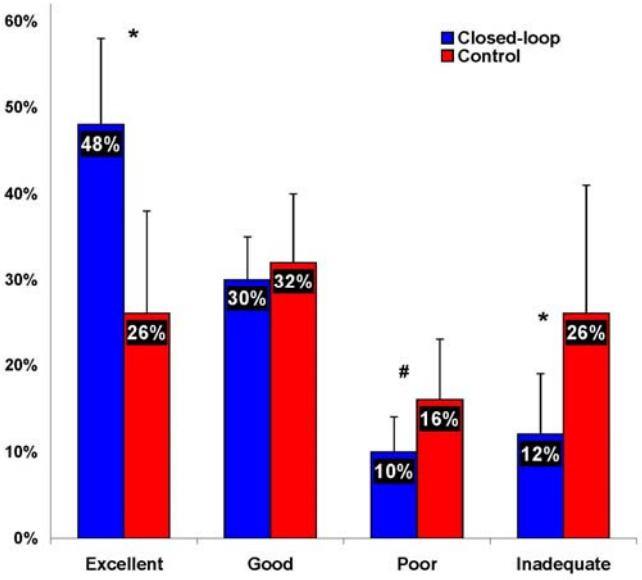

Figure 2: Control performance during maintenance of anesthesia. * P < 0.005; # P < 0.05

TABLE 2: Clinical data

	Closed-loop Group	Control Group	P value
Anesthesia duration (min)	178 ± 68	115 ± 68	0.06
Median infusion dose (µg/Kg/min)	101.6 ± 46.7	97.27 ± 20.1	0.68
Time to extubation (min)	9 ± 2	11 ± 4	0.64

TABLE 3: Controller Performance

	Closed-loop Group	Control Group	P value
Median BIS	43.8 ± 3.0	41.9 ± 7.8	0.58
MDPE [%]	1.0 ± 6.4	-11 ± 17.4	0.09
MDAPE [%]	10.4 ± 2.2	18.8 ± 8.5	0.0001
Wobble [%]	9.6 ± 2.4	15.6 ± 10.4	0.04

BIS = Bispectral Index; MDPE = median performance error; MDAPE = median absolute performance error

DISCUSSION

In comparison to manual control, the closed-loop system seems to be able to maintain anesthesia closer to a given target. The PDA module allows remote monitoring.

Future studies will focus on the stability of the system, its ability to further reduce the time of inadequate control and the integration of remote monitoring and control in a clinical setting.

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