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ORIGINAL RESEARCH

Automated titration of propofol and remifentanil decreases the anesthesiologist's workload during vascular or thoracic surgery: a randomized prospective study

Corinne Dussaussoy · Marine Peres · Virginie Jaoul · Ngai Liu · Thierry Chazot · Jean Picquet · Marc Fischler · Laurent Beydon

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Abstract Closed loop target-control infusion systems using a Bispectral (BIS) signal as an input (TCI Loop) can automatically maintain intravenous anesthesia in a BIS range of 40–60 %. Our purpose was to assess to what extent such a system could decrease anesthesia workload in comparison to the use of a stand alone TCI system manually adjusted to fit the same BIS range of 40–60 % (TCI Manual). Patients scheduled for elective vascular or thoracic surgery were randomized to the TCI Loop or TCI Manual method for administering propofol and remifentanil during both induction and maintenance of general anesthesia. Assessment of workload was performed by an independent observer who quoted each time the physician looked at the BIS monitor. The number of propofol and remifentanil target modifications, the percentage of time of adequate anesthesia i.e. BIS in the range 40–60 and hemodynamic data were recorded. Eighteen patients per group were enrolled. Characteristics, duration of surgery and propofol-remifentanil consumption were similar between groups. However, the percentage of time in the BIS range 40–60 % was higher in the TCI Loop versus TCI Manual groups (94 % ± 12 vs. 74 % ± 19, $p < 0.001$). Mean arterial pressure was lower with TCI Manual (78 ± 6 vs. 88 ± 13 mmHg, $p < 0.001$). The number of times the anesthesiologist watched the controller or BIS monitor ($p < 0.05$) and the number of manual adjustments ($p < 0.001$) performed in each group was lower with TCI Loop group during induction and maintenance of anesthesia. An automated controller strikingly frees the anesthesiologist from manual intervention to adjust drug delivery.

Keywords Drug delivery systems · Pharmacokinetics · Anesthesia · Intravenous · Ergonomics · Intravenous drug delivery systems

1 Introduction

Computer technology has opened rapidly growing new avenues in the field of drug delivery. Indeed, since a pioneer work which described a close-loop control of insulin infusion in 1979, [1] such systems have been adapted for drug infusion in anesthesia. The first clinical application including a Bispectral (BIS) index guided closed loop control of propofol appeared in 1998 [2]. Since this time, it has been shown to be safe [3, 4]. We and others have shown it to be superior to manual control of propofol guided by the BIS [5, 6]. Indeed, in a large series of patients under closed loop control of propofol target concentrations, patients spent significantly more time with BIS values within the 40–60 range [5]. Moreover, such closed-loop systems have been proven to be effective in performing the induction of intravenous anesthesia [5, 7]. The induction phase requires rapid adaptation of anesthetic depth and is highly demanding for anesthesiologists [8].

C. Dussaussoy · M. Peres · V. Jaoul · L. Beydon (✉)
Pôle d'Anesthésie Réanimation, CHU d'Angers, 49933 Angers Cedex 9, France
e-mail: lbeydon.angers@invivo.edu

N. Liu · T. Chazot · M. Fischler
Service d'Anesthésie, Hôpital Foch, 40 rue Worth, 92150 Suresnes, France

N. Liu
Outcomes Research Consortium, Cleveland, OH, USA

J. Picquet
Service de chirurgie vasculaire et thoracique, CHU d'Angers, 49933 Angers Cedex 9, France

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Recently, we evaluated a controller allowing the automated BIS-targeted titration of propofol and remifentanil during induction and maintenance of general anesthesia [9]. This study was undertaken to assess the efficacy of this controller to reduce the anesthesiologist's workload.

2 Methods

2.1 Design

This prospective, randomized, single-blind study had received approval from our institutional ethics committee and the relevant French Regulatory Office (Agence Française de Sécurité Sanitaire des Produits de Santé and ClinicalTrial.gov, #NCT00392158). Our study was conducted in a single university hospital (Centre Hospitalier Universitaire d'Angers). Patients scheduled for elective vascular or thoracic surgery, aged 18–80 years with ASA physical status $\leq$ III were informed of the nature of the study and gave their written informed consent during the preoperative visit. Exclusion criteria included psychiatric illness, supraspinal neurological disorders and patients equipped with a pacemaker. All patients were premedicated one hour before surgery with hydroxyzin (75 mg orally) and randomly assigned to dual closed-loop (TCI Loop) or skilled manual (TCI Manual) anesthesia delivered via a target-controlled-infusion (TCI) system controlling propofol and remifentanil infusion. Randomization was balanced within blocks of 10 (five TCI Loop and five TCI Manual groups), and determined using a random number generator. Assignments were kept in sequentially numbered opaque envelopes.

2.2 Procedures

On arrival in the operating room, a dedicated intravenous cannula was inserted, and routine monitoring commenced including temperature and neuromuscular function. A BIS electrode (Zipprep, ®Covidien, Dublin, Ireland) was positioned 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 remifentanil during induction and maintenance of general anaesthesia. 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 adjusted TCI target concentrations to maintain BIS in the range 40–60 %.

The controller [9] was implemented using Infusion Toolbox 95® software (version 4.11) [12] which served as a platform. It allowed: (1) calculating effect-site concentrations of propofol and remifentanil using the pharmacokinetic 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, Hampshire, 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 concentration 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 previous controlled study [9]. Throughout anesthesia, the anesthesiologist could temporarily override the controller without restriction by manually adjusting target concentration of remifentanil, as judged necessary by BIS readings or for any clinical reason. At the end of surgery, the TCI Loop controller was switched off to allow emergence from anesthesia.

In the *TCI Manual group*, the investigator chose the induction effect site concentrations of propofol and remifentanil according to his clinical experience. Anesthesia maintenance was then handled by the investigator who manually controlled TCI, targeting a BIS in the range 40–60. Accordingly, in the *TCI Manual group,* the controller behaved like a conventional TCI delivery system, manually operated.

In both groups, patients received atracurium to facilitate tracheal intubation. Atracurium was not reinfused during the procedure according to our routine practice.

We defined *Induction* as the time elapsed from the start of administration of anesthetic drugs to the moment of skin incision and *Surgery* denoted the period starting at the end of *Induction* to the end of drug infusion. Thus, our study did not include emergence from anesthesia.

The same two anesthesiologists (CD, VJ) were in turn in charge of all cases. Both had a 1-year experience of the automated controller which they had used in more than 100 previous cases. Assessment of the anesthesiologist workload was performed by an independent observer resident in our department (MP) who attended each case and constantly watched the anesthesiologist in charge during the

whole case. She remotely quoted each time the anesthesiologist either looked at the BIS monitor and/or adjusted the target concentration of propofol and/or remifentanil. She did not transmit her observations to the anesthesiologists in charge of the case. Noteworthy, in order to identify each time the anesthesiologist watched the BIS monitor, this device had been installed on the left side of the patient, i.e. away from the cardiovascular monitor which was placed at his/her right side (attached to the ventilator). Accordingly, there was no ambiguity on knowing what monitor the anesthesiologist watched.

All patients were asked the day after surgery for signs of explicit memory and were invited to comment on their procedure.

Our a priori sample-size estimate was based on 95 % power for 40 % decrease of BIS watching at an alpha risk of 0.01, 15 patients were necessary. Data are presented as mean ± SD, continuous data were compared by the Mann–Whitney test and categorical data were compared using the Fischer exact test. Significant differences were achieved at the $p < 0.05$ threshold.

3 Results

Demographic data are shown in Table 1. Mean induction target concentrations of propofol (4.4 ± 1.4 vs. 4.0 ± 1.3 μg/ml) and remifentanil (4.3 ± 1.4 vs. 4.9 ± 1.3 ng/ml) were similar in TCI Loop and TCI Manual groups, respectively. Moreover, propofol and remifentanil consumptions were similar between groups during surgery (Table 1).

Hemodynamics recorded during the whole case and its subparts (Induction and Surgery) appear in Fig. 1. The mean heart rate was similar between groups (66 ± 7 vs. 63 ± 3 beats/min), but mean arterial pressure was higher when using the closed-loop controller (88 ± 13 vs. 78 ± 6 mmHg, $p < 0.001$, respectively).

Adequate anesthesia ($BIS_{40–60}$) was significantly different between groups (94 % ± 12 vs. 74 % ± 19, in TCI Loop versus TCI Manual, respectively; $p < 0.001$), during the entire case duration.

The workload corresponding to the delivery of anesthesia was strikingly different by group during both phases of the procedure (Fig. 2). In the TCI Loop group, the anesthesiologist did not need to adjust target concentrations at induction in 15 out of 18 patients. In the remaining three patients, one adjustment was performed in two of them and two adjustments in one. During surgery, due to noxious stimuli and hemodynamic issues, no manual adjustment was achieved in only 10 out of 18 patients. This contrasts with the TCI Manual group in which adjustments were always needed, cumulating up to 24 in one patient. The anesthesiologist looked at the BIS monitor at least once in each patient within the TCI Loop group i.e. in average 53 % less than in the TCI Manual group. Among the nine patients in the TCI Loop group who underwent major surgery and required the placement of radial and central venous catheters, once anesthetized, six did not require manual TCI adjustment.

One day after surgery, no patients disclosed intra-operative memorization. We did not observe behavioral abnormalities.

Table 1 Demographics

	TCI Loop	TCI Manual
Demographics (n)	18	18
Gender (Males/Females)	12/6	8/10
Age (year)	63 ± 11	67 ± 15
BMI (kg/m^2)	25 ± 4	25 ± 3
ASA (I/II/III)	1/10/7	2/4/12
Type of surgery		
Lung resection	3	2
Major vascular	3	3
Carotid	3	4
Peripheral vascular	5	3
Miscellaneous minor	4	6
Duration		
Anesthesia + preparation (min)	30 ± 17	26 ± 13
Surgery (min)	120 ± 50	138 ± 79
Total (min)	15 ± 60	164 ± 87
Drugs consumption during surgery		
Total propofol (mg/kg/h)	5.4 ± 1.2	5.4 ± 1.8
Total remifentanil (mcg/kg/min)	0.22 ± 0.09	0.19 ± 0.07

TCI Loop Dual automated titration of propofol and remifentanil, *TCI Manual* skilled manual titration of propofol and remifentanil, *Induction* time elapsed from the start of propofol and remifentanil to the moment of skin incision, *Surgery* denotes the period from *Induction* to the end of Induction to the end of drugs infusion

4 Discussion

We showed that a TCI/BIS-targeted dual closed-loop controlled system could steer anesthesia better than a skilled anesthesiologist using TCI and setting it manually according to BIS, in a conventional way. Indeed, the closed loop system facilitated the induction of anesthesia by freeing the anesthesiologist from the need to adjust TCI during the surgical procedure, in more than 80 % of patients.

The principle of automatism in medicine has been acknowledged since 1995 [13] but may still raise safety issues [14]. Therefore, BIS values as processed by the automated controller should remain visible as a safeguard.

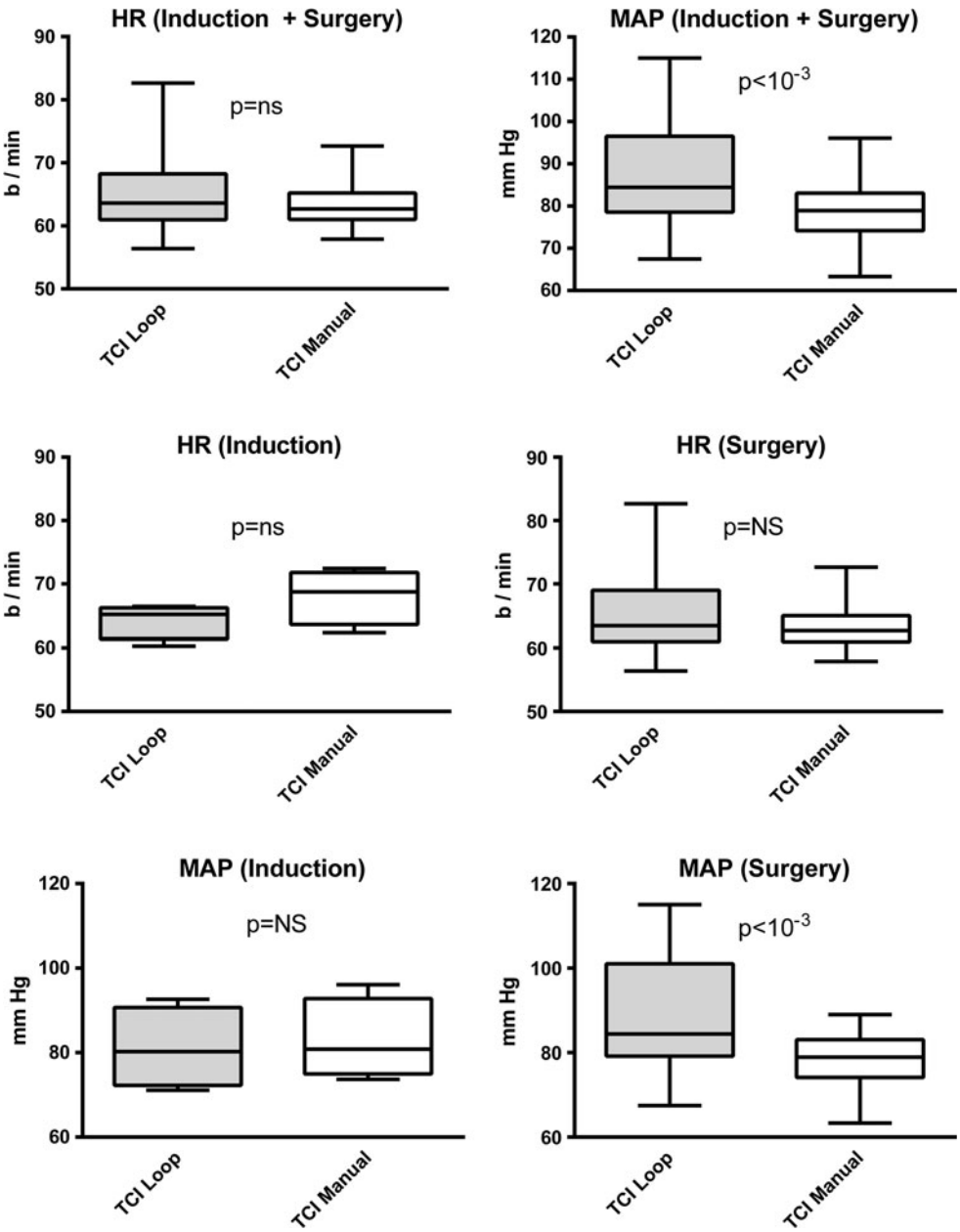

Fig. 1 Hemodynamics *HR* heart rate, *MAP* mean arterial pressure, *TCI Loop* Dual automated titration of propofol and remifentanil, *TCI Manual* skilled manual titration of propofol and remifentanil, *Induction* time elapsed from the start of propofol and remifentanil to the moment of skin incision, *Surgery* denotes the period starting from the end of Induction to the end of drug infusion, *NS* not significant. *Boxes* and *bars* represent median and 25–95 % range

This issue was confirmed by the fact that the anesthesiologist using the loop controlled system still looked at the BIS display, even if he/she did it significantly less often than in the TCI Manual group. Thus, under TCI Loop, the anesthesiologist task was simplified especially e.g. catheter placement which requires sterile gowning and during which an adjustment of TCI would require participation of another skilled person. Hence, freeing hands at induction can be considered as a major breakthrough in daily practice, especially in departments like ours in which anesthesiologists work alone in many instances without the help of a nurse anesthetist. Considering that the workload in anesthesia can be divided into 4 components: task demand, effort, performance, and attention, [15] our automated controller did lighten three of these tasks: demand, effort and attention.

The hemodynamic profile was different by groups, in particular the mean arterial pressure was higher in the TCI Loop group. This fact deserves comments. We consider two possible reasons to explain this difference. The patients in the TCI Manual group were slightly sicker than in the TCI Loop group (12/18 ASA III patients vs. 7/18, respectively). Conversely, a closed-loop controller has been shown to favor hemodynamic stability in patients during elective cardiac surgery [16] or in the context of automated sedation in critical care [17]. One should also consider that hemodynamic response during surgery is not only related to anesthetic drugs. It is influenced by chronic patient's

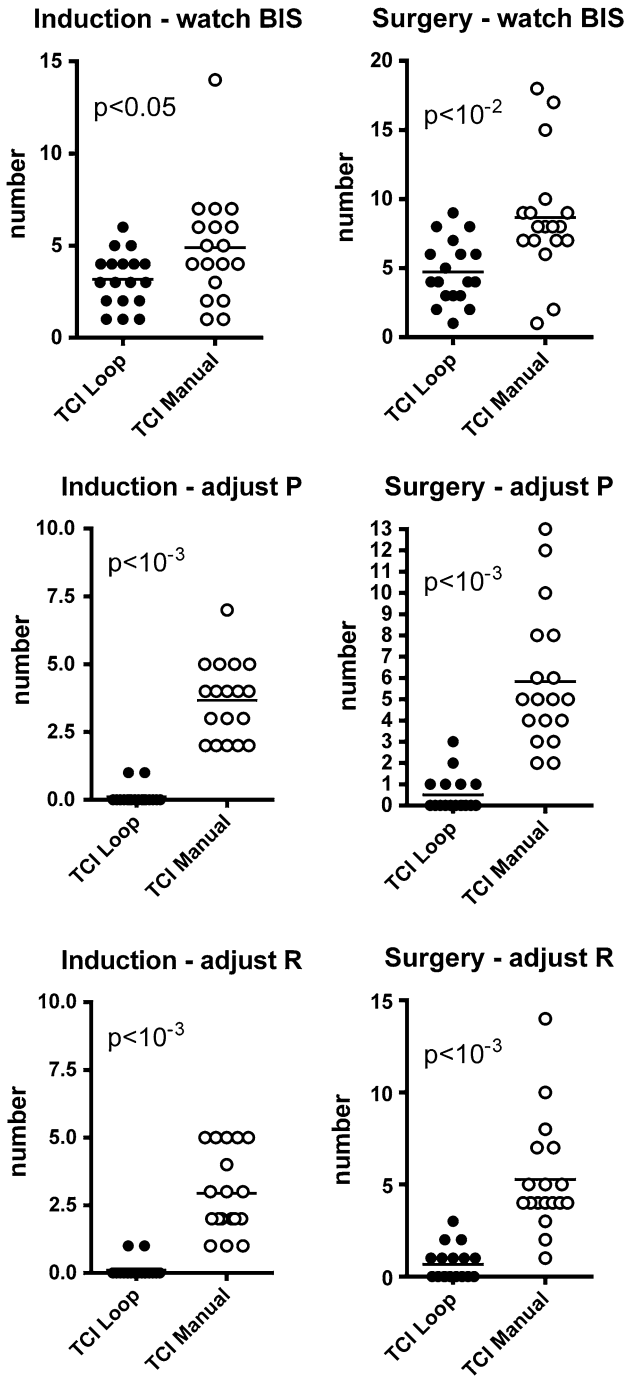

Fig. 2 Number of times that the anesthesiologist in charge of the patient looked at the BIS monitor and manually adjusted the target concentration. Same legends as in Fig. 1

cardiovascular medication and peroperative events like blood loss, fluid administration, arrhythmia, manipulation of great vessels, etc. Considering these competing phenomena, a fine interpretation of the hemodynamic disparities we observed between groups is not straight forward. This issue would deserve a dedicated study with a design focused on hemodynamics and at least, a continuous measurement of blood pressure. However, the difference in mean arterial pressure we observed remains slight and probably clinically insignificant (the median difference was 5 mm Hg, only). One should also discuss the validity of our single observer design to assess workload. We believe the remote and silent presence of the observer did not influence nor disturb the anesthesiologist in charge of the patient. Moreover, this observer was highly motivated and strived to capture all required events. This methods was in principle not as accurate as a video recording followed by a remote analysis by twin observers. However, this latter methodology was not accessible to us. Moreover, it may raise further difficulties leading to possible inaccuracies. Indeed, choosing a two-rater setting would address the issue of inter-rater variability which is a potential source of bias. A video camera with its fixed and limited field could miss some events as the anesthesiologist in charge may move outside the camera field, in many instances during the procedure. Our human observation thus appeared to us simpler and more versatile than a video recording, despite its appealing aspect. To improve the reliability of human observation, we had purposely paid attention to separate the BIS from the cardiovascular monitor to avoid ambiguity when rating the anesthesiologist in charge looking at the BIS monitor. Finally, this methodological choice for a human observation was preferred for the sake of simplicity and seems robust enough to support the interest of the automated controller in clinical practice; especially if one considers our work as a pilot study.

Another issue is worth discussing. Only two anesthesiologists were in charge of all cases. One may argue that these investigators were highly trained and may have put an excess confidence in the controller, thus unduly limiting TCI adjustments in the TCI Loop group. We believe that users of the loop system, considering their experience had a fair knowledge of its capability and merely used it accordingly. Thus, far from generating a bias, this study seems to reflect what one may expect from the device, once achieved the learning process.

In conclusion, the controlled-loop TCI/BIS-based technology may be regarded as a means to relieve the anesthesiologist from the burden of repeated adjustments of target concentrations during BIS based intravenous anesthesia. This is especially promising during the early phase of surgery, when the anesthesiologist is involved in additional tasks such as central and arterial line placements which require manipulations in a sterile environment.

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Conflict of interest The authors declare they have no conflict of interest.

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