Closed-loop IV Anesthesia: Impact on routine Anesthesia

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Introduction

The benefit of an automated controller is to obtain precise control of the variables with continuous analysis and frequent changes in anesthetic drug concentrations. Thus, the drug infusion is titrated to the specific needs of each patient, taking into account inter- or intra-individual dynamic variability, specificity of the surgery thus avoiding drug accumulation. Currently, over 4100 surgical patients have been anesthetized with different automated controllers. For automated propofol titration our team has published studies involving 70 % of these patients.

Automated titration of propofol

Since 2006 we have developed different Closed-loop controllers allowing the automated titration of intravenous anesthesia guided by the Bispectral index (BIS). In particular, we have developed the first prototype allowing the automated titration of propofol during the induction period[1], the controller modifies the propofol effect concentration using the pharmacokinetic model of Schnider.[2] We have combined the induction and the maintenance of general anesthesia (GA) and the controller was evaluated by a randomized controlled study including more than 180 patients with patients ASA II and III in different centers.[3] The same controller was used in an observational study in patients undergoing lung transplantation.[4] Lung transplantation is a major procedure including patients ASA IV. In this context, the controller appears safe as shown by its use by several physicians for patients presenting high anesthetic risk with or without cardiopulmonary bypass. Finally, these studies demonstrated that the electro-cortical activity measured by the BIS is a measure of the depth of hypnosis allowing the automated titration of propofol.

Multiple controllers

General anesthesia is a dynamic balance between hypnosis, analgesia and muscle relaxation. The clinical relevance of automated administration of neuromuscular blocking agents is limited since the introduction of a specific antidote[5]. Finally, the ultimate challenge is probably the automated control of analgesia.
The first automated administration of alfentanil guided by electrocortical activity was published 20 years ago[6]. A study reported that a mixture of propofol and alfentanil in the same syringe can be administered automatically using the BIS[7]. We have developed a proportional-integral-derivative controller for automated propofol infusion[3]. After this first controller, we implemented a second controller allowing the

automated titration of remifentanil also guided by BIS using the pharmacokinetic model of Minto.[8] The principle of this controller is based on the assumption that rapid BIS increase is secondary to noxious stimulation and is related to a deficit of anti-nociception and not to a deficit of the hypnotic component. The controller first administers remifentanil if the error is small and administers remifentanil and propofol when the error is higher. This controller has been validated by a randomized controlled multicenter study including 167 patients ASA II and III.[9] The dual-loop controller outperforms skilled manual control to maintain the BIS in the range 40-60 and decrease the number of episodes of too deep anesthesia.

A similar controller was developed using the M-Entropy monitor® (GE Healthcare, Helsinki, Finland). The monitor calculates two parameters:"State Entropy" which is the measure of the irregularity of frontal cortical electrophysiological activity and "Response Entropy". The difference between "Response Entropy and Entropy State" represents the activity of facial electromyography which is a surrogate measure to quantify the deficit in antinociception. The controller allows the automated titration of propofol and remifentanil during induction and maintenance of general anesthesia. In a randomized controlled study including 61 patients, we reported the feasibility of automated titration of propofol and remifentanil guided by the M-Entropy monitor®.[10] However, this controller has not been tested clinically under physiologically challenging conditions during major surgery.

The dual-loop controller of propofol and remifentanil with the BIS was evaluated in different clinical situations and has been studied most extensively. Rigid bronchoscopy is a particularly challenging condition: it involves the management of high-risk patients with central airway obstruction, with co-morbidities, an unpredictable duration and with intense noxious stimuli during rigid bronchoscopy mobilizations. We have reported the use of the dual-loop controller during this procedure and demonstrated that the controller acts similarly to manual control to maintain the BIS in the desired range.[11] In an observational study, we have reported with the dual-loop controller the occurrence of suppression ratio related to too deep anesthesia. During 3742 hours of automated titration of propofol and remifentanil or after more than 210000 modifications of target concentrations we found that the occurrence of suppression ratio was 0.5‰ after a decision made by the controller. [12] This study involving 1494 adult patients demonstrated that the dual-loop controller was feasible in routine anesthesia. We have reported the use of the dual-loop controller in a patient who suffered from gigantism with a height of 248 cm[13] and in a 9-year-old boy requiring emergency lung volume reduction.[14] The dual-loop controller has been evaluated in pediatric and adolescent patients during GA. In a randomized controlled study with 42 pediatric patients the controller outperforms skilled manual control to maintain the BIS in the desired range while the adult pharmacokinetic models were used.[15] The dual-loop was used in obese patients while the pharmacokinetic model of propofol was Schnider[2] and Minto for the remifentanil.[8] Propofol and remifentanil consumptions were evaluated using the dual-loop controller between 30 obese and 29 lean patients.[16] The dual-loop controller delivered half as much remifentanil and no propofol overdosing was reported. The controller was based on individual patient responses and was independent of the underlying pharmacokinetic model. We have evaluated the impact of postoperative nausea and vomiting in 117 obese patients undergoing sleeve gastrectomy.[17] The study demonstrated that the combination of 4 mg of dexamethasone and 4 mg of ondansetron was not effective in prevention of postoperative nausea and vomiting in obese patients. The dual loop was also used during orthotopic liver transplantation

and propofol requirements were reduced during the anhepatic phase.[18]
During major vascular and thoracic surgery, the dual-loop controller improved the patient hemodynamic and decreased the anesthesiologist's workload.[19] As compared to manual titration of total iv anesthesia, desflurane or sevoflurane guided by the BIS, the dual-loop controller avoided emergence delirium by decreasing the period of deep anesthesia.[20]
The dual-loop controller of drug delivery is a robust, reproducible and unbiased method for the assessment of anesthetic requirement when an adjunct such as nitrous oxide was used,[21] dexmedetomidine[22], thoracic epidural analgesia[23] or when different propofol formulations[24] were evaluated because investigator bias is eliminated.
These prototypes have been used only as a research tool and there is currently no dedicated automated controller marketed for anesthesia[18]. However, the dual-loop controller was used in routine care for more than 500 lung transplantation procedure and it was included in the strategy for extubation patients in the operating room after bilateral lung transplantation.[25]

CONCLUSION

Published studies have reported the clinical relevance and the technical performance of automated administration of anesthetic agents. But drug administration is only one task of the patient care during anesthesia. The presence of an anesthesiologist remains essential to maintain cardiopulmonary homeostasis during all procedures. However, the introduction of automated systems in the clinical setting will become a reality and will modify anesthesia practice. The next challenge will be to determine whether the introduction of the automated controller in a clinical setting can decrease the cost, morbidity or mortality associated with anesthesia or sedation.

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