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Comentario sobre: Feasibility of closed-loop titration of propofol and remifentanil guided by the bispectral monitor in pediatric and adolescent patients: A prospective randomized study

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Automation is entrenched in our daily lives and aviation provides the safest and most efficient example. The implementation of automation in our speciality has not been as swift as it has been the case in other medical fields, for example, the development of the artificial pancreas[1] – a device that automatically regulates the level of glycaemia – or robotic surgery[2,3]. A number of automated devices were originally developed for research purposes, for administering inhaled anesthesia[4], intravenous anesthesia[5], muscle relaxants[6], and regional anesthesia[7].

A study by Orliaguet et al[8]. evaluated the performance of a device for the automated propofol and remifentanil infusion in 23 patients, 10–14 years old, with ASA I and II scores; these patients underwent elective surgery for 58 h. The administration of the induction drugs was guided using the Schnider and Minto PK/PD models. The automated control variable was the depth of anesthesia measured by BIS™ (Bispectral Index™). A PI algorithm was used to estimate the percentage error between the measured and the programmed depth of anesthesia, and the integral of accumulated error over time. The

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interval between the automated changes considered the time to reach the concentration at the effect site for each drug, plus one additional minute required because of the delay in processing the signal as measured by BIS[TM].

Automation of anesthesia will result in several advantages since it improves patient safety, cost, and efficiency of anesthesia[9]. Anesthesia shall be safer since under and over-dosing will be avoided during induction and maintenance, because the algorithms in these devices titrate the doses administered, increasing the frequency of interaction per hour, as compared to the manual approach. This is illustrated by Orliaguet et al[8]. with a number of programmed concentration changes in the automated group of 3.9 and 9.5 times more than the number of changes of propofol and remifentanil in the manual control group. As can be seen, in order to get the same performance with the automated system, with a larger proportion of anesthesia time within the desired BIS range $_{40-60}$ (87% with automated control vs. 72% with manual control), there is a 15% absolute risk reduction (ARR) in the time beyond the BIS range $_{40-60}$ and a number needed to treat (NNT) of 7 patients. Changes every 3 and 1 min in the programmed concentration of propofol and remifentanil would have been required with manual control; this can be impractical and dangerous because the anesthesiologist gets distracted from the rest of the activities and parameters that should be monitored.

It must be underscored that the hemodynamic parameters were not included in the controller's algorithm in the trial and these are frequently considered a requirement to make the programmed drug concentration changes and hence maintain the hemodynamic stability, improving the clinical performance of the automated device; the use of ephedrine is mentioned just in one patient in the automated group. The inclusion of a large percentage of patients with combined general/regional anesthesia, 36% and 42% in the automated and manual groups, may have biased the data about the actual analgesic and anti-nociceptive requirements that the controller could have used in these patients, adjusting the dose of remifentanil, particularly when no other opiate was administered during maintenance, except for morphine at the end of the procedure.

This device was previously evaluated in a multicenter trial[10] in 83 adult patients, including ASA III and IV, undergoing medium complexity elective surgery for 312 h and with blood losses exceeding 500 ml in 8% of the patients. In the automated group a 9% ARR was identified in the time outside the desired BIS range$_{40-60}$ and a NNT of 11. These results make us think that the controller was enhanced or that the manual control of pediatric anesthesia with just these two agents is more complex. This dual controller has been evaluated in morbid obese patients[11]; it has shown improved control and less drug changes during vascular and thoracic surgery[12]; has enabled double blind trials to assess the effects of dexmedetomidine[13] and nitrous oxide[14] on the use of propofol and remifentanil; in addition to comparing the equipotency of the different commercial propofol formulations[15]. In brief, we have in our hands a controller that has been evaluated under various conditions since 2006, including 239 patients with the dual version and 519 patients with the initial version only for propofol.

From the control theory perspective[9] this is a SIMO type device (*single input multiple output*). The device input control variable is unique, the anesthetic depth and the output variables are the settings of the two drugs infusion rates. Relying on a single input variable leads to a faster control and less processing as compared to multiple variables. However if this variable is affected due to inter-individual biological variability, the delay in signal processing time, the interference caused by other medical devices, in addition to other clinical conditions such as hypovolemia, hypotension, brain ischemia, hypoglycemia and hypothermia, the system could potentially under/over-dose. Furthermore, we must keep in mind that despite the accepted use of BIS[TM], a 0.04% of intraoperative explicit memories are still reported, and depending on the type of anesthesia used, there are limitations with sevoflurane and it does not perform well with ketamine, nitrous oxide or xenon.

Wehbe et al[16]. highlight the large number of annual deaths due to human error in medicine. One of the main sources of human error in anesthesia is fatigue or tiredness. The number of variables an anesthesiologist monitors is considerable and the human brain can only process four to five parameters simultaneously. Automation and decision-making support systems could be used more often to lower the number of medical errors.

Canneson et al. described the most important considerations about automation for the administration of general anesthesia[17]. The hindrances that delay its implementation are the regulatory standards and total acceptance by anesthesiologists. The author says: "If we believe that our job in just to push the plunger of a propofol-filled syringe, turning the vaporizer's dial, or adjusting the intravenous fluid infusion rate, then the automation systems are indeed a threat to our profession. But if on the contrary, we believe that our job is to optimize our patients from the preoperative stage, to establish strategies and therapeutic goals to preserve homeostasis during surgery, and manage complex physiological disorders resulting from surgical stress and then to admit the patient to the recovery room and the ICU, automated devices will become what the automatic pilot is to airline pilots". The question is then the following: "What's the role of anesthesiologists in healthcare? Do we want to be the brain or the hand? Or assumption is that we rather be the brains…"

Another obstacle to automation is the way technologies are introduced to the medical field. The SEDASYS® (Ethicon®, Endo-Surgery, Cincinnati, EE.UU.)[18], is the first FDA approved automatic device available in the market for administering sedation in endoscopic procedures, but the device has been marketed to be used by gastroenterologists or their subordinates, rather than by anesthesiologists. Although the device standardizes the administration of propofol during sedation and provides a certain level of assurance, it may result in an additional risk for the patient by replacing the best-trained professional in resuscitation during sedation. The FDA acknowledged this fact and required that SEDASYS® "should only be used in an environment where the anesthesiologist is immediately available to the patient, either for assistance or consultation as needed."

Evidently, we the anesthesiologists increasingly rely on various medical devices to do our job swiftly and safely. The new developments in the devices we use have changed the way in which anesthetic agents are administered, so that our specialty has become safer and more scientific[19].

Finally, these new devices may optimize the routine tasks during the intraoperative management of the patient so that we may focus more on the job we are so adamant to perform: the art of medicine, providing ethical and compassionate care for our patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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REFERENCES

1. Kraegen EW, Whiteside R, Bell D, Chia YO, Lazarus L. Development of a closed-loop artificial pancreas. Horm Metab Res Suppl. 1979;8:38–42.
2. Rassweiler J, Binder J, Frede T. Robotic and telesurgery: will they change our future? Curr Opin Urol. 2001;11:309–20.
3. Turchetti G, Palla I, Pierotti F, Cuschieri A. Economic evaluation of da Vinci-assisted robotic surgery: a systematic review. Surg Endosc. 2012;26:598–606.
4. O'Callaghan AC, Hawes DW, Ross JA, White DC, Wloch RT. Uptake of isoflurane during clinical anaesthesia. Servo-control of liquid anaesthetic injection into a closed-circuit breathing system. Br J Anaesth. 1983;55:1061–4.
5. Schwilden H, Stoeckel H, Schüttler J. Closed-loop feedback control of propofol anaesthesia by Quantitative EEG analysis in humans. Br J Anaesth. 1989;62:290–6.
6. Mendonça T, Magalhães H, Lago P, Esteves S. Hipocrates: a robust system for the control of neuromuscular blockade. J Clin Monit Comput. 2004;18:265–73.
7. Hemmerling TM, Taddei R, Wehbe M, Cyr S, Zaouter C, Morse J. First robotic ultrasound-guided nerve blocks in humans using the Magellan system. Anesth Analg. 2013;116:491–4.
8. Orliaguet GA, Lambert FB, Chazot T, Glasman P, Fischler M, Liu N. Feasibility of closed-loop titration of propofol and remifentanil guided by the bispectral monitor in pediatric and adolescent patients: a prospective randomized study. Anesthesiology. 2015;122:759–67.
9. Lan JY, Abbod MF, Yeh RG, Fan SZ, Shieh JS. Review: intelligent modeling and control in anesthesia. J Med Biol Eng. 2012;32:293–307.
10. Liu N, Chazot T, Hamada S, Landais A, Boichut N, Dussaussoy C, et al. Closed-loop co administration of propofol and remifentanil guided by bispectral index: a randomized multicenter study. Anesth Analg. 2011;112:46–57.
11. Liu N, Lory C, Assenzo V, Cocard V, Chazot T, Le Guen M, et al. Feasibility of closed-loop co-administration of propofol and remifentanil guided by the bispectral index in obese patients: a prospective cohort comparison. Br J Anaesth. 2015;114:605–14.
12. Dussaussoy C, Peres M, Jaoul V, Liu N, Chazot T, Picquet J, et al. Automated titration of propofol and remifentanil decreases the anesthesiologist's workload during vascular or thoracic surgery: a randomized prospective study. J Clin Monit Comput. 2014;28:35–40.
13. Le Guen M, Liu N, Tounou F, Augé M, Tuil O, Chazot T, et al. Dexmedetomidine reduces propofol and remifentanyl requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg. 2014;118:946–55.
14. Liu N, Le Guen M, Boichut N, Genty A, Hérail T, Schmartz D, et al. Nitrous oxide does not produce a clinically important sparing effect during closed-loop delivered propofol–remifentanil anaesthesia guided by the bispectral index: a randomized multicentre study. Br J Anaesth. 2014;112:842–51.
15. Le Guen M, Grassin-Delyle S, Cornet C, Genty A, Chazot T, Dardelle D, et al. Comparison of the potency of different propofol formulations: a randomized, double-blind trial using closed-loop administration. Anesthesiology. 2014;120:355–64.
16. Wehbe M, Giacalone M, Hemmerling TM. Robotics and regional anesthesia. Curr Opin Anaesthesiol. 2014;27:544–8.
17. Cannesson M, Rinehart J. Closed-loop systems and automation in the era of patients' safety and perioperative medicine. J Clin Monit Comput. 2014;28:1–3.
18. Pambianco DJ, Whitten CJ, Moerman A, Struys MM, Martin JF. An assessment of computer assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. Gastrointest Endosc. 2008;68:542–7.
19. Ingrande J, Lemmens HJ. Medical devices for the anesthetist: current perspectives. Med Dev (Auckl). 2014;7:45–53.