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ORIGINAL RESEARCH

Implementation of a Bayesian based advisory tool for target-controlled infusion of propofol using qCON as control variable

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Abstract
This single blinded randomized controlled trial aims to assess whether the application of a Bayesian-adjusted Ce_{PROP} (effect-site of propofol) advisory tool leads towards a more stringent control of the cerebral drug effect during anaesthesia, using qCON as control variable. 100 patients scheduled for elective surgery were included and randomized into a control or intervention group (1:1 ratio). In the intervention group the advisory screen was made available to the clinician, whereas it was blinded in the control group. The settings of the target-controlled infusion pumps could be adjusted at any time by the clinician. Cerebral drug effect was quantified using processed EEG (CONOX monitor, Fresenius Kabi, Bad Homburg, Germany). The time of qCON between the desired range (35–55) during anaesthesia maintenance was defined as our primary end point. Induction parameters and recovery times were considered secondary end points and coefficient of variance of qCON and Ce_{PROP} was calculated in order to survey the extent of control towards the mean of the population. The desired range of qCON between 35 and 55 was maintained in 84% vs. 90% ($p=0.15$) of the case time in the control versus intervention group, respectively. Secondary endpoints showed similar results in both groups. The coefficient of variation for Ce_{PROP} was higher in the intervention group. The application of the Bayesian-based Ce_{PROP} advisory system in this trial did not result in a different time of qCON between 35 and 55 (84 [21] vs. 90 [18] percent of the case time). Significant differences between groups were hard to establish, most likely due to a very high performance level in the control group. More extensive control efforts were found in the intervention group. We believe that this advisory tool could be a useful educational tool for novices to titrate propofol effect-site concentrations.

Keywords Pharmacology · Closed-Loop · Propofol

1 Introduction

Target-controlled infusion (TCI) has been developed towards a mature technology for propofol infusion during anaesthesia and procedural sedation, hereby targeting a specific plasma or effect-site concentration [1–3]. The resulting cerebral drug effect from this propofol infusion can be measured applying a processed EEG system. Using the actual propofol effect-site concentration (Ce_{PROP}) displayed on the pump screen and the measured cerebral drug effect calculated as a numerical value by the processed EEG monitor, the anaesthetist has to optimize drug administration by selecting the most appropriate target concentration to maintain an accurate anaesthetic drug effect and can make adjustments if needed. Stepwise adjustments in target concentrations are based on clinical observations. Previous studies show that

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clinicians often fail to maintain the most appropriate and stable cerebral drug effect due to the "trial-and-error" strategy when making adjustments to the target concentrations [4].

Pharmacodynamically, Ce_{PROP} can be linked to the drug effect as measured by the processed EEG monitor and can be quantified using the sigmoidal "E-max" model [3]. Displaying this pharmacodynamic relation on an advisory display will offer the clinician quantitative information on the optimal target concentration (Ct) for a given cerebral drug effect and might allow more accurate "one-step" adjustments in the Ct. However, the relationship between Ce_{PROP} and an EEG monitor is patient-specific and changes dynamically and continuously over time due to alterations in the surgical situation and the co-administration of other drugs (e.g. opioids). Therefore, a computer algorithm could be helpful to personalise the sigmoidal "E-max" curve on the advisory display towards the individual patient and his/her surgical and pharmacological condition. Adjusting predictions using prior information, based on measurements, could continuously update the E-max curve. This can be done by applying Bayesian-based adjustments implemented in an advisory tool [5]. This tool provides dose titration advices for the clinician aiming to reach a corresponding preset desired EEG derived target value in a continuous matter [5–7]. This technology has been used previously in closed-loop anaesthesia control systems and have proven to be effective in altering the clinicians behaviour [8, 9].

This single blinded randomized controlled trial assessed whether the accuracy of a newly designed Bayesian-based, patient-individualized, pharmacodynamic advisory system to optimize propofol administration using an EEG derived index as a controlled variable (intervention group) improves compared to a "standard-of-care" propofol administration, defined as an EEG-guided effect-compartment controlled propofol administration without the input of the advisory system (control group).

2 Methods

2.1 Study management and registration

This trial was conducted at the Department of Anesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, and in compliance with Good Clinical Practice and applicable regulatory requirements. This study was approved by the University's Institutional Review Board (UMCG Ethics' Committee, Groningen, The Netherlands, METc NL 64961.056.18) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at the Dutch Trial Register (Dutch Trial Register, NTR7011, Principal investigator: Johannes P. van den Berg, https://trialsearch.who.int/Trial2.aspx?TrialID=NTR7011, date of registration: February 5th, 2018) prior to the start of the study. All patients provided written informed consent before participation.

2.2 Subjects

Patients between 18 and 75 years of age, American Society of Anesthesia Physical Status Classification (ASA score) of I–IV, scheduled for elective surgery under general anaesthesia with propofol with a duration of more than one hour were eligible for this study. Subjects were excluded in case of the use of psycho-active drugs, overt sign of alcohol abuse or recreational drug use.

2.3 Study execution

This study was designed as a prospective, single blinded randomized controlled trial. After screening of eligibility and obtaining written informed consent, subjects were randomized using the sealed envelope technique with two equal groups. The ethics committee agreed that patients who signed informed consent but were excluded for technical or managerial reasons prior to the start of the maintenance phase of anaesthesia could be replaced to maintain two equally sized groups with enough power.

All patients received 1000 mg of paracetamol as premedication, as per standard care. No benzodiazepine or other sedative drug was administered to the patient prior to the procedure.

After the patient's arrival in the operation room, standard monitoring (3 or 5-lead electrocardiogram (ECG), non-invasive or invasive blood pressure blood pressure (if required for the clinical case and not part of the study), pulse-oximetry and capnography were applied using a vital signs monitor (Philips, Eindhoven, NL). A large forearm vein was cannulated for drug and fluid administration, as per standard care. Other venous access or monitoring was added (additional peripheral line, central venous line, temperature probe etc.) if deemed necessary by the attending anaesthetist. qCON (CONOX monitor, Fresenius Kabi, Bad Homburg, Germany) electrodes were placed on the patients forehead and the qCON index was derived from the frontal electro-encephalogram. Index values range between 100 and 0 whereby a range between 35 and 55 indicates clinically acceptable hypnotic effect for qCON [10].

After accurate positioning and pre-oxygenation, remifentanil effect-compartment-controlled TCI was administered using effect-site targets as clinical required, judged by the attending anaesthetist. Remifentanil administration was started 2 minutes before the start of the propofol administration. Initial propofol

effect-compartment-controlled TCI was started and the initial target concentration was selected at the discretion of the anaesthetist. In the control group Ce_{PROP} were adapted as clinically required by the attending anaesthetist in order to reach and maintain a qCON value of 45, as advised by the validation studies [10]. In the intervention group, with an online advisory display, the anaesthetist was informed which Ce_{PROP} he/she has to set in order to reach or maintain the desired qCON. This advised Ce_{PROP} was displayed on the advisory system's display (Fig. 1). The clinician could use this information together with all other vital signs information to make the clinical decision which Ce_{PROP} is most appropriate for the patient under the specific condition. In the control group, the advisory system's display was blinded for the clinician. However, all data, including advised Ce_{PROP}, were recorded and calculated for comparison between groups. Clinical decision was left to the discretion of the clinician, based on the available vital signs and measurements (as per standard clinical practice). qCON was not blinded in the control group. Prior to the start of the case, all clinicians were reminded to maintain an accurate level of cerebral drug effect, being a qCON target value between 35 and 55 (mean 45), as instructed during the training sessions.

At the discretion of the attending clinician, all required additional drugs to support cardiovascular and respiratory homeostasis were allowed. In both groups, participating anaesthetists had at least 5 years of experience in intravenous drug administration using Target-Controlled Infusion (TCI). Regarding the use of the advisory system the attending anesthetic team was instructed before the procedure in the use of the advisory system. The display is relatively simple, only displaying the advised Ce_{PROP}.

2.4 Bayesian advisory tool

The advisory tool implements a patient-individualized, pharmacodynamic advisory system to optimize propofol administration. It is based on a previously published and validated Bayesian-based closed-loop control system. This system is described in earlier publications by our research group [11, 12]. Similar to the closed-loop system, the advisory tool will continuously calculate a target propofol concentration to reach a target qCON value entered by the

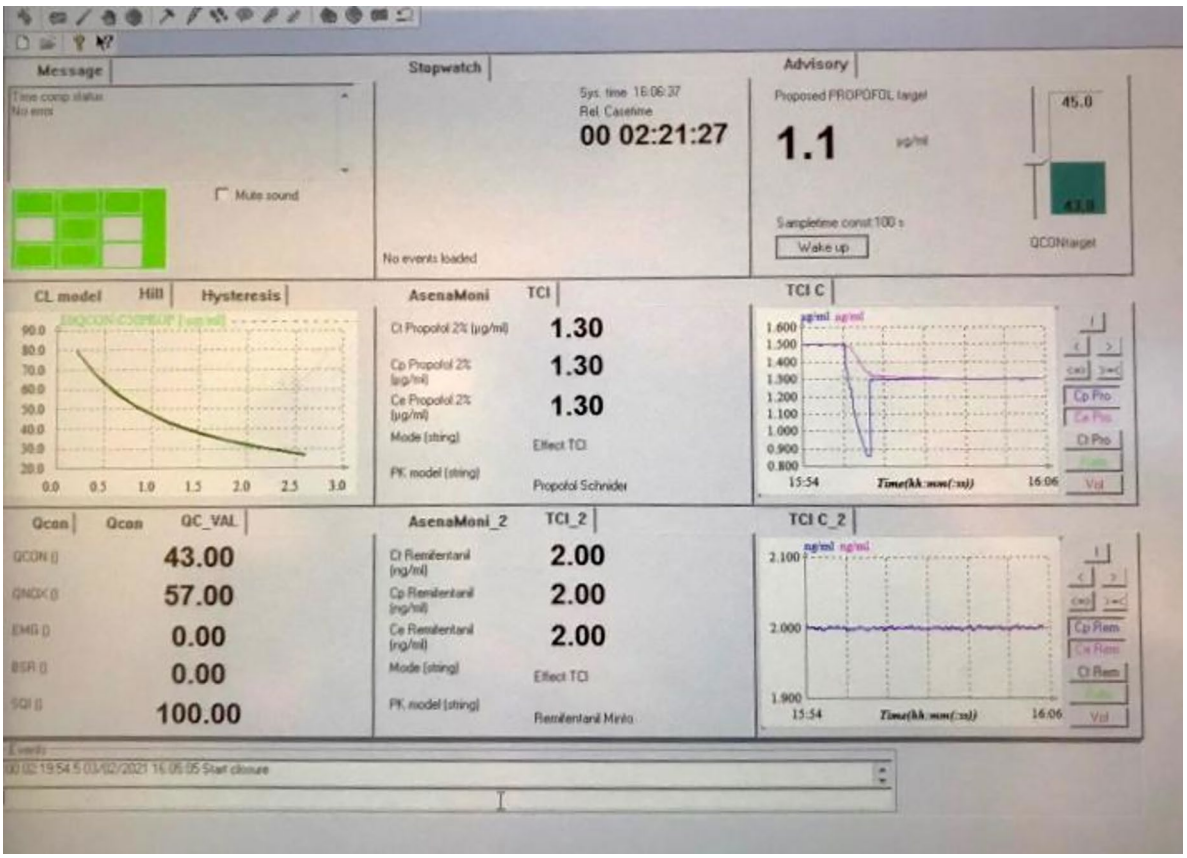

Fig. 1 The RUGLOOP II software module showing the advisory display software. In the left middle panel the actual Bayesian-updated E-max curve is displayed, that is continuously changing over time. Based on this and the actual propofol targets (center panel, middle panel below), in the right upper corner the advised propofol target concentration is displayed

anaesthetist. However, it differs in the way that the closed-loop controller automatically applies the calculated target concentration, whereas the advisory tool proposes it to the anaesthetist. The clinician can apply the target concentration on a TCI-pump targeting the desired propofol concentration using the propofol pharmacokinetic-dynamic model published by Schnider et al. [13]. A schematic depiction of the advisory system is displayed in Fig. 2.

The basis of the advisory tool is a sigmoid E-max model describing the non-linear relationship between qCON and the propofol effect-site concentration, as shown in Eq. 1.

$$PD = PD_0 \times \left(1 - \frac{E_{max} \times C^{\gamma}_{e,prop}}{C^{\gamma}_{e50,INT} + C^{\gamma}_{e,prop}}\right) \quad (1)$$

In this model, the PD endpoint, qCON, is related to the Ce_{Prop} according to a nonlinear function with γ defining the steepness of the concentration-effect relation. PD_0 is the baseline qCON when no drug is present, and E-max is the maximum drug effect. The effect-site concentration which produces 50% of the maximal drug effect modified by the interaction effect between propofol and remifentanil ($Ce_{50,INT}$) is the predicted Ce_{PROP}, which produces 50% of the maximal drug effect. The target concentration presented to the anaesthetist is calculated by projecting the target qCON value entered by the clinician on the sigmoid E-max to obtain.

The E-max model combines a population reference model which is patient-individualized using Bayesian adaptation to take into account the specifics of the patient as well as the events of the ongoing surgery. To this purpose, the Bayesian sigmoid E-max model estimator requires a population curve, the observed qCON/effect-site concentration data pairs and the model's variances determining the degree of freedom for the estimator to divert from the population reference model and to make the model patient specific. The population reference sigmoid E-max model as well as the model variances are obtained from an earlier study [14].

For implementation reasons, the number of estimable parameters in the E-max model [14] was reduced by assuming a baseline qCON (PD0) value of 100 and a maximum propofol drug effect (E-max) of 1. To clarify the concept, it was opted to also fix the gamma constant to the population value-resulting in the horizontally moving sigmoid E-max concept [11, 12]. This results in the table that is added as Supplemental Table S1.

The advisory controller will re-estimate the E-max sigmoid curve model for each incoming qCON/concentration pair. Upon availability of a new model or when the user changes the target qCON, a new calculated target concentration is advised. Since a patient-individualized curve is

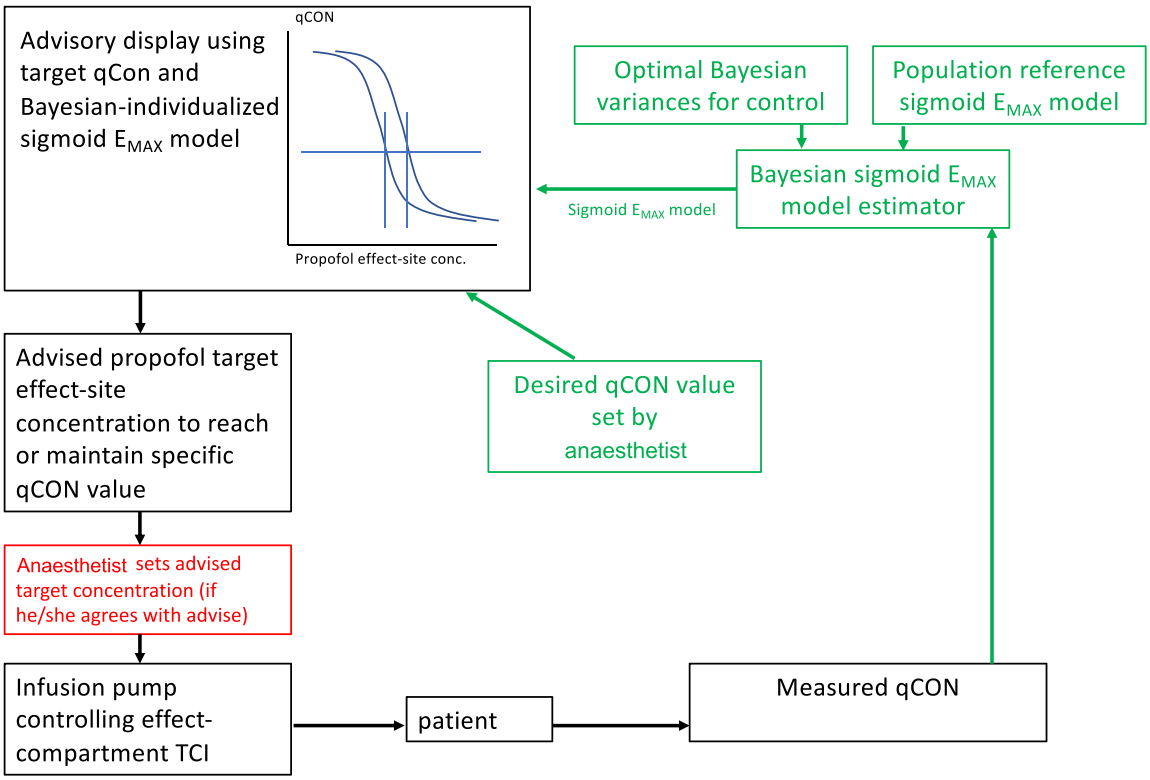

Fig. 2 A schematic depiction of the Bayesian Advisory Tool

always the result of the population curve and a range of qCON concentration data pairs, this approach smoothens the otherwise frequent abrupt changes in advised target concentrations resulting from the inevitable noise on subsequent incoming values.

For any patient, it is debatable whether data captured during induction is relevant for a model applied in later stages of the operation. More generally, one can wonder how many historic samples of this specific patient need to be taken into account for the Bayesian adaptation of the E-max model. Especially since the model is only tuned towards the C_{50}, expressing the likelihood to be asleep in the current condition, the immediate samples are more relevant. This "fade out time" of data relevance can be configured by the operator in a value between 100 and 900 s. If the operator wants a faster (but more flexibly) advise, he/she can set a lower number. If (during steady-state conditions) a slower behavior is appreciated, the user sets a longer decay time. In the study, the number is fixed at 100.

2.5 Study drug administration

Propofol and remifentanil TCI was used for drug administration. Infusion pumps (Alaris PK, Becton Dickinson, San Diego, California, USA) were used for TCI. For propofol, the three-compartment model developed by Schnider et al. was used [13]. The model by Minto et al. is used for remifentanil administration [15, 16].

2.6 Sample size calculation

Sample size calculations are based on the difference between case time within ± 10 units from targeted qCON, based on a previous publication from our group using a Bispectral Index (BIS) controlled Bayesian-based closed-loop system for propofol administration [17]. This showed that when using BIS-guided full closed-loop controlled propofol administration, the percentage of case time [mean (standard deviation [SD]) across all study participants] with BIS ± 10 from the target was 82% (14%). Assuming similar results in the intervention group in this study and the estimation that the case time in the control group for qCON within ± 10 qCON units from targeted is 10% lower (with a similar SD), 42 patients per group are needed to reach 90% power with a type 1 error rate of 5% (two samples, 2 sided equality). Taking into account possible variability in behavior between the qCON and BIS applied in the power calculation, we assumed 50 subjects in each group were required to reach enough power.

2.7 Data collection and analysis

RUGLOOP II software (Demed, Sinaai, Belgium) was used to record all data from the infusion pumps and qCON and to control and display the advisory display.

Vitals of the patient were added to the dataset afterwards using extracted data from the hospital electronic health record (EPIC, Verona, WI, USA). A moving median with a time frame of five seconds before and after the concerning time point was applied.

The primary end point of this study is the percentage of case time the qCON remained between 35 and 55, during steady state (i.e. first occurrence in interval 35–55 until termination of propofol infusion).

Secondary end points are:

- The percentage of case time with qCON higher than 55 or lower than 35, during maintenance (= the time from the moment of propofol first steady-state concentrations until stop of the administration).
- The time until loss of consciousness (LOC) from the start of propofol infusion. The patient was asked a series of repeated questions, every 15 seconds, to define the moment of absence of response to the verbal and tactile stimulus, defined as loss of consciousness (LOC).
- The control performance during induction was studied taking into account the following parameters:
  - $qCON_{LOC}$: qCON value at the moment of loss of consciousness.
  - $T_{qCON\ TARGET}$ = observed time required for reaching the target qCON range within ± 10 units from targeted qCON.
  - $T_{PEAK,\ qCON}$ = observed time required for reaching maximal drug effect (lowest qCON value).
  - $qCON_{PEAK}$ = observed qCON value at T_{PEAK}, qCON.
  - T_{EQ} = Equilibration time, i.e. first time of qCON in interval 35–55 after overshoot (T_{PEAK}).
- The time until return of consciousness (ROC), which is defined as the moment the patient opened their eyes.
- The return of orientation (ROO) from the time of cessation of propofol infusion. This was defined as the moment the patient was able to state their date of birth. The patient was asked every 15 seconds until the moment the patient was able to do so.
- The cumulative dose of propofol and remifentanil (mg) was calculated per group and compared between groups.
- The coefficient of variance (CV) of qCON and Ce_{PROP} was calculated per group and compared between groups in order to survey the extent of variability in relation to the mean of the population.

- The number of changes in Cet_{PROP} (targeted effect-site) between groups.

The control performance on the controlled variable (qCON) was calculated during maintenance using the performance-error based method of Varvel et al., which is more extensively described in previous work [18, 19]. Hemodynamic variables [Mean arterial pressure (MAP) and Heart Rate (HR)] during the steady state phase were measured and compared between groups. For this, a technique was used in which at each time step, 95% Confidence intervals (CI) were calculated for the difference between the mean values [20, 21]. Significance is reached when zero is not included in the 95% CI.

Statistical significance was set at $p < 0.05$. Continuous data is written as mean (standard deviation) or median [25–75th percentiles]. Either non-parametric (Mann–Whitney U) or parametric tests (t-test) were used, dependent on the distribution of the data (Shapiro–Wilk test). Analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria).

3 Results

The CONSORT diagram shows an overview of the inclusion of subjects (Supplemental Fig. S1). 136 patients signed an informed consent, 27 subjects were excluded before start of the study (e.g., subjects received concomitant drugs after signing informed consent, there was no member of the study team available to perform the study or subjects had a positive COVID-19 test for surgery). After inclusion 9 subjects were replaced due missing data points. In total 100 subjects were included for analysis. Patient characteristics are described in Table 1. No serious adverse events occurred during the conduct of this study.

Patient individual data over time, mean values and confidence intervals for measured qCON, Ce_{PROP}, mean arterial blood pressure and heart rate are plotted in Fig. 3 for both groups. Figure 4 shows the deviation over time for measured qCON values versus the targeted qCON for both groups (panel A and B), predicted Ce_{PROP} versus advised Ce_{PROP} over time for both groups (panel D and E) and the difference between groups on these intergroup deviations (panel C and F). Titration deviations did not differ between groups as shown in Fig. 4 panels C and F, depicted by the fact that zero is always included within the confidence intervals over time.

Table 1 Patient characteristics presented as mean (SD) or median [IQR]

	Control N = 50	Intervention N = 50
Age (year)	59.8 [31.7]	61.4 [15.2]
Gender (M/F)	26/24	28/22
Weight (kg)	81.8 (17.0)	82.9 (15.2)
Length (cm)	172.9 (10.1)	175.8 (9.2)
OR-duration (min)	140 [110]	147 [105]

The findings shown in Fig. 4 are also reflected in the results for the primary and secondary end points as presented in Table 2. The primary end point of this study, being the percentage of case time the qCON remained between 35 and 55, was not different between both groups. The percentage of case time with a qCON lower than 35 was comparable between groups, significant more qCON values higher than 55 were found in the intervention group.

There was no statistical difference on either the time to and value of $qCON_{LOC}$, $T_{qCON<55}$, $T_{peak,\ qCON}$ and $T_{eQ,}$ ROC and ROO between groups. There was no difference in total amount of administered propofol or remifentanil between groups. Vasopressor use was comparable between groups.

For the difference between targeted qCON and measured qCON, similar results were found for Median Performance Error (MDPE), Median Absolute Performance Error (MDAPE), Divergence and Wobble between groups. There was no difference between measured Ce_{PROP} and advised Ce_{PROP} between groups in terms of MDPE, MDAPE, Divergence and Wobble. The coefficient of variance did not differ between groups for qCON. For Ce_{PROP} Coefficient of Variance was significantly smaller in the control group compared to the intervention group. More alterations where made to Cet_{PROP} in the intervention group (10 [5.5]) compared to the control group (7 [6]).

4 Discussion

The Bayesian-based Ce_{PROP} advisory system applied in this trial enabled the anaesthetist to titrate qCON between 35 and 55 for 90% [IQR 18] of the case time. For only 2% [IQR 3] and 6% [IQR 18] of the case time, qCON values were above 55 and below 35, respectively. Titration based on the advisory system resulted in a tight control with a small median bias of 4%, indicated by MDPE and an MDAPE of 5% illustrating inaccuracy. Divergence and wobble, indicating oscillation of the clinical control behavior (wobble) and the tendency of the clinician to converge on the target over a longer time (divergence) revealed clinically acceptable control using the advisory display. These results are comparable with previously published work using a Bayesian-based closed-loop system for propofol administration using the Bispectral Index as controlled variable [11].

However, this randomized-controlled trial applying this Bayesian-based Ce_{PROP} advisory tool could not establish a more stringent control of qCON within 35–55 during general

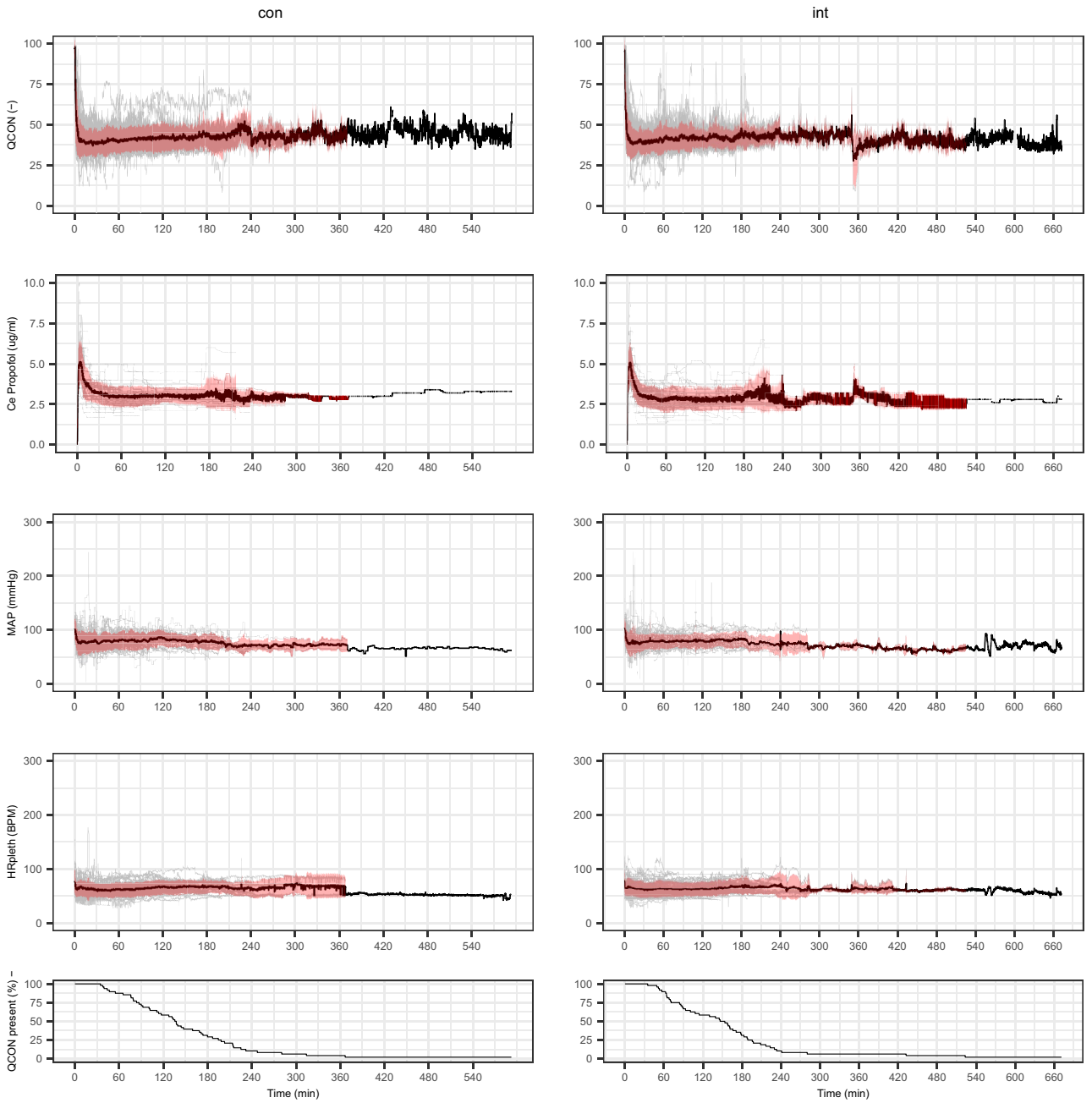

Fig. 3 "Spaghetti plots", displaying the 'raw' data from the patients. The bold black line indicates the mean of the variable at a certain time. The red shade indicates the standard deviation at that time point. *Ceprop* effect site concentrations of propofol, plotted over time, *MAP* mean arterial pressure. HRpleth is the heart rate, calculated from plethysmogram

anaesthesia compared to a "standard-of-care" propofol administration, defined as an EEG-guided effect-compartment controlled propofol administration without the input of the advisory system. As such, this study showed no significant changes in the primary outcome caused by the fact that the performance in the control group was also very high. Although low in absolute percentage, the case time with a qCON > 55 was significantly longer in the intervention group when compared with the control group. Comparisons were also applied on the data, using a narrowed range of target values, but this neither lead to significant differences.

The selection of the control group plays a crucial role in the study design and can easily influence significance between groups. It has to be mentioned that in a well-performing group of clinicians, as reflected by the control group, a significant improvement is hard to establish. The

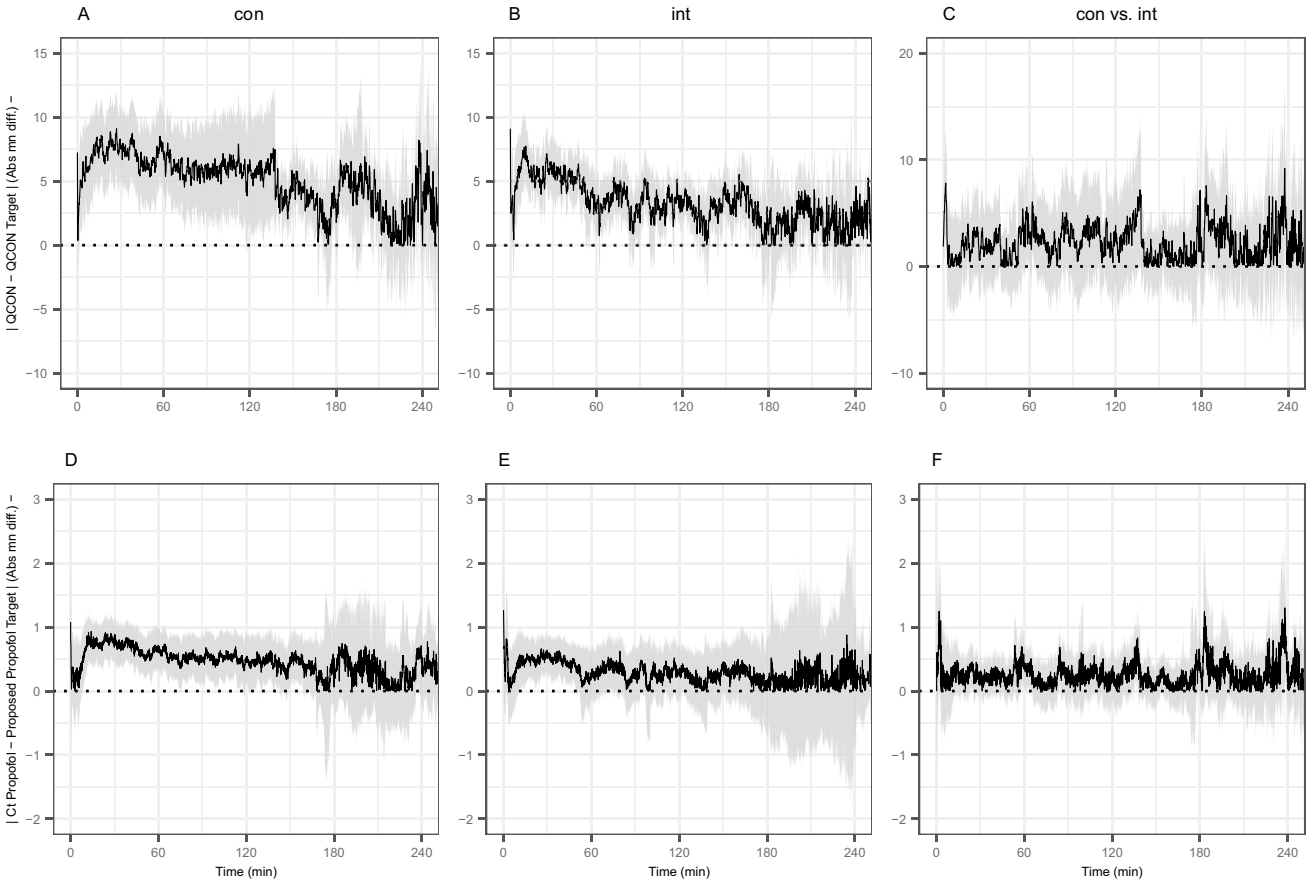

Fig. 4 In **A** and **B**, the difference between qCON and the targeted qCON is displayed within each group. At each time step, 95% confidence intervals (CI) were calculated for the difference between the mean values. When the CI's overlap with y = 0, there is non-significant difference between measurements. In **C**, the groups were compared with each other. **D**–**F** describe the difference between target propofol effect site concentration and advised target effect site concentration from the advisory system

performance of the control group may result from the fact that in our department, clinicians have a longtime experience in the use of TCI and EEG monitoring to titrate propofol administration and both modalities are standard of care. It has been shown in previous work that the level of experience and the willingness of the clinician to accept advises from advisory systems influences the level of control and as such the results of the trial [22].

The lack of difference between groups in the non-steady state (Time to LOC, Time to qCON < 55, $T_{PEAK,qCON}$, T_{EQ}) could also be related to the fact that the induction phase was in the first few minutes at the discretion of the anaesthetist, when the advisory screen is in a 'learning phase'. In this non-steady phase there is a fast alteration of drug dose advices that is practically almost impossible to accurately follow. Thereby, the processing time of the EEG monitor could be a limiting factor of the accuracy of the system in this non-steady state. An improvement is likely to be expected, when steps are taken slower, e.g. using a step-up wise induction which provides the system more time to learn and the clinician more time to adjust. No difference in the time to ROO was measured during the recovery phase. This can possible also be explained by the fact that our control group is already well performing, combined with the fact that altering the effect-site targets in the end was also at the discretion of the clinicians, providing the opportunity to already decrease targets at the end of surgery.

To evaluate the clinician's compliance to the advises, we compared targeted propofol with the advice propofol concentration, in terms of MDPE, MDAPE, Wobble and Divergence [19]. There were no differences between groups. This may also explain the lack of difference of propofol and remifentanil infused volumes. Nevertheless, median values are lower in the intervention group, but broad interquartile ranges proves that there was no maximal compliance from the clinician in every patient, which is essential for the advisory tool to work.

Some behavioral change was evoked as reflected by the coefficient of variance of Ce_{PROP}. We used this coefficient of variance as a derivative of the variability of the data. For

Table 2 Primary end point and secondary end points (Median [Inter Quartile Range]) or mean (SD)

	Control	Intervention	p value
Total time qCON 35–55 (% of case time)	84 [21]	90 [18]	0.15
Total time qCON < 35 (% of case time)	14 [19]	6 [18]	0.14
Total time qCON > 55 (% of case time)	0.7 [2]	2 [3]	0.04*
Time to LOC (s)	70 [19]	70 [30]	0.66
qCON at LOC	90 [25]	86 [27]	0.52
Time to qCON < 55 (sec of case time)	120 [107.50]	120 [102.50]	0.67
Time to peak qCON (sec of case time)	284 [102]	286 [109]	0.92
Time to equilibration 35–55 (s)	335 [144]	318 [154]	0.57
Total infused volume of propofol (2%) (ml)	65.75 [44.94]	56.95 [43.91]	0.80
Total infused volume of remifentanil (50 µg/ml)	28.79 [23.84]	24.80 [26.54]	0.79
Median Ce_{PROP}	2.99 [0.50]	2.88 [0.80]	0.22
Median Ce_{REMI}	3.99 [0.77]	3.99 [0.10]	0.46
Time to ROO (s)	750.00 [333.75]	655.00 [481.25]	0.21
Time to ROC (s)	621 [256]	525 [390]	0.14
qCON MDPE	−5 [6]	−4 [4]	0.14
qCON MDAPE	6.00 [4.25]	5.00 [3.13]	0.17
qCON Wobble	3 [2]	3 [2]	0.63
qCON Divergence	0.001 [0.00]	0.002 [0.003]	0.78
Propofol MDPE	25.16 [22.51]	18.62 [19.19]	0.15
Propofol MDAPE	24.20 [28.04]	19.44 [20.00]	0.22
Propofol Wobble	12.25 [6.77]	10.82 [3.00]	0.07
Propofol divergence	0.01 [0.02]	−0.009 [0.01]	0.99
CV qCON	0.12 [0.05]	0.13 [0.06]	0.56
CV Ce_{PROP}	0.17 [0.09]	0.19 [0.11]	0.036*
Changes in Cet_{PROP} (n)	7 [6]	10 [5.5]	< 0.001*

LOC loss of consciousness, *ROO* return of orientation, *ROC* return of consciousness, *MDPE* median performance error, *MDAPE* median absolute performance error, *CV* coefficient of variance, Ce_{PROP} propofol effect-site concentration, Ce_{REMI} remifentanil effect-site concentration, Cet_{PROP} targeted propofol effect-site concentration

*Significance was set as $p < 0.05$

qCON, we saw a comparable relationship with the target value. However, we noted a significant change for Ce_{PROP}, which was higher in the intervention group, showing a higher variability of the data in the intervention group. This could be attributed to a behavioral change of the clinicians in the intervention group in terms of effect-site targeting. This is supported by the fact that significantly more changes in Cet_{PROP} were found in the intervention group compared to the control group. Our results are in agreement with the statement from Minto and colleagues and Schnider et al. [23, 24]. suggesting that a direct correlation exists between the range of required propofol target concentrations and the effort from the clinician to maintain BIS between 40 and 60 in all patients at all times.

This study has some limitations that need to be addressed. First, as mentioned earlier in this discussion, more stringent control of drug titration is hard to achieve, when the group of professionals is already well performing, based on the control group. A significant improvement is likely to expected in for example, a group of novices in the use of TCI and total intravenous anesthesia (TIVA). This tool could then be helpful as an educational tool to learn the professionals to improve their drug titration skills. Second, this study is sensitive for the Hawthorne effect. As only the advisory tool was blinded, and not the EEG-monitor, the clinician may be more focused on titrating on the effect, compared with a situation that the clinician is not fully aware of this end point. This may positively over reflect the control group. However, the lower CV in the control group is a plea against this, as more Ce-adjustments have been applied in the intervention group compared with the control group. Third, it could be argued that the interaction opioid/hypnotic could constitute a confounder for the study results. Given the observational nature of the study, the anaesthetists were not forced to a different approach than the standard intraoperative opioid titration. The amount of remifentanil in the two arms of the study did not differ (Table 2), as they were titrated on the different phases of anaesthesia and surgical stimulation independently from the presence or absence of the advisory tool. Last, this study is fully dependent on the fidelity of the clinicians. As

the advisory tool was developed as a 'half closed-loop' system, its efficacy is dependent on the accurateness in which the advices were followed. There even could be cases in which the clinician decides from clinical grounds not to follow the advices on forehand, such as during surgery in which deeper levels of anaesthesia were preferred. In order to make studies like these successful, novice devices such as these advisory tools should be treated like any other device that is used in the operating theater [22, 25].

The fact that an advisory tool has at least not proven to be worse than the expert-level anaesthetist in suggesting an individualized anaesthesia plan implies that it is worthwhile to focus research efforts on this direction. Automatic technologies in drugs delivery have been recently shown to improve the haemodynamic profile during general anaesthesia and reduce the duration of postanaesthetic recovery [26, 27] An advisory tool capable of suggesting appropriate drug target concentrations to the anaesthetist based on patient-derived information could be interpreted as a safe instrument for bringing clinicians closer to this type of technology.

5 Conclusion

The Bayesian-based Ce_{PROP} advisory system applied in this trial enabled the anaesthetist to titrate qCON between 35 and 55 for 90% [IQR 18] of the case time. Significant differences with the control group were hard to establish, most likely due to a very high level of performance in the control group.

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Declarations

Conflict of interest E.W. Jensen: CEO at Quantium Medical and VP at Fresenius Kabi Barcelona, Spain, the manufacturer of the Conox monitor; M.M.R.F. Struys: His research group/department received (over the last 3 years) research grants and consultancy fees from Masimo (Irvine, CA, USA), Becton Dickinson (Eysins, Switzerland), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Medcaptain Europe (Andelst, The Netherlands), Baxter (Chicago, Il, USA). He receives royalties on intellectual property from Demed Medical (Temse, Belgium) and the Ghent University (Gent, Belgium); J.P. van den Berg, R. Vellinga, M. Introna, K. van Amsterdam, X.Y.T. Zhou, T. De Smet: no conflicts of interest reported, For departmental conflicts of interests, see MMRFS.

Ethical approval This trial was conducted at the Department of Anesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, and in compliance with Good Clinical Practice and applicable regulatory requirements. This study was approved by the University's Institutional Review Board (UMCG Ethics' Committee, Groningen, The Netherlands, METc NL 64961.056.18) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at the Dutch Trial Register (Dutch Trial Register, NTR7011, Principal investigator: Johannes P. van den Berg, https://trialsearch.who.int/Trial2.aspx?TrialID=NTR7011, date of registration: February 5th, 2018) prior to the start of the study.

Informed consent All patients provided written informed consent before participation.

Human and Animal rights Not applicable.

References

1. Kuck K, Egan T. Getting the dose right: anaesthetic drug delivery and the posological sweet spot. Br J Anaesth. 2017;119(5):862–4.
2. Absalom AR, Glen JL, Zwart GJ, Schnider TW, Struys MMRF. Target-controlled infusion: a mature technology. Anesth Analg. 2016;122(1):70–8.
3. Van den Berg JP, Vereecke HEM, Proost JH, Eleveld DJ, Wietasch JKG, Absalom AR, et al. Pharmacokinetic and pharmacodynamic interactions in anaesthesia. A review of current knowledge and how it can be used to optimize anaesthetic drug administration. Br J Anaesth. 2017;118(1):44–57.
4. Short TG, Campbell D, Frampton C, Chan MT, Myles PS, Corcoran TB, et al. Anaesthetic depth and complications after major surgery: an international, randomized controlled trial. The Lancet. 2019;394(10212):1907–14.
5. Introna M, Van den Berg JP, Eleveld DJ, Struys MMRF. Bayesian statistics in anesthesia practice: a tutorial for anesthesiologists. J Anaesth. 2022;36(2):294–302.
6. Cirillo V, Zito Marinosci G, De Robertis E, Iacono C, Romano GM, Desantis O, et al. Navigator and Smartpilot View are helpful in guiding anesthesia and reducing anesthetic drug dosing. Minerva Anestesiol. 2015;81(11):1163–9.
7. Kuizenga MH, Vereecke HEM, Absalom AR, Bucher CH, Hannivoort LN, Van den Berg JP, et al. Utility of the SmartPilot View advisory screen to improve anaesthetic drug titration and postoperative outcomes in clinical practice: a two-centre prospective observational trial. Br J Anaesth. 2022;128(6):959–70.
8. Struys MMRF, De Smet T, Greenwald S, Absalom AR, Binge S, Mortier EP. Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. Anesthesiology. 2003;100(3):640–7.
9. Obara S, Syroid N, Ogura T, Pace NL, Johnson KB, Albert R, et al. A pharmacokinetic-pharmacodynamic real-time display may change anesthesiologists' behavior. J Clin Monit Comput. 2021;35(3):547–56.

10. Jensen EW, Valencia JF, López A, Anglada T, Agustí M, Ramos Y, et al. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. Acta Anaesthesiol Scand. 2014;58:933–41.
11. De Smet T, Struys MMRF, Neckebroek MM, Van den Hauwe K, Bonte S, Mortier EP. The accuracy and clinical feasibility of a new Bayesian-based closed-loop control system for propofol administration using the bispectral index as a controlled variable. Anesth Analg. 2008;107:1200–10.
12. Sahinovic MM, Eleveld DJ, Kalmar AF, Heeremans EH, De Smet T, Seshagiri CV, et al. Accuracy of the composite variability index as a measure of the balance between nociception and antinociception during anesthesia. Anesth Analg. 2014;119:288–301.
13. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88:1170–82.
14. Sahinovic MM, Van den Berg JP, Colin PJ, Gambus PL, Jensen EW, Agustí M, et al. Influence of an "electroencephalogram-based" monitor choice on the delay between the predicted propofol effect-site concentration and the measured drug effect. Anesth Analg. 2020;131(4):1184–92.
15. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 1997;86(1):10–23.
16. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology. 1997;86(1):24–33.
17. Neckebroek M, Bolding JWHL, De Smet T, Struys MMRF. Influence of remifentanil on the control performance of the bispectral index controlled Bayesian-based closed-loop system for propofol administration. Anesth Analg. 2020;130(6):1661–9.
18. Van den Berg JP, Eleveld DJ, Van den Heerik AVM, van Amsterdam K, Lichtenbelt BJ, Scheeren TWL, et al. Influence of Bayesian optimization on the performance of propofol target-controlled infusion. Br J Anaesth. 2017;119(5):918–27.
19. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm. 1992;20:63–94.
20. De Baerdemaeker LE, Struys MM, Jacobs S, Den Blauwen NM, Bossuyt GR, Pattyn P, et al. Optimization of desflurane administration in morbidly obese patients: a comparison with sevoflurane using an 'inhalation bolus' technique. Br J Anaesth. 2003;91(5):638–50.
21. De Baerdemaeker LE, Jacobs S, Pattyn P, Mortier EP, Struys MMRF. Influence of intraoperative opioid on postoperative pain and pulmonary function after laparoscopic gastric banding: remifentanil TCI vs sufentanil TCI in morbid obesity. Br J Anaesth. 2007;99(3):404–11.
22. Sessler DI, Turan A, Stapelfeldt WH, Mascha E, Yang D, Farag E, et al. Triple-low alerts do not reduce mortality: a real-time randomized trial. Anesthesiology. 2019;130(1):72–812.
23. Minto CF, Egan TD, Schnider TW. Drug titration paradox: an emerging concept in clinical pharmacology. Anesthesiology. 2023. https://doi.org/10.1097/ALN.0000000000004686.
24. Schnider TW, Minto CF, Luginbuhl M, Egan TD. The drug titration paradox: more drug does not correlate with more effect in individual clinical data. Br J Anaesth. 2022;129(6):861–7.
25. Sessler DI. Decision support alerts: importance of validation. Anesthesiology. 2018;128(2):241–3.
26. Spataru A, Eiben P, Pluddemann A. Performance of closed-loop systems for intravenous drug administration: a systematic review and meta-analysis of randomised controlled trials. J Clin Monit Comput. 2023. https://doi.org/10.1007/s10877-023-01069-3.
27. Coeckelenbergh S, Joosten A, Cannesson M, Rinehart J. Closing the loop: automation in anesthesiology is coming. J Clin Monit Comput. 2023. https://doi.org/10.1007/s10877-023-01077-3.