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Pilot Study

PILOT STUDY

Using the TI.VA algorithm to titrate the depth of general anaesthesia: a first-in-humans study

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Abstract

Background: The dose of anaesthetic and opioid drugs must be continuously adjusted after the induction of general anaesthesia to maintain an adequate depth of anaesthesia. The TI.VA algorithm is a multiple-input/multiple-output algorithm designed to optimise the balance between anaesthetic and opioid concentrations during general anaesthesia. It applies vector analysis to a two-dimensional matrix to quantify any inadequacy of the depth of anaesthesia at any given moment and determine any drug dose adjustments required to achieve an adequate depth of anaesthesia. This study aimed to capture preliminary data on the performance and safety of the TI.VA algorithm during total i.v. anaesthesia in patients.

Methods: This prospective study enrolled nine patients with breast cancer scheduled to undergo surgery. General anaesthesia was induced under manual control using propofol and remifentanil. Anaesthesia was guided using the TI.VA algorithm from skin incision until surgical resection was completed. The quality of anaesthesia was assessed through an analysis of performance errors. A bispectral index global score (GS_{BIS}) <50 was considered an acceptable target for algorithm performance.

Results: All nine procedures were completed without any adverse events and none of the patients recalled any intraoperative event. Overall, we analysed 3417 monitoring points corresponding to 285 min of surgery. All patients presented a GS_{BIS} below the cut-off value of 50.

Conclusions: The TI.VA algorithm provides adequate control of clinical anaesthesia. A more sophisticated prototype needs to be developed before the trial is expanded to include larger patient populations.

Clinical trial registration: NCT05199883.

Keywords: computer-assisted decision-making; intravenous anaesthesia; medication systems; pharmacology

Balanced anaesthesia is characterised by the combined administration of anaesthetic and opioid drugs to render the patient unresponsive to the surgical stimulus.[1,2] An anaesthesia control task consists of an arrangement of proactive and reactive interventions to adjust drug concentrations according to the intensity of the surgical stimulus. A proactive approach entails adjusting the concentrations of anaesthetic drugs before an insult is applied with the intention of preventing the patient from reacting, after which the anaesthetist switches to a reactive approach, titrating drug administration according to the patient's response.

In recent years, several algorithms have been proposed for automated anaesthesia control. Most of the tested systems use proportional-integral-derivative (PID) controllers[3] designed to regulate unconsciousness and analgesia as separate dimensions of anaesthesia. Based on the interactions between the neural circuits involved in consciousness and to noxious stimuli[4] and the synergistic interactions between anaesthetic and opioid drugs,[5] neither a consciousness signal nor a noxious response signal alone is appropriate to quantify the patient's anaesthetic and analgesic requirements.

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Accordingly, instead of considering each factor separately, we designed a multiple-input/multiple-output algorithm—named TI.VA—capable of managing the balance between anaesthetic and analgesic needs with the main purpose of standardising the reactive approach of the anaesthesia control task. The algorithm's inputs include the bispectral index (BIS) and mean arterial pressure (MAP) combined in a two-dimensional matrix (Fig. S1), as proposed by Gurman.[6] The optimal range of the BIS and MAP determines an area of appropriate anaesthesia state, labelled the optimal anaesthesia zone. Anaesthesia inadequacy can be quantified through a vector connecting the patient's current position to the central point of the two-dimensional matrix, where the reference values for the control functions of the BIS and MAP are arranged. The analysis of the vector's main components generates two coefficients (D_H and D_S) used to identify a new balance between anaesthetic and opioid concentrations that is appropriate to keep a patient in the optimal anaesthesia zone.

The TI.VA algorithm can thus be viewed as a method to calculate the 'P' of a PID controller consistent with the complex interaction between consciousness and the response to surgical stimulus. This study aimed to characterise the algorithm's behaviour in clinical practice to highlight potential biases and gather preliminary safety data.

Methods

Ethics

This study was approved by the ethics committee of our research centre (*Istituto di Ricovero e Cura a Carattere Scientifico* Foundation, National Cancer Institute of Milan [INT], Italy; approval number: INT 150/20). The trial was registered at ClinicalTrials.gov after completion of the patent proceedings (NCT05199883, Principal Investigator: Emiliano Tognoli, approved 19 January 2022). The study was conducted in accordance with the principles of the Declaration of Helsinki, and this report was prepared according to the STROBE checklist for a cohort study. Written informed consent for study participation was obtained from each patient on the day of their surgical procedure.

Study design and population

This was a prospective study within a single cohort of patients. We planned to test the algorithm in a setting where it was possible to intervene easily to correct anaesthesia strategies that failed to guarantee the therapeutic goals and to mitigate any harmful consequences of potential algorithm biases. Given this risk mitigation strategy, only patients without severe comorbidities scheduled for minor surgery were considered. Each participant had to meet all of the following criteria to be enrolled in this study: (1) age 18–65 yr at the time of recruitment, (2) candidates for curative surgery for breast cancer, and (3) American Society of Anesthesiologists (ASA) status 1/2. The exclusion criteria were as follows: (1) ASA status >2, (2) contraindications for the use of the drugs used in this protocol, (3) pregnancy or lactation, and/or (4) lack of capacity to understand the study explanation and sign the informed consent form.

TI.VA algorithm

The architecture of the TI.VA algorithm is described in the Supplementary Material. In the first test, the algorithm was used to manage total i.v. anaesthesia with propofol and remifentanil. Both drugs were administered using a target-controlled infusion (TCI) system in effect-site mode. The minimum and maximum concentration limits were set at 1.2 μg ml^{-1} and 10 μg ml^{-1} for propofol and at 3.0 ng ml^{-1} and 20 ng ml^{-1} for remifentanil. All concentrations were considered to be related to the effect site, unless otherwise specified.

Fig 1. TI.VA prototype. The components of the first prototype system for managing the TI.VA algorithm are shown. The MacBook® screen shows the user interface constructed using a number spreadsheet (Apple Inc., Cupertino, CA, USA). The same stand holds the BIS™ monitor (Medtronic, Dublin, Ireland) and the Alaris® Gateway Workstation (Becton-Dickinson, Co., Franklin Lakes, NJ, USA), with two target-controlled infusion pumps dedicated to propofol and remifentanil administration. Communication of the Alaris® workstation with the MacBook is enabled using an Ethernet port, while communication with the bispectral index system is achieved using an RS232 port. The CNAP® monitor (CNSystems Medizintechnik GmbH, Graz, Austria) is connected via a separate port. In this case, the implementation of a communication interface with numbers is more problematic. Thus, we ultimately decided on optical character recognition technology guaranteed by a camera mounted in front of the monitor. The monitor screen is masked to optimise the recognition process. Data (i.e. mean arterial pressure and heart rate) are shown in the window directly in front of the camera. TI.VA, total intravenous anaesthesia.

TI.VA device prototype

We assembled a low-fidelity prototype setup composed of a personal computer running the algorithm and all devices

Table 1 Patient characteristics. ASA, American Society of Anesthesiologists; Pt, patient.

Patient number	Sex	Age (yr)	Weight (kg)	Height (cm)	ASA	Premedication	Surgery
Pt 1	Female	63	63	164	2	Pregabalin	Mastectomy
Pt 2	Female	57	63	163	2	Pregabalin	Resection
Pt 3	Female	47	54	157	2	Pregabalin	Resection
Pt 4	Female	48	54	158	2	Pregabalin	Mastectomy
Pt 5	Female	64	58	164	2	Pregabalin	Resection
Pt 6	Female	47	63	162	1	Pregabalin	Mastectomy
Pt 7	Female	46	50	152	1	Pregabalin	Mastectomy
Pt 8	Female	42	50	160	1	Pregabalin	Mastectomy
Pt 9	Female	48	53	162	2	Pregabalin	Mastectomy

necessary for anaesthesia management (Fig 1). The TI.VA algorithm and the additional functions described above were implemented through a number spreadsheet running on a MacBook Air computer (Apple Inc., Cupertino, CA, USA). The devices used to communicate with the spreadsheet were as follows: two Alaris™ PK syringe pumps (Becton-Dickinson, Co., Franklin Lakes, NJ, USA), a BIS monitor (BIS Vista™, version 3.2, Medtronic, Dublin, Ireland), and a continuous noninvasive blood pressure monitor (CNAP® Monitor 500, software version 5.2, CNSystems Medizintechnik GmbH, Graz, Austria). Communication of the Alaris® workstation with the MacBook was enabled using an Ethernet port, while communication with the BIS system was enabled via an RS232 port. The CNAP® Monitor 500 was connected via optical character recognition (OCR) technology through a camera mounted in front of the monitor.

Data were transmitted from the devices to the spreadsheet using a dedicated application custom-designed by Digital Forest Co. Ltd. (Milan, Italy). The data inputs into the number spreadsheets were as follows: target, plasma, and effect-site concentrations of propofol and remifentanil (according to the TCI system); BIS (measured by the Bispectral Index™ Monitor); and MAP and heart rate (measured by the CNAP® monitor). The sampling frequency depended on the standard communication protocol for each device. The incoming data occupied the relevant cell on the spreadsheet until a new value was transmitted. The data shown on the graphical interface were transposed on a dedicated number spreadsheet every 5 s.

Anaesthesia management and study procedure

All patients received total i.v. anaesthesia in the TCI mode using the population pharmacokinetic/pharmacodynamic sets of Schnider and colleagues[7] and Minto and collegues[8] for propofol and remifentanil, respectively. Upon arrival in the operating theatre, the anaesthesiologist inserted an i.v. cannula and administered a crystalloid load of 2 ml kg^{-1} for each hour of fasting. Physiological variables were monitored throughout the procedure following standard protocols. This included electrocardiography, pulse oximetry measurements, end-tidal oxygen levels, carbon dioxide concentrations, and noninvasive blood pressure measurements. All interventions that went beyond the control function of the TI.VA algorithm were managed according to the principles of good clinical practice.

The TI.VA algorithm was tested within the limits of the anaesthesia maintenance phase, defined as the period between skin incision and the completion of surgical resection. The algorithm was first consulted when the surgeon was ready for the skin incision. At this point, the algorithm required a minimum concentration of 2 μg ml^{-1} for propofol and 4 ng ml^{-1} for remifentanil. After the skin incision, the titration strategy was defined by the TI.VA algorithm to maintain patients in the optimal anaesthesia zone, defined as a BIS between 40 and 60 and MAP between 65 and 85 mm Hg. The implementation of any intervention proposed by the TI.VA algorithm was subject to the judgment of the attending anaesthesiologist, who manually inputted the new concentrations proposed by the algorithm into the TCI system.

Clinical safety and study termination

Adverse events were monitored using an institutional incident reporting system. Furthermore, patients were assessed for intraoperative awareness using the Brice questionnaire[9] administered by the nursing staff before discharge from the recovery room. Any adverse events, or any responses that raised suspicion about the patient's awareness, were defined as criteria for early suspension of the study.

Algorithm behaviour analysis, cohort size, and statistical analysis

To characterise the algorithm behaviour and potential biases, the stability of the BIS and MAP as the controller variables during the test period was analysed using the the performance error (PE) analysis as proposed by Varvel and colleagues[10] and the global score (GS).[11] The analysis was performed using the following equation:

$$PEij=(controllerij-controller\text{-}target)/controller\text{-}target\times 100$$

$$MDPEi=median\ \{PEij,\ j=1,\ \ldots,\ Ni\}$$

$$MDAPEi=median\ \{|PEij|,\ j=1,\ \ldots,\ Ni\}$$

$$Wobblei=median\ \{|PEij-MDPEi|,\ j=1,\ \ldots,\ Ni\}$$

where Ni is the number of PEs obtained in the ith subject.

GS: (MDAPE+Wobble)/% of time in range.

The analysis was applied to the BIS and MAP separately, with a BIS of 50 and MAP of 75 mm Hg used as reference values. Based on the targets proposed by a recent meta-analysis by Pasin and colleagues,[12] a GS <50 and median absolute PE (MDAPE) <20 for the BIS were considered acceptable targets for algorithm performance. The MDAPE centres on algorithm

Table 2 BIS and MAP for individual patients.The parameters proposed by Varvel and colleagues[10] and the GS are reported for all enrolled patients to characterise BIS and MAP control in response to the titration strategy generated by the TI.VA algorithm. BIS, bispectral index; GS, global score; MAP, mean arterial pressure; MDPE, median performance error; MDAPE, median absolute performance error; Pt, patient.

BIS					
Patient number	MDPE (%)	MDAPE (%)	Wobble (%)	GS	BIS in range (%)
Pt 1	−16.00	18.00	6.00	39	62
Pt 2	−18.00	18.00	4.00	30	74
Pt 3	8.00	11.00	11.00	27	81
Pt 4	−2.00	12.00	12.00	30	79
Pt 5	−8.00	10.00	6.00	20	80
Pt 6	−10.00	12.00	10.00	28	79
Pt 7	−4.00	8.00	8.00	18	87
Pt 8	−4.00	6.00	6.00	13	91
Pt 9	−18.00	18.00	6.00	41	59
MAP					
Patient number	MDPE (%)	MDAPE (%)	WOBBLE (%)	GS	MAP in range (%)
Pt 1	5.33	8.00	8.00	21	75
Pt 2	14.67	14.67	6.67	75	28
Pt 3	−10.67	10.67	1.33	13	94
Pt 4	−4.67	5.33	4.67	11	92
Pt 5	−9.33	10.67	6.67	26	66
Pt 6	−9.33	10.67	6.67	21	83
Pt 7	−5.33	5.33	5.33	21	80
Pt 8	−1.33	8.00	9.33	26	68
Pt 9	2.67	6.67	9.33	22	72

performance, while the GS provides the criteria to define the minimal performance the algorithm has to guarantee for all patients despite the expected uncertainty in the clinical setting, that is, the robustness of the control system.[3] Accordingly, the safety of the TI.VA algorithm was defined as the ability to guarantee the minimum performance criteria described above.

Approximately 50% of patients have a GS_{BIS} ≥50 under manual control.[13] Therefore, a cohort size between six and 10 subjects[14,15] has a power of 0.9844–0.9990 to observe at least one case of underperformance of the TI.VA algorithm, similar to manual control. Our cohort size was thus in agreement with the need to define a reliable criterion for the test outcome and with the principle of caution, which suggested minimising the number of participants exposed to a treatment that has never been tested.[16]

Results

Nine patients completed the protocol, while three dropped out because of technical problems related to OCR technology. This cohort size guaranteed the detection of at least one patient with a GS_{BIS} ≥50 with a probability of 0.9980. The subjects' characteristics are summarised in Table 1. The procedures were completed without any adverse events. Feedback based on the Brice questionnaire indicated that none of the patients recalled any intraoperative event. Only one patient reported dreaming: she dreamed of her family.

Overall, 3417 monitoring points corresponding to 285 min of surgery were analysed. All monitoring points were managed according to the suggestions of the TI.VA algorithm. Permanence in the optimal range for BIS was 82% of monitoring points. All patients presented with a negative MDPE result and a GS_{BIS} under the cut-off value of 50 (Table 2). Permanence into the optimal range for MAP was 78% of monitoring points, with MDPE being positive in three patients, only one of whom presented with a GS_{MAP} >50 (Table 2).

The drug concentrations proposed by the TI.VA algorithm are presented in Fig 2. We recorded 85 interventions with regard to propofol concentration. On average, each concentration was confirmed at a total of 38 monitoring points (190 s). The minimum concentration limit for propofol (1.2 μg ml^{-1}) was reached in one patient. With regard to remifentanil concentration, 88 interventions were recorded. On average, each concentration was confirmed at a total of 37 monitoring points (185 s). The lower limit for remifentanil (3 ng ml^{-1}) was reached in three patients.

Discussion

This study tested the use of the TI.VA algorithm as a guide for the administration of propofol and remifentanil during general anaesthesia. In all nine patients involved in this study, the titration strategy using the TI.VA algorithm allowed the control of the BIS variable within clinically acceptable performance limits. No patient had a GS_{BIS} ≥50, which corroborates the safety and robustness of the architecture of the algorithm.

Additionally, when our GS_{BIS} results were pooled across patients, the mean and corresponding 95% confidence intervals (27.34 and 21.06–33.62, respectively) were fully within the confidence region for automated control reported in the meta-analysis by Pasin and colleagues.[12] These results were obtained despite the low level of prototype development. The sound modelling of the process to be controlled is a key factor in conditioning the performance of any algorithm. In the literature, most automated anaesthesia systems are designed to control BIS or other quantitative electroencephalogram indices through the administration of propofol.[17–21] In the TI.VA algorithm, the two control variables—BIS and MAP—are combined in a two-dimensional matrix to characterise the equilibrium between the consciousness and response to noxious stimuli dimensions of anaesthesia instead of mapping each component separately.

Controlling the state of consciousness without intervening in the administration of opioids means overlooking one of the variables that contribute to the uncertainty of the patient's reaction to the anaesthesia control strategy used.[22] In accordance with this complexity, the MAP has been chosen as control variable to weigh the opioid requirement in the TI.VA algorithm. Arterial blood pressure is one of the easiest indicators of sympathetic response to measure during anaesthesia; it has already been used for the control of opioid administration, with results slightly better than those of the TI.VA algorithm.[23]

During anaesthesia, optimal control of arterial blood pressure is a primary goal to ensure tissue perfusion and the best

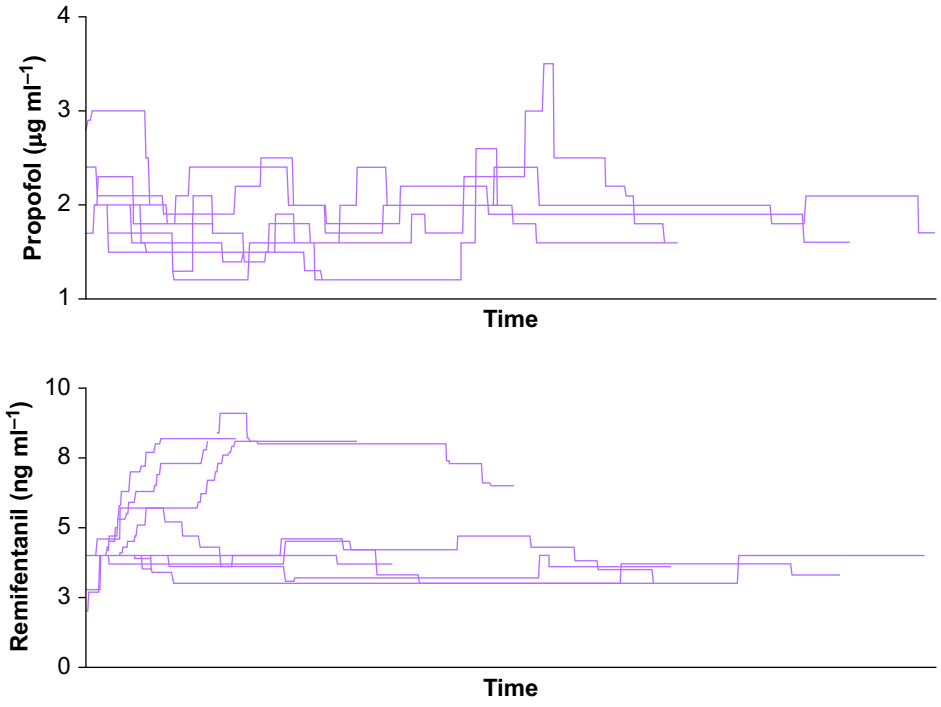

Fig 2. Anaesthetic drug concentrations during TI.VA control of anaesthesia. Concentrations are expressed as target effect-site levels. TI.VA, total intravenous anaesthesia.

patient outcome.[24,25] The opioid regimen contributes to optimisation of tissue oxygenation by attenuating = vasoconstriction caused by surgical stimulus and adrenergic response.[26] Studies on anaesthetic/opioid interactions have shown that different combinations of effect-site concentrations of propofol and remifentanil are associated with significant differences in arterial blood pressure.[27,28] This supports the reliability of arterial blood pressure as a guide to control a strategy toward a definite point of synergy between unconsciousness and analgesia.

In recent years, other physiological variables have been proposed to better characterise the sympathetic response during surgical procedures. Among them, heart rate variability (HRV) is included in nociception measurements and is considered a hypotension-predicting index during anaesthesia.[29,30] As such, HRV appears to be a promising variable for optimising analgesia when the patient is in the optimal anaesthesia zone. A comparative analysis of HRV behaviour in response to the strategy proposed by the TI.VA algorithm will provide the necessary information for further development.

The TI.VA system is aimed at becoming an automated system, but the current prototype requires the anaesthetist in charge to manually set new target concentrations during the intraoperative period. The frequency of interventions registered in this first test supports automation as a useful strategy to reduce anaesthetist workload.

The main limitations of this study were the small number of patients investigated and the homogeneous clinical context, as a findings of which the results of this preliminary study cannot be generalised. Nevertheless, this pilot study provides valuable data that can be used to better design future research.

In conclusion, the TI.VA algorithm seems to be an effective method to characterise the anaesthetic and analgesic requirements of patients under general anaesthesia. The development of a complete PID controller will allow the evaluation of the full potential of this approach.

Authors' contributions

Designed the TI.VA algorithm and performed the clinical trials: ET
Contributed to the study design, data analysis, and drafting of the manuscript: ML
Read and approved the final version of the manuscript: both authors

Declarations of interest

ET owns the patent for the TI.VA algorithm. ML declares that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2023.100203.

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