Statistical Analysis Plan

Study title	Automatic Control of Total Intravenous Anesthesia: Closed-loop Delivery of Propofol and Remifentanil Using Bispectral Index as Feedback Variable. Acronym: ACTIVA 2.
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List of abbreviations

ACTIVA = automatic control of total intravenous anesthesia;
BIS = bispectral index scale;
GUI = graphical user interface;
HR = heart rate;
MBP = mean blood pressure;
PONV = postoperative nausea and vomiting.

Introduction

This study concerns the clinical evaluation of a closed loop control system for the automatic administration of anesthetic drugs in TIVA (Total Intravenous Anesthesia). The purpose of the experimentation is to demonstrate that the control system under study is reliable, safe, applicable and capable of inducing and maintaining an optimal anesthetic level.

Study design

The clinical study ACTIVA 2 is a pragmatic, interventional, nonrandomized, single-arm, single-center.
The population considered in the clinical study consists of adult patients scheduled for elective surgery for whom total intravenous general anesthesia is indicated, using the hypnotic drug propofol and the analgesic drug remifentanil, and who have provided appropriate informed consent. Patients under the age of 18 and patients incapable of understanding and consenting are excluded from the study.
The selection of patients is made regardless of age (provided they are over 18), gender, weight, height, as well as anesthetic risk and the type of surgical procedure. This reduces systematic errors associated with specific patient selection for enrollment in the study.
The enrolled patients underwent an anesthesiological treatment conducted in a closed-loop system following the clinical protocol and under the constant supervision of the experimenter. The experimentation took place in a single operating room at the experimenter's center where plastic surgery procedures are performed. This allowed for maintaining a consistent surgical and environmental setting.
Patients are informed of the possibility to participate in the study during the preoperative anesthesia visit, which typically occurs two weeks before the surgical procedure. If the patient chooses to participate in the study, informed consent is obtained before the start of the medical procedure subject to the experimentation.
The patient enrolled in the study arrives in the operating room on the day of the procedure and undergoes the standard preoperative preparation, which is administered to all patients undergoing intravenous general anesthesia, regardless of their enrollment in the study. In particular:

- Venous access is established.
- Instrumental monitoring includes blood pressure, electrocardiogram, peripheral oxygen saturation, and Bispectral Index Scale (BIS).
- Infusion pumps are connected to the venous access.

The ACTIVA control software is then initiated by the lead experimenter, who enters the necessary anthropometric data into the GUI, initializes the system, and starts the automatic control. During the surgical phase, the experimenter supervises the system and ensures its proper functioning. If necessary, annotations are added to the system according to the protocol. Once the surgical procedure is completed, the experimenter stops the drug infusions through the graphical user interface (GUI) but continues recording the BIS and other patient monitoring parameters. The patient awakens spontaneously. After awakening, the ACTIVA software is turned off by the experimenter.
The patient is then transferred to the recovery room where they undergo standard post-operative procedures. The study concludes 24 hours after the patient awakens from anesthesia with a postoperative anesthesia visit.

Sample size calculation

The sample size was determined based on the primary outcome measure concerning the depth of hypnosis adequacy provided by the ACTIVA control software. Specifically, it was calculated with the aim to assess the proportion of patients for whom the percentage of the anesthesia maintenance duration in which the BIS is kept inside the recommended range from 40 to 60 is greater than 43%. This latter value is the average percentage that was observed in a previous data acquisition campaign concerning manually controlled TIVA, which was performed in the same clinical setting considered for the present clinical trial (Study acronym: ACTIVA 1, Id code: NP-1843).
The proportion was estimated to be 90% of patients with a 95% confidence interval and a margin of error of 10%. The resulting sample size is 139 patients. This number of enrolled subjects also ensures that the ACTIVA control software is adequately tested for safety, reliability, feasibility, and applicability. Secondary outcome measures were not considered in the sample size calculation.

Aims and objectives

The primary objective of the clinical investigation is to investigate the clinical performances obtainable by the control system under study in terms of depth of hypnosis adequacy.
The secondary objective is to evaluate the reliability, safety and applicability of the control system under study and to carry out the clinical evaluation of the automatic control system during the induction, maintenance and recovery of general intravenous anesthesia.

Outcomes

The primary outcome measure is the depth of hypnosis adequacy. It is assessed by means of the percentage of the anesthesia maintenance duration in which the BIS is kept inside the recommended range from 40 to 60. The percentage of the anesthesia maintenance duration in which the BIS is kept below 40 is also specified. Maintenance duration is the period of time that goes from the end of anesthesia induction to the point at which the automatic control is turned off at the conclusion of surgery. The end of anesthesia induction is defined as the time instant when the BIS drops below 40 for the first time and remains there for the subsequent 30 seconds.

The secondary outcomes measures are:

- Number and types of dysfunctions of the ACTIVA automatic infusion system.
- Level of satisfaction of the experimenter. It is expressed on a scale from 0 to 10 regarding the ease of use of the ACTIVA software and its infusion system, the induction phase of anesthesia and the maintenance phase of anesthesia.
- Effect of drugs delivery on heart rate. It is assessed by means of the percentage of the anesthesia maintenance duration in which the heart rate (HR) is kept inside the range from 50 to 100 beats per minute. The percentage of the anesthesia maintenance duration in which the HR is kept below 50 is also specified.

- Effect of drugs delivery on mean blood pressure. It is assessed by means of the percentage of the anesthesia maintenance duration in which the non-invasively measured mean blood pressure (MBP) is kept inside the range from 65 to 110 mmHg. The percentage of the anesthesia maintenance duration in which the MBP is kept below 65 is also specified.

- Postoperative heart rate stability. It is assessed by measuring the HR in bpm.

- Postoperative Mean Blood Pressure Stability. It is assessed by non-invasive measuring of the mean blood pressure in mmHg.

- Postoperative sedation. It is assessed by means of a Sedation Score scale. It is a 3 point scale from 0 (fully awake) to 3 (fully sedated).
- Postoperative nausea and vomiting (PONV). It is assessed by means of the Bellville PONV scale. It is a 3 point scale from 0 (no nausea and vomiting) to 3 (vomiting present).

- Postoperative analgesia. It is assessed using a 10-point numeric rating scale (NRS). It is a 10 point scale from 0 (no pain) to 10 (maximum pain).

Population to be analyzed

The population considered in the clinical study consists of adult patients scheduled for elective surgery for whom total intravenous general anesthesia is indicated, using the hypnotic drug propofol and the analgesic drug remifentanil, and who have provided appropriate informed consent. Patients under the age of 18 and patients incapable of understanding and consenting are excluded from the study.
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Analyses

For each patient enrolled in the study, the following variables will be collected:

- Age.
- Gender.
- Weight
- Height
- Type of surgical procedure
- Anesthesiological risk assessment according to the American Society of Anesthesiologists physical status classification system.
- PONV risk assessment according to the Apfel simplified risk score.

These data are collected by the principal investigator at patient arrival in the operating room, before surgery and they are noted on the patient's anesthesiology clinical record form.
The following variables are automatically collected by the ACTIVA software, they are recorded in real-time every second and stored on a ".csv" file:

- HR.
- Peripheral oxygen saturation.
- MBP.
- BIS.
- BIS signal quality index.
- Burst suppression ratio[1] .
- Infusion rates of propofol and remifentanil.

[1] Burst suppression is defined as a period on the electroencephalogram trace characterized by attenuated or suppressed signal (<10 mV) alternating with brief periods of cortical activity, precisely termed 'bursts.' More than 50% of this period is dominated by attenuated/suppressed activity. This effect may sometimes be intentionally induced, for example, during neuroanesthesia, as a protective measure against cerebral ischemia, as it coincides with a reduction in cerebral metabolism. However, it is important to consider that it is also associated with a higher incidence of postoperative delirium.

The following data are collected by the principal investigator after surgery and noted on the patient's anesthesiology clinical record form.

- System dysfunctions.
- Level of satisfaction of the experimenter.
- HR.
- MBP.
- Postoperative sedation.
- PONV.
- Postoperative analgesia.

Descriptive statistics will be performed on all study variables.
Quantitative data will be presented as mean (SD) or median (IQR) according to their distribution. Normality of the data will be tested using a Shapiro-Wilk test. Categorical data will be presented as frequency (proportion).

Data management

The data management activities have been carried out in such a way as to ensure that data processing is complete, consistent, and logical, and that all data described in the clinical investigation are included in the study. The file recorded by the ACTIVA control software allows for the analysis of the control system's performance regarding malfunctions and/or critical issues identified by the experimenter, recorded in the form of notes. Furthermore, it contains recordings of time series data for drug infusion rates, BIS (Bispectral Index), and other standard monitoring data for general anesthesia. The report file allows for offline analysis of the control system's performance. The report file is generated automatically by the ACTIVA control software. Post-operative data, on the other hand, are manually recorded by the experimenter on the designated data collection sheet. Experimenters have filled out the data collection sheet and entered notes on the GUI during the operation of the ACTIVA software as prescribed. During the conduct of the clinical study, the data resulting from the study are stored by the lead experimenter in their original form on the PC dedicated to the ACTIVA software and backed up on the experimenter center's PC. At the end of the study, all data have been migrated and are stored on a dedicated PC at the experimenter center. Access to the data is restricted to authorized individuals.