Impact of Propofol Dose Reduction in Relation to the Time Since Administration of Fentanyl During Anesthesia Induction

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STUDY PROTOCOL

Study center:

Hospital Central de la Defensa “Gómez Ulla”

Researchers data:

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Expected duration of the project:

Approximately three years depending on the number of patients who meet inclusion criteria.

Hypothesis:

The dose of propofol necessary to reach an optimal anesthetic depth could be reduced if the time since the administration of fentanyl is prolonged, thus avoiding the pre-intubation hypotension and postintubation hypertension.

Objectives:

General

To determine if, by increasing the time elapsed between the administration of fentanyl and propofol and decreasing the dose of the latter, fewer hemodynamic changes related to orotracheal intubation occur.

Specifics

• Assess whether the patient's age is a determining factor in hemodynamic variations dependent on time-dose.

• Evaluate hemodynamic variations after anesthetic induction according to the dose of propofol and the time since administration of fentanyl.

• Determine if hypertensive patients and those treated with antihypertensives or heart rate regulating drugs suffer greater hemodynamic variations during anesthetic induction.

• Analyze if the time is delayed from the administration of fentanyl delays the moment until reaching the optimal anesthetic depth.

• Determine if premedication with benzodiazepines alters the time to reach hypnosis.

Subjects and Methods

Subjects

All adult patients scheduled for surgery that, under the care of the same anesthesiologist, require general anesthesia with tracheal intubation, that meet inclusion criteria and accept participation and sign written consent.

• Inclusion criteria:

- Older than 18 years
- Requiring general anesthesia with tracheal intubation
- Same operator
- Accepting participation and signing written consent

• Exclusion criteria

- Cardiac surgery
- Hemodynamic instable patients: systolic blood pressure (SBP) ≤ 90 mmHg with clinical signs of low cardiac output (impaired state of consciousness, diuresis <0.5 ml/kg/h, central venous saturation <60% with normal arterial saturation or lactate >3 mmol/l).
- Increased risk of bronchoaspiration: absence of fasting for 6 hours for solid foods and 2 hours for clear liquids or presence of pathologies that imply an absence of gastric emptying.
- Predictors, known or unexpected difficult airway.
- Airway management with other supraglottic devices.
- Known allergy to anesthetic drugs (muscle relaxants, hypnotics, etc.), egg or soy proteins.

Methods

Design

This is a prospective and randomized clinical trial. Estimating a possible loss of 15%, 192 patients are recruited. They will be distributed in two time-groups (2 and 1 minute) and in three propofol dose-subgroups (2, 1.5 and 1 mg/kg) as seen in table 1. The distribution in groups is done with a computerized randomizer that assigns each patient (1-192) to each group. Data collection begins consecutively until the sample size is reached.

Table 1. Study groups

Group	Time to propofol (min)	Propofol dose (mg/kg)
1	2	2
2		1.5
3		1
4	1	2

5		1.5
6		1

Action protocol

On the day of the surgery, it is verified that the patient accepted the participation and has signed the informed consent. Confirmation of suspension or administration of usual medication indicated in the preoperative evaluation is performed.

The patient is monitored with a 5-lead electrocardiogram, pulse oximetry, non-invasive blood pressure cuff to the Dräger Infinity Delta monitor and Bispectral Index (BIS) monitor (Covidien Complete Monitor System P/N 185-0151, 2016, USA).

In case the patient don´t have a venous access previously channeled, a peripheral variable-gauge venous cannula is placed according to the type of intervention (22-18 gauge).

Without prior fluid loading, but with a perfusion of 0.9% physiological solution at 100 ml/h, pre-oxygenation is carried out through a facial mask with 100% O2 until the expired fraction of O2 in the respirator gas analyzer (Dräger Primus, Germany) exceeds 80%. Once this point is reached, fentanyl 2 µg/kg is administered intravenously and, depending on the group to which the individual belonged (1, 2 and 3 or 4, 5 and 6), hypnotic is given after 1 or 2 minutes.

According to the corresponding group, 1, 1.5 or 2 mg/kg of propofol are administered, with intravenous lidocaine 0.5 mg/kg, and the time elapsed until the BIS drop below 60 is determined. When BIS does not reach the level of hypnosis after 2 minutes an extra dose of 0.5 mg/kg of propofol is administered. Subsequently, rocuronium 0.6 mg/kg is given and patient is maintained with manual ventilation until orotracheal intubation (Mackintosh # 3-4 laryngoscope).

In the case of hypotension: SBP <90 mmHg, SBP fall >30% or mean blood pressure (MBP) <60 mmHg; vasoactive drugs (VAD) (ephedrine or phenylephrine equivalent doses) are administered. In the presence of bradycardia (heart rate -HR- fall >30% or HR <50 bpm), atropine 0.1 mg/kg is administered intravenously.

Data collection and study variables

Data is collected manually, recording patient's identification number (1-192), age, sex, weight, ASA, antihypertensives or beta-blockers or calcium channels previous treatment. The hemodynamic parameters (SBP and HR) are established as follows: baseline value (SBPb and HRb) is recorded before administration of fentanyl, preintubation value (SBP1 and HR1) is noted after the administration of propofol and once BIS has dropped from 60 and, finally, post-intubation value (SBP2 and HR2) is

recorded 15 seconds after placement of the endotracheal tube. Baseline BIS values, time (seconds) it takes BIS to fall below 60, requirement of extra dose of hypnotic or VAD are also registered. Baseline, preintubation and post-intubation MBP (MBPb, MBP1 and MBP2 respectively) are calculated using the formula MBP = (SBP + 2DBP)/3.

Statistical methods

Statistical analysis is performed using the Statistical Package for Social Sciences program (IBM SPSS Inc., USA) version 22 for Windows. For the descriptive statistics, central tendency and dispersion indices were used for the qualitative and quantitative variables. Confidence intervals were estimated with a 95% confidence level.

Age, weight, BIS, time at BIS less than 60, blood pressure, HR and reduction percentages of the BP and HR are treated as continuous quantitative variables. The remaining variables, such as sex, ASA risk (low: I and II – high: III and IV), antihypertensives, beta blockers or calcium blockers treatment, VAD and extra dose of propofol requirements are considered dichotomous quantitative variables. Study groups and age groups are classified as categorical variables.

For inferential statistics, normality is evaluated with Kolmogorov-Smirnov test and, in case of normal distribution, the results are expressed as arithmetic mean ($\bar{x}$) and standard deviation (DS). In the absence of normality, the data are expressed in median (M) and interquartile range (IQR). For quantitative variables, if the data presents a normal distribution, a T student test is used. In cases with no normality criteria, Mann-Whitney U test. In qualitative variables, Chi-square and Fisher's exact test are used if more than 20% of the expected frequencies in the tables have a value less than 5. Finally, for comparisons of qualitative variables with quantitative variables, ANOVA or Kruskal-Wallis are used. To compare time to hypnosis between the groups, Kaplan-Meyers curve is used.