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PROTOCOL

Analyzing the Relationship Between Speed Propofol is Given and Low Blood Pressure

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ANALYZING THE RELATIONSHIP BETWEEN RATE OF INDUCTION AND PERIOPERATIVE HYPOTENSION USING PROPOFOL

A PROSPECTIVE RANDOMIZED STUDY

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Background:

Propofol is one of the most common drugs used for induction and maintenance of general of anesthesia. The main advantage of propofol, which contributed to its popularity, is its rapid onset and short duration of action. When administered as an IV bolus, the clinical effects wane within a few minutes[1]. The main mechanism of action of propofol is its interaction with the GABA receptor; and it has a short duration of action due to rapid distribution into peripheral tissues[2].

One of the main disadvantages of propofol is iatrogenic hypotension, with an incidence as high as 68% [3-5], associated with increased requirement of vasopressor administration[6] and higher mortality and negative outcomes[7, 8]. One study reported that general anesthesia with propofol at doses 125 and 200 μcg/kg/min decreases the mean arterial pressure from 85±3 to 69±5 and 66±4 mmHg, respectively[9].

Another author reported that increasing the mean propofol Cb 3.0 (0.9), 4.5 (1.0), and 6.5 (1.2) μg ml^{-1} decreases bispectral index spectrometry (BIS) measurements to 54 (13), 39 (8), and 29 (7), respectively. Increasing concentrations of propofol led to venous dilatation; and mean arterial pressure from 82 (12) to 75 (12) and 66 (10) mm Hg, respectively, at the three propofol Cb levels ($P < 0.001$)[10].

On the other hand, a prospective, double-blind, open-label, randomized study in the United States has reported only 17.4% incidence of propofol-induced hypotension[11].

There are multiple risk factors and comorbidities which increase the relative risk (RR) of propofol-induced hypotension. In his study, Abdelmonem et al. (2019) demonstrated that advanced age, higher APACHE II score, sepsis, diabetes, acute and chronic kidney diseases, cirrhosis, atrial fibrillation are associated with higher RR of Propofol induced hypotension development, when compared with the cohort group [34]

Age is an independent factor associated with severe hypotension. A study reported that approximately half of patients sedated with propofol experienced hypotension are above the age of 60 [35]. It has been shown that age is the

strongest risk factor for propofol-induced hypotension, and propofol should be given with significant caution within certain age groups[12].

Multiple studies describe the mechanism of this phenomenon, yet the exact mechanism is fully unknown. Possible reasons of hypotension after propofol administration may be either due to propofol-mediated decreases in preload, cardiac output and contractility[13, 14], decreased in afterload and systemic vascular resistance[15-20], or sudden cessation of sympathetic vasomotor activity[21-24]. The above described hypothesis is supported with the fact that a preoperative bolus of fluids helps maintain the hemodynamic stability during induction with propofol[25]. However, in animal models, propofol demonstrated a property of direct relaxation of vascular smooth muscle[26-33]. Moreover, this property of propofol most likely has been achieved via nitric oxide[28] and veins seems to be more sensitive than arterioles[26, 31].

An anonymous survey conducted at the Department of Anesthesiology at UTMC revealed that 63% of anesthesiologists starting their induction with the sequence of follow medications: Fentanyl-Lidocaine-Propofol-Succinylcholine. 27% of them administer propofol within 10 seconds via manual push, 45% within 10-20 seconds and less than 30% of anesthesiologists administer propofol in 60 seconds or longer.

Majority of anesthesiologists (45%) are calculating the dose of propofol based on ideal body weight and titrating it until desired hypnotic effect is achieve instead of administering of full pre-induction calculated dose (72%).

This wide variability in anesthesiologic practice at The Department of Anesthesiology UTMC is based on training, experience, and a comfort level of the provider. Nevertheless, all anesthesiologic approaches mentioned above are acceptable and being safely used for routine daily management for years.

Summary of Background:

The pharmacokinetic and pharmacodynamic properties of propofol, such as fast onset of action, rapid distribution, smooth awakening, and low rate of nausea/vomiting make propofol the most preferable hypnotic medication for induction and maintenance of anesthesia. Compared to midazolam, propofol allows better and precise control of the depth of anesthesia with less side effects.

However, the induction of anesthesia with propofol is associated with hypotension with marked reduction of sympathetic outflow and plasma catecholamine levels. This side effect becomes more significant in elderly patients undergoing a surgical procedure. Thus, the study is required to evaluate the association between the speed of propofol administration and post-induction and intra-operative hypotension.

Significance of the Study

Considering the wide variety of current anesthesiologic management during the induction at our Department, we decided to conduct a study to evaluate the benefit of slow speed propofol induction. This prospective study will evaluate the influence on hemodynamic changes with a controlled, slow rate of induction of general anesthesia with propofol compared to the standard induction rate (manual push within 10-20 seconds). By gathering this information, we will be able to determine the optimal rate of induction in order to avoid propofol-related hypotension during elective surgeries.

Study Objectives:

Primary Aim

To evaluate the association between induction rate using propofol and post-induction hemodynamic stability in patients.

Secondary Aim

To evaluate the necessity of inotropic or vasoactive medication use in the early post-induction period, required to correct propofol-induced hypotension.

Tertiary Aim

To evaluate the association between hemodynamic stability, delay in surgical procedure start time, length of hospital stay, as well as early post-operative complications and 30-day mortality and morbidity.

Primary Hypothesis

We hypothesize that a slow rate of induction using propofol over at least two minutes may be associated with a lower incidence of post-induction and perioperative hypotension. In turn, this will result in less inotropic and vasoactive medication use in the early intra-operative phase.

Secondary Hypothesis

We hypothesize that hemodynamic stability during and after induction, less administration of vasoactive and inotropic medications is associated with less complications during early post-operative period, shorter length of hospital stay and a lower 30-day mortality.

Study Designs:

Cluster randomized, non-blinded, cohort trial. Study will be conducted, and patient will be enrolled at the main Operating Unit of The University of Toledo Medical Center, Toledo Ohio.

Study Methods:

Propofol can be administered during induction as fast (within 10-20 seconds), as well as slow for 60 seconds and longer. Both types of inductions are being safely used at our department. To compare the benefit of slow speed

propofol induction on hemodynamic stability, we decided to compare two practices.

We plan to compare the rate of propofol administration: a bolus within approximately 10-20 seconds vs. slow administration of propofol within 120 seconds. The hypnotic properties of propofol will not be affected by the change, as propofol is approved by FDA for maintenance (continuous infusion) anesthesia. *[FDA revised form: DIPRIVAN® (propofol) injectable emulsion, USP, 451094H Revised: April 2017]* [36].

As this study does not aim to change any anesthesiologic practice, but simply trying to compare difference in current practices, we are planning to apply to Institutional Review Board for patient consent waiver. Our rational behind this, is that we do not plan to add, or change any medication that anesthesiologist will plan to use for each patient. And the patient does not choose the provider, and with equal odd can be taken care of either one or another provider.

On the morning of the surgery, eligible and consented subjects will be randomized into two groups: groups A and B. Randomization will be done in advance using Excel Randomization function with allocation 1:1 per groups: Sample size of 100, two groups, 50 patients in each group. After patient is consented by a research personnel, Patient will get the next randomization spot in the list.

Group A: Staff anesthesiologist will calculate the dose of Propofol (Any patient, who was not planned to get Propofol for induction does not meet the Inclusion Criteria and will not be enrolled in this study). Current study has no intervention on Propofol dose calculation. The Research Member will ensure that the calculated dose of Propofol is being administered by a primary anesthesia provider intra-venously during 10-20 seconds via manual bolus per FDA approved administration speed (20-40 mg/per 10 seconds).

Group B: Staff anesthesiologist will calculate the dose of Propofol (Any patient, who was not planned to get Propofol for induction does not meet the Inclusion Criteria and will not be enrolled in this study). Current study has no intervention on Propofol dose calculation. The Research Member will ensure that the calculated dose of Propofol is being administered by an anesthesia provider intra-venously during 120 seconds via Alaris Syringe Module. The reason of a syringe pump use is to eliminate any duration differences among patients in Group B.

After induction the hemodynamics, administered inotrop and vasoactive medication data will be collected for the first hour after induction. The research personnel will collect the information about the start of surgery, to compare possible delays in surgery starts between the groups, 30 days mortality and morbidity. All necessary information will be collected by using intra-operative Electronic Medical Record system, as well as Outpatient Athena Electronic system.

Propofol has been used for decades in anesthesiology and ICU settings. It is being safely used as a bolus administration for induction (as stated in FDA form: 20-40 mg for 10 seconds) as well as continuous intra-venous infusion for sedation of patients in ICU. Additionally, Total Intra-Venous Anesthesia (aka. TIVA) represents a constant prolong Intra-Venous Administration of IV anesthetics (nowadays Propofol is the drug of choice for TIVA) instead of volatile anesthetic as a sedation agent of general anesthesia. Considering that both fast bolus and continuous prolong Intra-Venous administration of Propofol has been safely used for decades, the research team hypothesize that:

1. Group A represents the Propofol administration group with FDA approved administration rate of 20-40 mg/ per 10 seconds. Considering this fact, patients in group A are not different than any other patient receiving an anesthesia care for an elective surgery at UTMC.
2. Group B patients are not in a higher risk associated with a longer Propofol administration (120 seconds) than any patient receiving a continuous prolong Propofol administration which is a common practice in medicine and has been safely used for years.

For the primary randomization, Patient's MRN will be collected which will be kept in Key code document. The information of Biometric data (such as weight, age, type of surgery, ASA status, surgery start and end time, proprofol administration time),constant vital data (such as blood pressure, heart rate, saturation) as well as any vaso-active or inotropic medication (such as Phhenylephrine, Ephedrine, Vasopressine, Norepinephrine, Epinephrine, Dobutamine), as well as amount of opioid medications (such as Fentanyl, Hydromorphone) and intravenous fluids (such as Lactated Ringer, Normal Saline, Albumin) administered during the surgery will be collected and stored in a "Data Collecting Sheet" attached to this IRB form. Additionally, any antihypertensive medications taken prior to surgery will be documented on the data collection sheet. Antihypertensive medication taken the day of the surgery can become a confounder for hypotensive events during the induction of anesthesia. Thus, the

antihypertiensive medication history should be obtained for future data analysis and group stratification.

No Identification data will be reflected on Data Collecting sheet but only randomization Key Code.

All details regarding the hemodynamic changes, administration of vaso-active and inotropic medications will be collected post-factum by using the intra-operative electronic system at UTMC.. Collected data will be kept in HIPAA friendly storages locked and allowed to be accessed by the IRB approved personnel only.

Collected raw data will be categorized, standardized, and provided to the statistician for the statistical analysis

Statistical analysis:

Assuming a standard deviation of 10 mm Hg, to have an 80% power at a significance level of 0.05 for a two-sided comparison, the sample size needed to detect a 10 mm Hg difference in mean arterial blood pressure (MAP) reduction is 23 for each group. With 50 in each group, we will be able to detect such reduction even when the standard deviation is 15 mm Hg. And this will increase the power of the study up to 90%.

Sample Size:

Total of 100 people will be approached to consent for this study. We hope to enroll total of 100 patients with equal allocation of 50 patients in each group. Despite our statistical calculations have shown that total of 46 patient should be the minimum sample size, we decided to double this number to improve the power of the study and detection of even small changes in hemodynamics alterations.

Eligibility Criteria:

Inclusion Criteria

- Any patient from 18 till 80 years of age
- Patient undergoing non-cardiac elective surgery
- Duration of the surgery longer than one hour
- Native/Fluent English speaker
- Patients whose staff anesthesiologist planned to use Propofol as a primary anesthetic for induction

Exclusion Criteria

- Any patient admitted for non-elective surgery
- Any patient undergoing cardiac surgery
- Any patient younger than 18 years of age
- Any patient older than 80 years of age
- Any patient with history of severe heart disease (CHF with significant limitations of activity due to severe symptoms, prior heart surgery, atrial fibrillation etc.)
- Any patient with pre-operative hemodynamic instability (e.g., Sepsis, Chronic Kidney Disease, Liver Cirrhosis) who requires constant or intermittent administration of vasoactive or inotropic medication to support vital signs (BP)
- Any patient on vaso-active or inotrop medications in early pre-operative period (within 24 hours prior to the surgery)
- Any patient who does not speak English or speaks with not fluently
- Any patient with cognitive impairment or mentally incapacitation
- Any pregnant or breastfeeding females
- Any Patient whose staff anesthesiologist planned to use a primary anesthetic other than propofol

Ethical Consideration

We will submit this protocol to our Institution Review Board. We will maintain confidentiality of patient data. Research personnel will store the paper copies of case report forms (CRFs) in locked cabinets. All study personnel will ensure no patient identifiers are present on any files transmitted. We shall also ensure de-identification of all data in final reports.

All collected data will be processed and stored till full completion of the trial in HIPAA securely storages. After completion of the trial, data will be cleaned and sent for statistical analyzes, to compare the cardiac functionality of the heart during NAVA and SIMV ventilation modes

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