Original Article

The Role of Entropy Monitoring in Reducing Propofol Requirements during Open Heart Surgeries. A Prospective Randomized Study

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Abstract

Background: Hypotension, which is commonly associated with propofol induction of general anesthesia in coronary artery bypass grafting (CABG) surgery, may cause adverse consequences in patients with coronary artery diseases undergoing this type of surgeries. The clinical absence of verbal response and eyelash reflex was used as an endpoint for hypnosis. Spectral entropy, as a novel monitoring method for the endpoint of hypnosis, affect the dose of required anesthetic agents for induction as well as the hemodynamic profile during general anesthesia in CABG surgery. **Aims:** We hypothesized that entropy monitoring might reduce the dose of propofol required for induction of anesthesia during CABG surgery and could maintain hemodynamic stability when compared with the conventional clinical monitoring. **Materials and Methods:** Sixty adult patients of both sexes, aged 30–60 years, ASA II and III, and scheduled for CABG surgery were enrolled in this prospective, controlled, randomized, double-blind study. These patients were randomly divided into two equal groups to receive intravenous propofol for induction of anesthesia guided by either the patients' clinical response (Group I) or by entropy monitoring (Group II). The total dose of propofol used for induction of anesthesia was recorded. Hemodynamic parameters and entropy values were also recorded. **Results:** Propofol consumption was significantly reduced in Group II than Group I (P = 0.000*). Heart rate showed no statistical significance between the two groups, whereas the mean arterial pressure significantly decreased at induction in group I compared to Group II (P = 0.000*). The entropy values were significantly lower in Group I than Group II at induction (P = 0.036* for state entropy; 0.002* for response entropy). However, during intubation, and after 1 and 5 min, entropy indices displayed a significant increase in Group I than Group II. **Conclusions:** Entropy monitoring significantly reduced the dose of propofol required for induction of anesthesia and maintained hemodynamic stability compared to the conventional clinical monitoring during CABG surgeries.

Keywords: *Entropy, open heart surgeries, propofol, requirements*

Introduction

Induction of anesthesia in cardiac patients undergoing coronary artery bypass grafting (CABG) surgery represents a significant challenge for anesthesiologists. Maintaining hemodynamic stability as well as preserving the balance between myocardial oxygen supply and demand is crucial in this population with limited cardiac reserve.[1] Propofol which is a famous intravenous anesthetic agent used for induction of anesthesia can produce hypotension; meanwhile, a lower or inadequate anesthetic dose during laryngoscopy and intubation may lead to an intense sympathetic stimulatory response that could be detrimental in such patients. Therefore, adjusting the anesthetic requirement during induction is a significant issue.[2,3]

Administration of hypnotic agents was usually based on a fixed dose regimen till achieving the traditional clinical endpoint for assessing the induction of anesthesia depending on the loss of verbal response, which may lack the accuracy for ensuring adequate anesthetic dose administration during induction.[4] With the emergence of monitoring devices such as bispectral index (BIS) and spectral entropy, optimal delivery of anesthetic drugs with an accurate assessment of the depth of anesthesia could be guaranteed, with entropy possessing the advantage of having a higher resistance against artifacts than BIS.[5]

Entropy measures the degree of irregularity in electroencephalogram (EEG) signals via

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a three-electrode sensor applied to the patient's forehead. As the levels of anesthetic drugs increase in the brain, the irregularity of the EEG signals decreases. Entropy monitor simultaneously displays two different parameters: state entropy (SE), which mainly consists of EEG, and response entropy (RE), which includes electromyography (EMG) along with EEG.[6] SE values vary from 0 (complete suppression of EEG activity) to 91 (awake state) whereas RE values range between 0 and 100. Targets for adequate anesthetic depth are SE between 40 and 60 and a difference of RE and SE of <10.[7,8]

The use of entropy has been beneficial in reducing the use of certain hypnotic drugs. Therefore, entropy may customize the administration of anesthetic agents according to each patient independently.[9] This research aimed to compare the dose of propofol required for induction of general anesthesia as well as the associated hemodynamic changes when the endpoint for hypnosis was assessed by either conventional loss of verbal response and eyelash reflex or entropy in patients scheduled for CABG surgery.

Materials and Methods

This prospective randomized, double-blind controlled study was conducted at the cardiothoracic surgery department of Tanta University Hospitals from January 2016 to January 2018. After approval of the local ethical committee and obtaining written informed consent from the patients, 60 patients of both sexes, aged 30–60 years, belonging to ASA I and II, and undergoing elective CABG surgery were enrolled in the study. Exclusion criteria included patients with heart failure, valvular involvement, ejection fraction of <45%, neurologic diseases, liver or renal dysfunction, known hypersensitivity to the study drugs, history of alcohol or drug abuse, chronic analgesic use, antipsychotics and/or anticonvulsant treatment, and refusal to give an informed consent.

The patients were randomized into two equal groups of 30 patients each according to the use of conventional clinical monitoring (Group I) or entropy (Group II). Randomization was performed using computer-generated randomization numbers concealed in sealed opaque envelopes, and a blinded nurse not involved in the study randomly chose the envelope that determined the group of allocation for each patient.

The patients were kept on their cardiac medications until the day of the surgical procedure, whereas angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics were stopped one day before the surgery. Upon reaching the operating theatre, an intravenous (IV) line was secured and standard monitors were attached to the patient including five lead electrocardiograms, noninvasive blood pressure, and pulse oximetry. An entropy sensor with three electrodes applied on the frontotemporal region was connected to the entropy monitor (M-Entropy plug-in Module S/5; Datex-Ohmeda, Finland), and baseline values of heart rate (HR), mean arterial pressure (MAP), SE, and RE were recorded.

Before induction of anesthesia, the radial artery in the nondominant hand was cannulated with an arterial line for invasive arterial blood pressure monitoring as well as arterial blood gases sampling, and a central venous catheter was inserted in the right internal jugular vein with the aid of local anesthesia along with sedation by IV midazolam 0.03 m/kg and morphine 2 mg.

After preoxygenation for 2–3 min, induction of anesthesia was started with the administration of fentanyl 5 μg/kg followed 2 min later by propofol injection. Patients in Group I were administered IV propofol 20 mg every 30 s till loss of eyelash reflex with no response to verbal commands, whereas patients in Group II were administered propofol in the same manner till reaching the endpoint of SE <50 and SE–RE difference of <10. Additional propofol boluses of 10 mg every 30 s were given in Group II if the SE values increased more than 50 before the endotracheal intubation was accomplished. Once achieving the target point of hypnosis in each group, IV cis-atracurium 0.15 mg/kg was given to facilitate endotracheal intubation after 3 min of mask ventilation with 100% oxygen. Anesthesia was maintained with a mixture of 50% air-oxygen and 1 MAC isoflurane, and ventilatory parameters were adjusted to maintain an end-tidal carbon dioxide between 35 and 40 mmHg.

In both groups, the total dose of propofol required to reach the target endpoint of hypnosis was recorded. Entropy values and hemodynamic parameters (HR, MAP) were recorded at the following intervals – baseline value before induction of anesthesia (T_1), after induction of anesthesia at endpoint of hypnosis for each group (T_2), during tracheal intubation (T_3), and at 1 (T_4) and 5 min after tracheal intubation (T_5), which was the endpoint for our study.

Hypertension and tachycardia were defined by >20% increase from the baseline MAP or HR, respectively, and were managed initially by bolus fentanyl 1 μg/kg, and the total dose of rescue fentanyl was recorded. If an inadequate response was obtained, IV nitroglycerine was infused. When hypotension (MAP less than 20% of the baseline value) was encountered, an initial injection of ephedrine 10 mg was started. If insufficient, the use of inotropic support was considered. Bradycardia (HR <50) was treated by 0.5 mg IV atropine.

Statistical analysis

Our primary outcome was the total dose of propofol required for induction of anesthesia. Based on the results of a previous study,[10] the sample size was calculated to be 27 in each group for detecting a significant difference of 22 mg in mean induction dose of propofol at a power of 80%, α error 0.05, and a standard deviation of 29.4 mg.

We decided to recruit 30 participants in each group assuming a 10% dropout rate. Our secondary outcomes included hemodynamic changes and entropy values. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY: USA). The Shapiro–Wilk test was performed to check the assumption of normality. Parametric data were presented as mean ± SD and analyzed by Student's *t*-test. Categorical variables were presented as patients' number or frequencies (%) and were analyzed by Chi-square or Fisher's exact test as appropriate. *P* value below 0.05 was considered significant.

Results

Seventy-three patients were eligible for the study. Six patients did not meet our inclusion criteria (three patients had EF <45%, one had associated valvular diseases, one had previous cerebral stroke, and one patient was on chronic analgesics) and 7 patients refused to participate; hence, 60 patients were enrolled and randomly allocated into two groups (30 patients each) [Figure 1].

Demographic data of the studied groups showed no statistically significant differences regarding age, sex, weight, ASA physical status, and associated co-morbidities [Table 1].

The mean dose of propofol used for induction of anesthesia in group II was significantly reduced when compared to group I (57.7 ± 15.2, 83.3 ± 16.3 mg respectively. *P* = 0.000*). No additional propofol doses were required in Group II to maintain entropy value below 50 before endotracheal intubation [Table 2].

HR values were comparable between the two studied groups at all times of measurement. Higher readings of HR were observed during intubation (T_3) and at 1 min following insertion of the endotracheal tube (T_4) in both groups compared to the baseline. However; this did not reach statistical significance. The MAP showed a significant drop at induction (T_2) in Group I when compared to the baseline value (*P* = 0.000*). Furthermore, it was significantly decreased in Group I than in Group II at the same point of measurement (*P* = 0.000*). Values of MAP at other time intervals were comparable between the two studied groups as well as when compared to the baseline within each group. Three patients in Group I had hypotension and were effectively managed. No bradycardia was detected till the endpoint of our study in both groups [Figure 2].

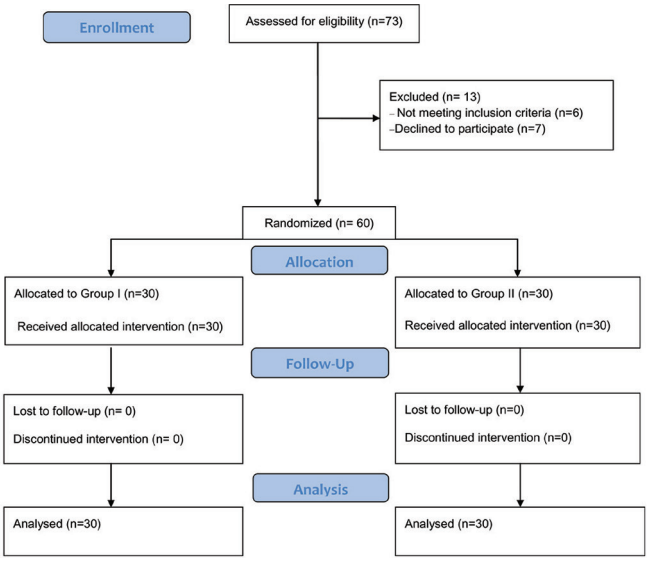

Figure 1: CONSORT flow diagram of participants through each stage of the randomized trial

After induction, a significant decrease in both SE and RE values were noticed in Group I (43.6 ± 4.15, 48.33 ± 4.57, respectively) as compared to Group II (45.47 ± 2.27, 51.53 ± 2.92, respectively). Both entropy parameters (SE and RE) were significantly higher in the control group compared to the entropy group from the time of intubation till 5 min later; however, the values of SE were still within the range of the anesthetic limit (40–60) and the RE–SE difference was <10 [Figure 3].

Discussion

Recent advances in clinical monitoring led to the introduction of EEG entropy as a new device for monitoring the degree of hypnosis and the depth of anesthesia.[11] It provided a useful tool for anesthesiologists to reduce the incidence of awareness in high-risk surgical patients while decreasing the delivered doses of anesthetic agents.[12] This is of paramount importance in patients with coronary artery diseases in whom concerns are always raised regarding adequate hypnosis during induction of general anesthesia

Table 1: Demographic characteristics of the studied groups

Variable	Group I	Group II	*P*
Age	59.60±8.69	58.80±9.90	0.741
Sex M/F	20 (66.66%)/10 (33.33%)	22 (73.33%)/8 (26.66%)	0.778
Weight	74.9±10.2	77.10±8.98	0.387
ASA II/III	23 (76.66%)/7 (23.33%)	25 (83.33%)/5 (16.66%)	0.746
Hypertension	17 (56.66%)	14 (46.66%)	0.605
Diabetes	9 (30%)	11 (36.66%)	0.784

Data presented as mean±SD or patient's number (%)

Table 2: Propofol consumption and rescue fentanyl requirements in both groups

Variable	Group I	Group II	*P*
The total dose of propofol (mg)	83.3±16.3	57.7±15.2	0.000*
Patients requiring additional propofol (*n*)	-	0 (0%)	
Rescue fentanyl (mg)	75.5±12.1	65.00±5.77	0.046*

Data presented as mean±SD or patient's number (%). *Denotes statistically significant difference

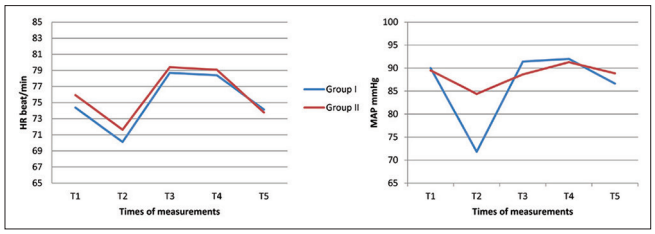

Figure 2: Mean arterial blood pressure (mmHg) and HR (beat/min) changes in the studied groups. Data presented as mean ± SD

to preserve hemodynamic stability and reduce the risk of myocardial ischemia.[13] Propofol, a widely acknowledged intravenous anesthetic used for induction of anesthesia in open heart surgery, possesses dose-dependent cardiovascular depressant properties leading to hypotension.[14]

The current study demonstrated the usefulness of entropy monitoring in reducing the dose of propofol required for induction of general anesthesia while maintaining a stable hemodynamic profile in patients undergoing CABG surgery compared to the traditional clinical endpoint of loss of verbal response and eyelash reflex.

Several reports referred to the role of EEG monitors such as BIS and entropy in reducing the anesthetic requirements and enhancing the recovery profile in patients administering general anesthesia for different types of procedures.[15-18] However, to our knowledge, no previous randomized trials investigating the effect of entropy monitoring on propofol requirements and hemodynamic profile during induction of anesthesia in open-heart surgeries have been published yet.

Propofol, rather than other agents used for induction of anesthesia in CABG surgeries, has been reported to produce a more significant reduction in MAP from the baseline values after induction.[1] With entropy guidance in our study, we were able to exhibit a decrease in propofol doses required for induction while preserving a stable cardiovascular status in this high-risk population.

Our results were consistent with the study of Yassen *et al*.,[19] who used EEG entropy for effective titration of anesthetic agents to an adequate depth of anesthesia in cirrhotic individuals scheduled for liver resection.

They reported that entropy monitoring significantly reduced the induction dose of propofol as well as intraoperative anesthetic consumption during surgery with favorable hemodynamic effects compared to the standard practice without entropy. Moreover, another study conducted among elderly patients receiving general anesthesia for ophthalmic procedures also demonstrated a similar impact of entropy monitoring in reducing the induction dose of propofol along with achieving adequate cardiovascular stability during induction.[20]

On the other hand, Rao *et al*.[21] evaluated the use of spectral entropy versus the conventional method of loss of response to verbal commands on the dose of propofol

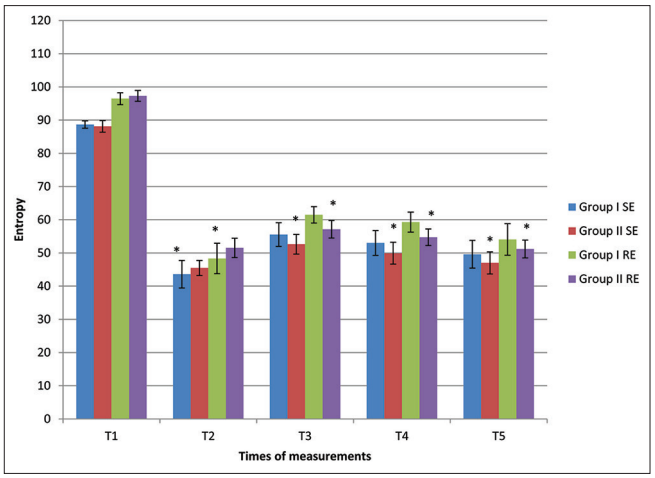

Figure 3: Changes in the entropy parameters at different time intervals. Data presented as mean ± SD. *Denotes statistically significant difference

required and the hemodynamic stability during induction of general anesthesia in patients undergoing elective orthopedic and general surgeries. However, they found an initial comparable reduction in the dose of propofol/kg for both groups.

When an additional propofol was given to maintain SE <50 till intubation was included in the dose calculation, the cumulative dose was significantly more in the study group. In our study, no additional propofol was given which might be attributed to the high dose of fentanyl (5 μg/kg) usually implemented for induction in open heart surgeries. Moreover, according to their explanation, the pain associated with injection of rocuronium might have led to an increase in entropy readings necessitating additional propofol. Furthermore, Arya *et al*.[15] observed no significant difference in the induction dose of propofol when assessed clinically (loss of verbal response) or by BIS monitoring in various surgical procedures under general anesthesia.

Our study showed that both SE and RE were significantly reduced in the control group after induction with an accompanying drop in the MAP at the same time. These findings were parallel to those of Riad *et al*.,[20] who observed a similar response in their study, which was probably due to the higher dose of propofol administered to achieve loss verbal response endpoint. They also recorded a comparable elevation in the entropy parameters in both groups following stress response of intubation; however, the rise of entropy values in our study was more significant in the control group compared to the study groups after intubation and till the end of the study, though it remained within the anesthetic range.

The incidence of hypotension in our study was very low (only three patients in the control group) as we used small increments of propofol (20 mg/s) due to the concomitant use of high doses of opioids for induction in CABG surgeries. We did not measure other cardiac

indices such as stroke volume, cardiac index, or systemic vascular resistance and relied only on simple measurements of MAP and HR, which was considered as a study limitation. Another limitation was that we included only patients with good cardiac performance. Further studies to investigate the effect of entropy on anesthetic consumption and cardiovascular parameters in patients with a reduced cardiac function would be advantageous.

In conclusion, entropy monitoring for cardiac patients undergoing CABG procedure reduced propofol consumption and maintained a favorable hemodynamic profile during induction of general anesthesia.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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