To Compare the Dose of Propofol for Induction of Anaesthesia by Entropy Monitoring against Standard Induction dose in Elderly Patients

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Abstract
Background: *Entropy monitoring is a new method for measuring depth of anaesthesia and degree of hypnosis. Two parameters are displayed in the monitor -State entropy (SE) and Response entropy (RE). Aging lead to decrease clearance of propofol. Hence when recommended induction dose of propofol (mg/kg) is used it may lead to haemodynamicinst ability especially in elderly patients. Little information is available regarding the use of EEG entropy in the prevention of   adverse hamodynamic side effects during induction of anaesthesia with propofol in elderly patients.*
Aim: *To compare the dose requirement of propofol in induction of anaesthesia with the end points indicated by entropy value verus recommended induction dose in elderly patients .*
Methodology: *This was aquasi - experimental open trial conducted in the department of anesthesiology, Government   Medical college, Thiruvananthapuram, a tertiary care centre, A total of 120 patients above 60 years of ASA class I and II were enrolled in the study. Enrolled patients were allotted to test group and control group randomly. Propofol was used for induction of anaesthesia in both groups and these groups were monitored with continuous electrocardiography, noninvasive blood pressure, pulse oximetry and capnography. In the test group depth of anaesthesia was monitored with entropy where the end point of induction was RE 50 and SE- RE difference less tha 10.Recommended dose of propofol was administered to the control group. Haemodynamic parameters during induction and intubation -were monitored along with entropy monitoring in both groups .Statistical tests used were Chi-square, student' t test and Mann-Whitney U test.*
Results: *-The total induction dose of Propofol and dose /kg were significantly reduced by 20% and 25% respectively in the entropy group and adequate haemodynamic stability was maintained.*
Conclusion: *The use of EEG entropy during induction of anaesthesia in elderly patients reduces propofol requirements and maintains cardiovascular stability.*
Keywords: *induction of anaesthesia, propofol, entropy.*

INTRODUCTION

Entropy monitoring is a new method for measuring the depth of anaesthesia and the degree of hypnosis. It relies on a method of assessing the degree of irregularity in EEG signals.

Monitoring the state of consciousness during anaesthesia can be achieved in more than one way. Because EEG slows down and becomes regular as anaesthesia deepens. One way of measuring the hypnotic component of anaesthesia is to measure the regularity of EEG. An irregular

unpredictable EEG reveals that the patient is awake or mildly sedated, whereas regular predict-able EEG is a sign of deeper consciousness.

The entropy of EEG measures the amount of disorder in the signal; high levels of entropy during anaesthesia show that the patient is awake, whereas low levels of entropy correlate with deep consciousness.

Entropy calculates two different spectral entropy indicators that are displayed simultaneously on the monitor. The state entropy (SE) is computed over the frequency range from 0.8 to 32 Hz. It includes the EEG-dominant part of the spectrum. The response entropy (RE) is computed over a frequency range from 0.8 to 47 Hz. It includes both the EEG- and EMG-dominant part of the spectrum. The two parameters SE and RE are clinically useful for the anaesthesiologist. State Entropy is a stable indicator of the effect of hypnotics on the cortex. Response Entropy, on the other hand, reacts rapidly to changes and serves as a nearly immediate indication of frontal electrom-yogram activity and impending awakening of the patient.

Response Entropy ranges from 0 to 100, whereas State Entropy varies between 0 and 91. For fully awake and responsive subjects, a value of 100 for Response Entropy and 91 State Entropy, respectively, is observed, i.e. the difference between these parameters is usually <10. For clinically meaningful anaesthesia and low probability of consciousness, a value between 40 and 60 is considered appropriate.

In the Entropy Module (Datex-Ohmeda, Helsinki, Finland), a spectral entropy algorithm is developed based on time and frequency. In order to optimize the response time, the actual time window used varies depending on the frequency being analysed. In this way, information is extracted from the signal as fast as possible.

As an indicator of adequate hypnosis, it is advantageous to normalize the entropy parameters so that Response Entropy becomes equal to State Entropy, while the RE-SE difference is equal to zero.

Propofol is one of the most commonly used intravenous anaesthetic agent today. It is also used for maintenance of anaesthesia and for sedation outside the operating room. The induction dose of propofol 1.5- 2.5 mg/kg. The induction dose of propofol decreases with increase in age. This is because reduction in hepatic blood flow and liver tissue in elderly patients decreases the clearance rates of propofol.

Elderly patients are more sensitive to the cardiodepressant action of anaesthetic agents than young patients. Cardiovascular pathology is an additional risk factor. Perioperative myocardial ischaemia could be avoided by minimizing decreases in arterial pressure or large changes in heart rate.

An induction dose based on weight might result in an excessively high dose with associated complications. Older patients differ from younger ones regarding the hypnotic effect of propofol and the spectral patterns in the EEG. The purpose of this work was to demonstrate the effect of EEG entropy on propofol requirement and haemodynamic parameters during induction of anaesthesia in elderly patients.

MATERIALS AND METHODS

The study was conducted as a Quasi-experimental open trial in the department of Anesthesiology, Government Medical College, Thiruvanantha-puram for a period of 6months, after obtaining clearance from institutional ethical committee.

A total of 120 patients of ASA I, II, classes undergoing surgery under general anaestheisa were enrolled in the study (60 patients in each group) after obtaining informed consent.

The sample size has been calculated to select sample for the present study. The sample size has been calculated using the formula:

$$E = z_{\frac{\alpha}{2}} . \frac{\sigma}{\sqrt{n}}$$

$$N = 2\,\sigma^2/E^2 \times f\,(\alpha\beta)$$

Where $z_{\frac{\alpha}{2}}$ is the critical value

σ is the population standard deviation and 'n' is the sample size. E is the maximum difference

between observed sample mean, $\bar{x}$ and true population mean, μ, f is the frequency, α and β are the errors.

With an error of (α) 5 %, the samples size required for the present study was calculated as 118 and a total rounded off to 120 elderly (age ≥ 65years) patients after considering all exclusion criteria.

The sample size was calculated using an alpha error of 5% and based on the findings reported in previous studies. The minimum required sample size to detect a significant difference between the groups was 120 (60 in each group).

Inclusion Criteria

A. Adult patients in the age group more than 60 years of either sex
B. ASA 1(American society of anaesthesiologists) or ASA 2 status

Exclusion Criteria

A. Patients who have history of allergy to Propofol.
B. Diagnosed Alzheimer disease, dementia, previous cerebrovascular accident
C. History of cardiac disease
D. ASA 3 or 4
E. Long term use of drugs affecting central nervous system

Method

Written informed consent was obtained from each patient. Patient data was recorded in the proforma. Details regarding age, sex, contact information, comorbidities, airway assessment and ASA class were recorded. Enrolled patients were allotted to one of the two groups (Test or Control) randomly. Group A (induction based onentropy monitoring) and group B (induction with standard technique). The procedure to be performed was explained in details to the patient.

On arrival in operation theatre an intravenous infusion of normal saline was started. The standard monitoring with continuous electrocardiography, non invasive blood pressure, pulse oximetry and capnography was used for both groups together with Entropy monitor.

Premedication with inj.Glycopyrrolate 0.2mg and inj. Midazolam 1 mg intravenous was given. All patients were allowed to breath 100% oxygen for 3 minutes before induction of anesthesia.

EEG entropy was measured at the frontal lobe of the dominant hemisphere and facial muscles after skin preparation with disinfectant alcohol and slight rubbing. A special composite electrode with 3 elements was applied to the forehead in accordance with the manufacturer's instruction and connected to the entropy monitor.

For the Entropy group, Propofol was given for induction in successive 30 mg doses every 2 min until Response entropyvalues dropped to 50 and the RE-SE difference was less than 10; this was confirmed clinically with loss of response to verbal commands.

The control group was given the recommended dose of propofol [1.75 mg/kg] at induction in the same manner ie successive, spaced bolus of 30 mg every 2 min and then confirmed clinically to ensure adequate hypnosis using OASS (observer's assessment of awakeness and sedation scale).If the patient still responds verbally even after recommended dose an additional 30 mg each were given.

OAAS 5: awake and responds readily to name spoken in normal tone

OAAS 4: lethargic response to name in normal tone.

OAAS 3: responds only after name is called loudly and /or repeatedly.

OAAS 2: responds only after name called loudly and mild shaking.

OAAS 1: does not respond when name is called and mild shaking.

During induction of anaesthesia in the control group, the anaesthesiologist was not guided by a fall in EEG entropy reading. Haemodynamic variables (heart rate & blood pressure), response entropy and state entropy were collected, at three different points.

1) Base line value before induction of anaesthesia.

2) After induction of anaesthesia and before intubation
3) At one minute after intubation.

After collection of the data at the second point, fentanyl 1 micro gm/kg intravenously was given for all patients together with Vecuronium 0.1mg/kg followed by endotracheal intubation.

During intubation, if there was any increase in the reading of entropy, an additional dose of propofol 30mg bolus was given until no increase in readings was observed, and then intubation was performed.

Total Dose of propofol was recorded and dose of propofol per kg was also calculated. Anaesthesia was maintained using sevoflurane and oxygen air mixture and muscle relaxation was continued with vecuronium. At the end of surgery, residual neuromuscular block was reversed with 0.05 mg/kg of neostigmine and 5microgram/kg of glycopyrolate intravenously.

Data was analyzed using suitable computer software and appropriate statistical tools will be used for analysis. Following statistical tests will be used for analyzing the data:

1. Chi square analysis for qualitative data
2. Student's t test for continuous data that follow normal distribution
3. Mann Whitney U test for continuous data that do not follow normal Distribution.

OBSERVATIONS AND RESULTS

The statistical analysis showed that the two groups – control group and test group (entropy group)- were comparable in terms of patient characteristics such as age, gender, weight, comorbid conditions and ASA status.

Table 1. Comparison of Base line parameters among test and control group (t-test)

Base Line Parameters	Group	Mean	$\pm$ SD	t value	p value
Systolic BP (mm Hg)	Test	128.92	23.45	- 2.051	P > 0.05 (NS)
	Control	139.75	14.38		
Diastolic BP (mm Hg)	Test	79.62	9.67	-1.584	P > 0.05 (NS)
	Control	83.95	8.67		
Mean BP (mm Hg)	Test	100.23	10.63	- 1.503	P > 0.05 (NS)
	Control	105.08	10.60		
Heart Rate (per minute)	Test	91.43	16.99	1.674	P > 0.05 (NS)
	Control	83.25	16.53		
Response Entropy	Test	98.30	1.28	0.869	P > 0.05 (NS)
	Control	97.93	3.01		
State Entropy	Test	89.10	11.64	- 1.429	P > 0.05 (NS)
	Control	89.67	0.75		

The table 1 shows that the baseline values of the measured hemodynamic parameters are comparable among test and control group

Table 2. Comparison of haemodynamic parameters and entropy changes among test and control group (t-test)

At Induction - Parameters	Group	Mean	$\pm$ SD	t value	p value
Systolic BP (mm Hg)	Test	110.87	7.63	3.546	< 0.01
	Control	106.72	1.03		
Diastolic BP (mm Hg)	Test	69.40	4.00	2.930	< 0.05
	Control	67.20	2.59		
Mean BP (mm Hg)	Test	87.35	2.68	3.468	< 0.05
	Control	84.40	1.03		
Heart Rate (per minute)	Test	87.87	2.85	3.912	< 0.01
	Control	82.92	5.39		
Response Entropy	Test	50.20	8.82	2.267	< 0.05
	Control	46.68	8.16		
State Entropy	Test	43.62	5.75	2.882	< 0.01
	Control	40.15	7.33		

Table 2 shows the values of measured hemodynamic parameters at the time of induction of anesthesia. They show that there is significant difference among the two group parameters at induction.

Table 3. Comparison of propofol dose among test and control group (t-test)

Parameters	Group	Mean	$\pm$ SD	t value	p value
Total Dose of Propofol (mg)	Test	88.92	15.49	-4.208	< 0.001
	Control	110.62	22.18		
Dose of Propofol (mg/Kg)	Test	1.45	0.17	-7.761	< 0.001
	Control	1.91	0.18		

Test group :Propofol induction with entropy monitoring
Control group : Propofol induction without entropy monitoring

The comparison of total dose of propofol and dose in mg/kg between test group and control group is shown in the table. This shows that in test group the total dose of propofol is less when compared to the control group. That is 88.92 mg in test group and 110.62 in control group.

The dose of propofol in mg /kg is also less in test group when compared to the control group. That is 1.45 mg/kg in test group and 1.91 mg/kg in control group.

DISCUSSION

Depth of anaesthesia or hypnosis is defined as a progressive central nervous system depression and decreased responsiveness to stimulation[1]   In the past the depth of anaesthesia was assessed by measuring haemodynamic changes to control the amount of anaesthetic use . Now various EEG based devices such as Bispectral index and spectral entropy are available. These monitors indicate the level of consciousness during anaesthesia.[1-3]. Studies demonstrated the usefulness of shannon entropy and the approximate entropy to describe the EEG changes during desflurane anaesthesia[4]. The Datex omeda S/5 entropy module is the first commercially available monitor based on the spectral entropy [5,6].

The induction of anaesthesia with propofol produce haemodynamic instability especially in elderly patients [7], Minimizing perioperative adverse events, especially in elderly patients, is of utmost importance. During induction of anaesthesia, it is important to preserve myocardial function and haemodynamic stability and avoid

adverse events such as myocardial ischaemia or infarction.[8,9] Along with ensuring haemodynamic stability, the depth of anaesthesia is to be maintained and awareness should be prevented .

Our study demonstrated that systolic, diastolic and mean arterial pressure were decreased in both groups after anaesthesia induction with Propofol, But the hypotension was significantly greater in the control group. These results were in agreement with result of W. Riad et.al and Anne Vakkurietal [10,11]. In our study, in the entropy group the total induction dose of propofol and mg /kg induction dose were reduced by 20% and 25% respectively. But in the study of W. Riad et.al the total dose of Propofol and dose /Kg reduction were 37.1% and 31.8% respectively. In agreement with the present work, Hug and colleagues and Michelsen and colleagues demonstrated a decrease in BP after induction of anaesthesia with propofol in the elderly and this appeared most often during the first 5-1O min after induction.

In agreement with this, Schultz and colleagues demonstrated that during induction of anaesthesia, older patients reached deeper EEG planes than younger patients with the same dosage of propofol.[12]

The results of our study on entropy are also consistent with a previous report that showed various electroencephalogram-derived indices could be useful in optimizing anaesthetic care. Sensitivity and specificity of the entropy were demonstrated in previous reports which showed that entropy is as efficient as Bispectral index in predicting changes in the hypnotic component of anaesthesia, and the changes in SE and RE values followed a similar pattern to the Bispectral index values during propofol induction in adults.[13,14] Also, Anderson and Jakobsson demonstrated good correlation between propofol sedation and entropy indices in young and elderly patients[15]. Valjus and colleagues showed low entropy recording during the first 5 min of the anaesthesia.[16]

Wheeler and colleagues demonstrated that Response Entropy, RE-SE difference, Heart Rate and Blood Pressure were significantly increased during painful stimulation. [17] It has been reported that excitability of subcortical structures evoked by noxious stimuli will increase the difference between RE and SE. Takamastu and colleagues also reported that frontal Electromyogram may be of value in assessing adequacy of anaesthesia and also reflects nociception, but it did not correlate with the intensity of the stimulation[18].

CONCLUSION

The study demonstrated that the induction dose of propofol was decreased using EEG entropy, and an adequate depth of anaesthesia was achieved. Adequate cardiovascular stability was observed in elderly patients with the guidance of EEG entropy reading. This study showed that total dose of propofol and the dose /kg were significantly reduced by 20% and 25%, respectively, in the entropy group. There was a significant drop of entropy values in the control group as compared with the entropy group which received a greater induction dose.

The use of EEG entropy during induction of anaesthesia in elderly patients reduced propofol requirements and maintained cardiovascular stability.

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