Clinical Investigation

Comparison of electroencephalogram entropy versus loss of verbal response to determine the requirement of propofol for induction of general anaesthesia

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ABSTRACT

Background and Aims: Propofol causes dose-dependent reduction in blood pressure (BP). This study was done to evaluate the use of spectral entropy on the dose of propofol required and the haemodynamic stability during induction of general anaesthesia (GA). **Methods:** In this randomised controlled study, 72 American Society of Anesthesiologists' physical status I and II patients undergoing general and orthopaedic surgeries were divided into Group S (n-36) and Group C (n-36). Patients in Group C were induced with propofol till loss of response to verbal commands and in Group S until the state entropy was <50 and state and response entropy difference was <10. The induction dose of propofol, haemodynamic parameters and the entropy values were recorded. Numerical data were expressed as a mean ± standard deviation and analysed using unpaired, two-tailed *t*-test. Categorical data were compared using Chi-square test. $P < 0.05$ value was considered significant. **Results:** The dose of propofol per kg was significantly more in the entropy group (1.80 ± 0.23 mg/kg in the Group C and 1.98 ± 0.217 mg/kg in the Group S [$P < 0.05$]). After induction, at intubation and 1 min after intubation, entropy values were lower in Group S than Group C ($P < 0.05$). The BP decreased significantly after induction compared with the baseline ($P < 0.05$), but there was no difference between the groups. **Conclusion:** Propofol required for induction of GA when guided by electroencephalogram entropy was significantly higher than the induction dose based on loss of verbal response. Both conventional induction and induction with entropy as the endpoint resulted in similar haemodynamic profile.

Key words: Electroencephalogram entropy, induction dose, propofol

INTRODUCTION

Propofol used commonly for intravenous (IV) induction of anaesthesia is associated with dose-dependent decrease in blood pressure (BP) and apnoea when compared to other IV induction agents.[1] Use of lower dose to reduce these side effects may result in inadequate anaesthesia and awareness during laryngoscopy and endotracheal intubation. However, due to the rapid nature of IV induction, it is often difficult to know when the patient becomes unconscious. Traditional end points for assessing induction of general anaesthesia (GA) depend on the absence of response to verbal commands or eyelash reflex. Use of neuromuscular blockers makes these clinical endpoints invalid for assessing whether the patient is sufficiently 'deep' during intubation after induction. Monitors such as Bispectral Index, Narcotrend and Spectral Entropy may be useful in the assessment of depth of anaesthesia (DOA) during this phase[2,3] and thereby may prevent awareness. The Entropy Module calculates two different spectral entropy indicators: State entropy (SE) reflecting the electroencephalogram (EEG) dominant part of the spectrum and response entropy (RE) which also

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includes electromyography (EMG) dominant along with EEG dominant components of the spectrum.[4] SE denotes adequacy of hypnosis and RE is an indicator of adequacy of analgesia.[5,6] Targets for adequate anaesthetic depth are an SE between 40 and 60 and a difference of RE and SE < 10. We hypothesised that entropy provides better guidance during induction of GA than the more commonly used loss of response to the verbal command. The primary objective of the present study was to determine the induction dose of propofol by two endpoints – loss of response to verbal commands (conventional induction) and SE of <50 (entropy guided induction). The secondary objectives of the study were to determine whether conventional induction provides adequate DOA and to compare the haemodynamic stability in both the groups.

METHODS

This prospective randomised trial was performed in 76 patients undergoing elective orthopaedic and general surgeries under GA from July 2012 to December 2012 after obtaining Institutional Ethics Committee approval and informed written consent. The patients belonged to American Society of Anesthesiologists' physical status class I and II, aged 18–58 years with body mass index <30. Pregnant patients, patients with severe cardiac disease, liver disease or renal dysfunction were not considered for the study. Patients with neurological disease, hearing disability and on drugs which may affect the entropy such as antipsychotics, benzodiazepines and/or anti-seizure medication, were also excluded. The patients were divided into two groups, study group (Group S) and control group (Group C) based on computer generated randomisation. Only the participants were blinded to the group to which they were allotted.

In the operating room, after establishing IV access, infusion of 100 ml/h of Ringer lactate was started. Electrocardiography, pulse oximetry (SpO_2), capnography ($EtCO_2$) and non-invasive arterial pressure were continuously monitored with the Datex-Ohmeda S/5® Anaesthesia Monitor, Finland. EEG entropy® (M-Entropy plug-in Module S/5®; Datex-Ohmeda) was used to measure the depth of anaesthesia (DOA) in both the groups. A special electrode with three elements was applied to the frontotemporal region as recommended by the manufacturer and connected to the monitor. Patients were pre-medicated with glycopyrrolate 0.2 mg and fentanyl 2 μg/kg IV. After pre-oxygenation, anaesthesia was induced. In both groups, injection 2% lignocaine 1 ml IV was administered to reduce pain due to propofol administration. In the Group S, propofol 30 mg was given IV every 30 s till the induction endpoint of SE < 50 was achieved and the RE-SE difference was <10. In the Group C, propofol was administered in similar manner till there was no response from the patient to repeated and loud verbal commands irrespective of the entropy (Modified observer assessment of sedation score <2)[7] The patient was paralysed with rocuronium 1 mg/kg IV and after one min of ventilation with 100% oxygen, the trachea was intubated. Additional propofol (30 mg/30 s) was given if the SE increased to >50 before endotracheal intubation was performed in the Group S. The Group C was not given any additional dose of propofol after the loss of verbal response. In both the groups, the total dose of propofol used for induction of anaesthesia was noted. The heart rate (HR), BP, RE and SE were recorded before induction, after induction (loss of verbal response or SE < 50), during intubation and at 1 min after intubation. Hypotension was defined as a fall in systolic BP (SBP) by more than 20% from baseline and bradycardia was defined as HR <50 beats/min. Once the readings were noted, maintenance of anaesthesia was started with N_2O: O_2 60%:40% and sevoflurane of 1 minimum alveolar concentration and the study was discontinued.

Sample size calculation was performed using power and sample size software by the NCSS-LLC Inc., (Number Cruncher Statistical System) from the data of a recently published study,[8] which reported a 31% decrease in propofol dose for induction (mean ± standard deviation [SD] of propofol in mg required/kg body weight was 1.27 ± 0.53 in the control group and 2.02 ± 0.26 in the entropy group). Thirty-six patients were needed in each group to achieve 80% power with the significance of 0.05 using two-sided *t*-test. Thirty-eight patients in each group were enrolled (to account for the loss of accrual from inability to complete the protocol or due to technical difficulty). Statistical analysis was performed with Statistical Package for Social Sciences 17.0 (IBM Corporation for Windows). Test of normality (two-sample Kolmogorov–Smirnov test) was done and distribution in both the control and study groups was found to be normal. Numerical data were expressed as a mean and SD and categorical data were expressed as number and percentages. Numerical data were analysed using unpaired, two-tailed *t*-test and categorical data were compared using Chi-square

test. $P < 0.05$ value was considered to be statistically significant.

RESULTS

The results obtained from the complete data of 72 patients were analysed. Four patients were excluded due to incomplete details. The mean age, gender and weight are shown in Table 1. Both the groups were comparable with respect to demographic variables [Table 1]. The dose of propofol/kg body weight required for induction was not different for both groups (1.80 ± 0.23 mg/kg in the control group and 1.78 ± 0.25 mg/kg). However, when the additional propofol given to maintain the SE < 50 till intubation was included in the dose calculation, the cumulative dose was significantly more in the study group [Figure 1]. Nearly 78% patients in the Group S required an additional dose of propofol as SE increased to >50 before intubation. The cumulative induction dose of propofol was 1.80 ± 0.23 mg/kg in the Group C and 1.98 ± 0.217 mg/kg in the Group S ($P < 0.05$). At all stages of data collection except the base line the SE and RE were lower in the Group S than Group C [Figure 2]. In the Group C, the entropy values were more than 50 at induction, intubation and 1 min thereafter. With intubation, SE and RE increased in both groups but the RE-SE difference was <10. There was no difference in the HR at baseline, induction, intubation in both groups [Figure 3]. In both the groups, the HR did not change from the baseline with induction but increased at intubation. However, this did not reach statistical significance. At 1 min after intubation, the HR was significantly lower in the study group ($P = 0.023$). There was no difference in the BP readings at baseline, induction, intubation and 1 min after intubation between the groups [Figure 4]. However, after induction, the SBP and diastolic BP decreased compared to the baseline ($P < 0.05$) in both groups.

Table 1: Demographic profile

Demographic data	Group C (*n*=36)	Group S (*n*=36)
Gender – male:female	21:15	17:19
Age years (mean±SD)	36.6±12.18	34.9±11.6
Weight kg (mean±SD)	57.6±9.74	56.2±8.23
ASA status I:II	36:0	33:3
Time for induction (s)	150±11	165±13
Patients requiring additional propofol (*n*)	-	28

n – Number; SD – Standard deviation; ASA – American Society of Anaesthesiologists, S – Seconds

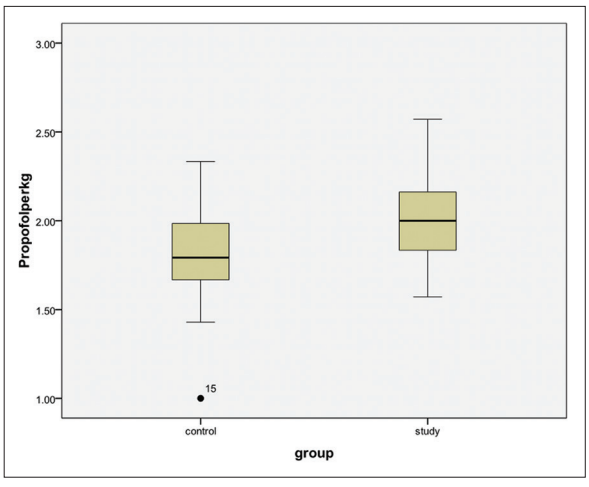

Figure 1: The dose of propofol required for induction of anaesthesia in the control and study group. * - $P < 0.05$ between the groups

DISCUSSION

Propofol has emerged as the most commonly used IV induction agent. The major disadvantage of propofol is the hypotension it produces. The hypotension is due to both myocardial depression and vasodilation, which are dose-dependent. Reducing the dose for induction of anaesthesia may attenuate these haemodynamic adverse effects, but may also increase the risk of inadequate depth especially during noxious stimuli such as endotracheal intubation. EEG-based indices such as Bispectral Index,[3,4,7] Spectral Entropy,[3,4,8-13] Narcotrend[14] and Patient State Index[15] may ensure better DOA and thus may help prevent awareness during intubation.

Several studies reported that monitoring with entropy may reduce the dose of propofol required for induction of GA.[8,13,16,17] Riad *et al*. studied the dose of propofol required for induction in elderly patients who were divided into control group (fixed dose of

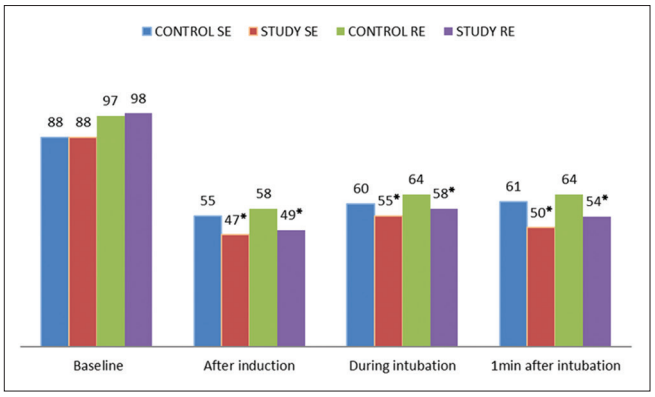

Figure 2: Entropy recordings in the control and study groups at baseline, induction, intubation and 1 min after intubation. SE - State entropy, RE - Response entropy * - $P < 0.05$ between the groups

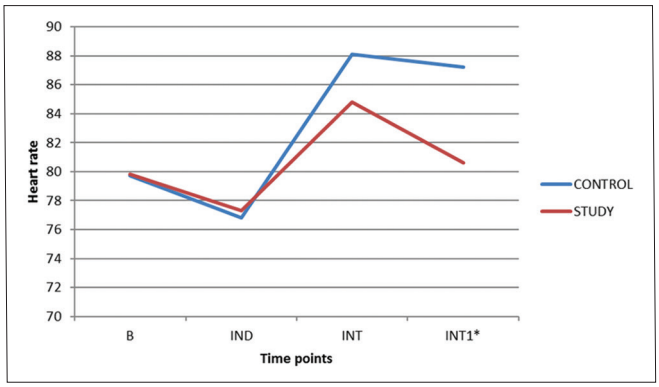

Figure 3: Heart rate in the control and study groups at baseline, induction, intubation and 1 min after intubation. B - Baseline, IND - Induction, INT - Intubation, INT1 - Intubation at 1 min. * - $P < 0.05$ between the groups

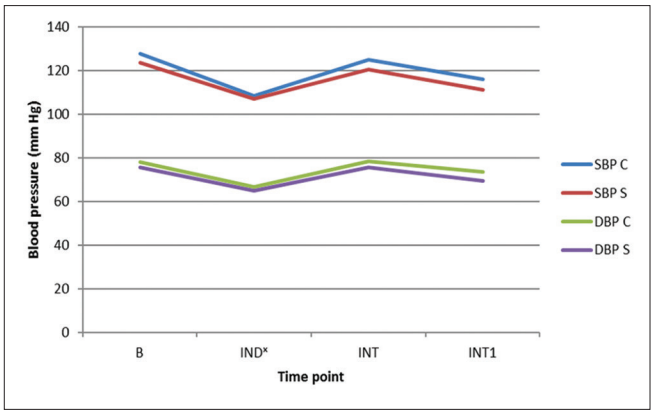

Figure 4: Blood pressure in the control and study groups at baseline, induction, intubation and 1 min after intubation. B - Baseline, IND - Induction, INT - Intubation, INT1 - Intubation at 1 min, SBP C - Systolic blood pressure control, SBP S - Systolic blood pressure study, DBP C - Diastolic blood pressure control, DBP S - Diastolic blood pressure study. x - $P < 0.05$ indicating a significant decrease in blood pressure after induction when compared to baseline in both groups

1.75 mg/kg propofol [30 mg every 2 min]) and the entropy group (induction till SE was 50 and SE-RE difference <10). Entropy guided induction decreased the requirement of propofol by 37.1%.[8] However, this study was performed in elderly patients who are known to be more susceptible to the hypnotic effects of propofol.[18,19] Schultz *et al*. reported similar age-related effects on EEG during propofol anaesthesia and found lower values of EEG in older patients than their younger cohorts for the same dose of propofol.[20] In a randomised controlled trial comparing standard clinical practice and entropy guided anaesthesia with propofol and remifentanil, Gruenewald *et al*. also found that entropy reduced propofol.[16] Vakkuri *et al*. evaluated the effect of spectral entropy on the consumption of anaesthetic drugs and recovery times after anaesthesia.[17] A larger dose of propofol was used in the controls than in entropy group which resulted in lower entropy values. They maintained more liberal limits of SE (45–65) in the entropy group until the last 15 min of anaesthesia. Propofol consumption was therefore reduced in the entropy group which in turn resulted in early recovery. In contrast, in the present study the entropy group required significantly more propofol than the control. This may be due to the following differences in the study methodology: (i) Maintenance of SE < 50 until completion of endotracheal intubation , (ii) inclusion of younger patients and (iii) use of cut-off value of SE < 50 for induction of anaesthesia which was more stringent than the range of 45–65 maintained by Vakkuri *et al*.

At all stages of data collection except the baseline the SE and RE were lower in the Group S than Group C. In the Group C, the SE was more than 50 but <65 at induction, intubation and 1 min thereafter and RE-SE difference was also <10.Though the entropy values were higher in Group C, they were still below the upper limit recommended by Vakkuri *et al*. This suggests that adequate DOA was achieved even in the control group. Around 78% patients in the Group S required an additional dose of propofol as SE increased to >50 before intubation could be done. This may be due to a decrease in the effect site concentration of propofol before intubation could be done. Propofol administered as continuous infusion may have been a better method than bolus injection to maintain the SE < 50.

No patient in either group had hypotension or other adverse cardiovascular effects as induction was done with small aliquots till the respective end points were attained. Slow and graded induction may be the reason for the cardiovascular stability seen in this study. Riad *et al*. (who also induced anaesthesia gradually) found significant hypotension in the control group after induction. This may be due to larger induction dose in the controls (>2 mg/kg). A larger dose, when given either as a single bolus or in a graded manner, has increased potential for hypotension.

Pre-operative anxiety, myoclonus following etomidate, hypotension and neuromuscular blocking drugs are some factors which may affect entropy.[21,22] Two mechanisms are postulated to explain the effect of neuromuscular blockade (NMB) on entropy: The effect of NMB directly on DOA and by affecting the EMG activity indirectly.[5] This effect is seen less in deeper planes of anaesthesia.

Atracurium, cisatracurium and rocuronium have been found to attenuate the increase in RE and the RE-SE gradient after noxious stimuli such as intubation and incision.[5,6,23,24] However, the effect of pain due to rocuronium injection on entropy was not mentioned in any of the studies.[5,6] Anaesthesia is a dynamic state in which anaesthetic agents depress the central nervous system and with increasing stimulation, the requirement of drugs to maintain the same DOA is increased. Choice of rocuronium as the muscle relaxant is thus, a limitation for this study. Injection pain of rocuronium may be another explanation (apart from the method of propofol infusion) for the increase in entropy necessitating additional propofol. This was seen in both groups but only in the study group was extra propofol given. Further research comparing the effect of rocuronium with other muscle relaxants on entropy is required.

CONCLUSION

The dose of propofol for induction of GA based on EEG entropy was significantly higher than the dose for induction based on loss of verbal response. Conventional induction results in entropy values consistent with adequate DOA. Both techniques result in similar haemodynamic profile.

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