Original Article

Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels

Shagun Bhatia Shah, Itee Chowdhury, Ajay Kumar Bhargava, Bhawnish Sabbharwal

Department of Anaesthesia, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Abstract

Background and Aims: This study aimed to compare the hemodynamic responses during induction and intubation between propofol and etomidate using entropy guided hypnosis.

Material and Methods: Sixty ASA I & II patients in the age group 20-60 yrs, scheduled for modified radical mastectomy were randomly allocated in two groups based on induction agent Etomidate or Propofol. Both groups received intravenous midazolam 0.03 mg kg^{-1} and fentanyl 2 μg kg^{-1}as premedication. After induction with the desired agent titrated to entropy 40, vecuronium 0.1 mg kg^{-1} was administered for neuromuscular blockade. Heart rate, systolic, diastolic and mean arterial pressures, response entropy [RE] and state entropy [SE] were recorded at baseline, induction and upto three minutes post intubation. Data was subject to statistical analysis SPSS (version 12.0) the paired and the unpaired Student's T-tests for equality of means.

Results: Etomidate provided hemodynamic stability without the requirement of any rescue drug in 96.6% patients whereas rescue drug ephedrine was required in 36.6% patients in propofol group. Reduced induction doses 0.15mg kg^{-1} for etomidate and 0.98 mg kg^{-1} for propofol, sufficed to give an adequate anaesthetic depth based on entropy.

Conclusion: Etomidate provides more hemodynamic stability than propofol during induction and intubation. Reduced induction doses of etomidate and propofol titrated to entropy translated into increased hemodynamic stability for both drugs and sufficed to give an adequate anaesthetic depth.

Key words: Entropy, etomidate, hemodynamic changes, propofol

Introduction

General anesthetic induction agents may decrease arterial blood pressure via myocardial depression, vasodilatation and attenuation of autonomic nervous activity.[1-4] Conversely, laryngoscopy and endotracheal intubation elicit unwanted cardiovascular responses such as hypertension, tachycardia and dysrhythmias.[1,5,6] This sometimes results in "alpine hemodynamic response" to the induction of general anesthesia. The exact induction dose for maintaining hemodynamic stability has not been zeroed upon.

The aim of this study was firstly to estimate the induction dose of each agent based on entropy and secondly to find out which agent is more cardiostable when used in equipotent dosages. We compared the hemodynamic responses while induction and intubation with intravenous (IV) etomidate versus propofol[3,4] with entropy guided hypnosis levels[7] instead of utilizing the standard per kilogram body weight induction doses and end points, like loss of response to verbal command (propofol) and loss of eyelash reflex (etomidate).

Material and Methods

Following approval from the Institutional Ethics Research Committee and written informed consent this prospective randomized clinical study was conducted on a study population which included 60 adult, normotensive, 20-60 year's age group, female patients (posted for modified radical mastectomy), American Society of Anesthesiologists physical status I and II, indoor patients mostly of urban background.

Address for correspondence: Dr. Shagun Bhatia Shah,
H. No: 174 - 175, Ground Floor, Pocket-17, Sector-24, Rohini,
New Delhi - 110 085, India.
E-mail: drshagun_2010@rediffmail.com

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/0970-9185.155145

This monocentric double-blind (subject, investigator) study comprised a sample size of 60 patients randomly allocated into two groups Group-E and Group-P each comprising 30 patients. After normal distribution had been ascertained by the Kolmogorov-Simirnov test, a sample size of 30 in each group was arrived at according to the standard normal distribution theory and fixing type-I error (α) at 0.05 and the power of the study (1-β) at 0.8. According to simple random sampling technique, out of all the cases being operated which fulfilled the inclusion criteria of the study, every odd numbered case was assigned to Group-P and every even numbered case to Group-E. The null hypothesis was that there is no difference between etomidate and propofol regarding hemodynamic changes while the alternate hypothesis was that there is a statistically significant difference in the hemodynamic changes seen with both the drugs during entropy guided induction and intubation.

A detailed preanesthetic evaluation was done including airway assessment, clinical history, general and systemic examination, routine biochemical investigations, chest X-ray and electrocardiography. All patients were premedicated with oral alprazolam 0.5 mg at night before surgery and oral ranitidine 150 mg and oral granisetron 2 mg 1 h prior to surgery. In the operation theatre, IV line was established with 18G IV cannula. All monitors including entropy sensor were attached. Midazolam 0.03 mg/kg IV, 2 min before induction and fentanyl 2 μ/kg 1 min prior to induction were injected.

Anesthesia was induced using IV propofol infusion titrated to response entropy (RE) of 40 in Group-P and IV etomidate was used in Group-E with similar titration to an RE of 40. The end point for the induction was an RE value of 40 since RE is more comprehensive than state entropy (SE) and includes uncovered nociception as well. Neuromuscular blockade was achieved by vecuronium 0.1 mg/kg. Anesthesia was maintained with 33% oxygen, 66% nitrous oxide and mask-ventilation. Trachea was intubated with portex cuffed endotracheal tube lubricated with KY jelly (Johnson and Johnson). No surgical stimulus was given; patients were not touched or otherwise disturbed for 5 min postintubation to discover the magnitude of RE-SE difference and the presence or absence of electromyography during anesthesia without surgery. Volatile anesthetic agents were started after 3 min of intubation. The cases in which orotracheal intubation could be performed successfully within 15 s in a single attempt were included in the study.

The rescue drugs utilized were ~ ephedrine 3 mg bolus was given if the mean arterial pressure (MAP) dropped by >20% from baseline. Boluses of 2 mg etomidate or 10 mg propofol at a time were given if at any time SE rose above 60.[7,8] A bolus was defined as 1 ml (10 mg) of propofol or 1 ml (2 mg) of etomidate, each injected over a period of 10 s. These boluses were presumed to be equipotent as they were in the same ratio (5:1) as standard per kilogram body weight induction doses of propofol and etomidate respectively. Diltiazem 2.5 mg IV was used if MAP increased >20% from baseline and esmolol 20 mg was employed in case the heart rate (HR) rose above 100 beats/min.

Observation and measurement of HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, RE and SE at baseline, and T1-T6 till upto 3 min postintubation was done using M-entropy module (S5 Datex Ohmeda, Instrumentarium Corp., Helsinki, Finland) The data was plotted on a specifically prepared proforma for each patient where:

- T0 = Baseline (before midazolam and fentanyl).
- T1 = Induction.
- T2 = 1 min postinduction.
- T3 = 3 min postinduction.
- T4 = Laryngoscopy.
- T5 = 1 min postintubation.
- T6 = 3 min postintubation (volatile anesthetic started at this point).

The entropy monitor displays two variables. SE is computed over the frequency range from 0.8 to 32 Hz and includes the electroencephalography (EEG) - the dominant part of the spectrum. Hence SE primarily reflects the cortical state of the patient. RE is computed over a frequency range of 0.8-47 Hz and includes both the EEG - dominant and electromyogram dominant parts of the spectrum. On the monitor display, SE values vary between 0 (suppressed EEG activity) and 91 (indicating an awake state). RE values vary between 0 and 100. The recommended range of adequate anesthesia for both parameters is from 40 to 60. When SE is in the recommended range for adequate anesthesia but RE discrepancy is 5-10 U or more, it indicates patient responsiveness to surgery and can be interpreted as a sign of uncovered nociception.[7-10]

Statistical analysis of the effect of etomidate and propofol on hemodynamic responses during induction and intubation with entropy guided hypnosis levels was studied. Total dose required from induction till 3 min following intubation was also analyzed.

Unless stated otherwise, data are expressed as mean ± standard deviation (SD). The mean value for each parameter was calculated using the formula, mean $= \sum Xi/n$ and SD was calculated using the formula $\sqrt{1/n\sum(Xi - X)^2}$. The unpaired Student's *t*-test for equality of means was employed for inter group comparison after obtaining the mean values and the

SD and the two-tailed significance (P) was calculated. The paired t-test was utilized for intra group comparison. SPSS statistical software (version 12.0 for Windows from IBM) was utilized for this purpose. A $P < 0.05$ was considered to be statistically significant (*), whereas a value of <0.01 was taken as statistically moderately significant (†). $P < 0.001$ were considered to be highly significant (‡) statistically.

Results

A randomized controlled trial was carried out between April and August 2010 and the flow of participants through each stage is seen in Figure 1. The demographic profile in both the groups was comparable [Table 1]. As seen in Figure 2, at T1 in both the groups there was a comparable fall in HR due to the anxiolytic action of midazolam and fentanyl premedication. In Group-P there was sustained increase in HR throughout induction and intubation. This was moderately significant statistically at T2 and T3 ($P < 0.01$). ($P < 0.01$). In Group-E, there was statistically insignificant increase in HR at T2, T3, T4, T5 and T6.

There was a fall from baseline for SBP values at T2 and T3 for both Group-E and Group-P, but the mean fall in SBP at T2 in Group-E (17%‡) was approximately half of that seen in Group-P (30%‡) at T2. Similarly at T3 the mean fall in SBP seen with Group-E (16.5%‡) was much less than that seen in Group-P (32%‡). At T4 (laryngoscopy), there was a 3.3% rise in SBP from baseline with Group-E, but in Group-P, the SBP continued to remain below (11.4%†) the baseline even at T4. At T5 and T6 (1st and 3rd min after intubation), the percentage fall in SBP in Group-E was 4.36% and 12.03%,† respectively, compared to baseline, whereas in the corresponding period in Group-P the fall in SBP was 12.23%† and 19.07%‡ respectively [Figure 2 and Table 2].

Table 1: Demographic variables

Demographic variables	Group-E (n = 30)	Group-P (n = 30)
Age (years)	46.13±9.299	46.67±9.495
Weight (kg)	60.47±7.951	60.37±6.162
Sex (male:female)	0:30	0:30
ASA-I	19	19
ASA-II	11	11

ASA = American society of Anesthesiologists

As illustrated by Figure 3 and Table 2, both Group-E and Group-P showed a fall in DBP at T2 and T3. The fall in DBP was much sharper in Group-P (27%‡ and 30%‡) as compared to Group-E (17%‡ and 16%‡ respectively at T2 and T3). There was a 10%† rise in DBP at T4 in case of the Group-E. In spite of the stimulus provided by intubation, the DBP remained 4.8% lower than baseline in Group-P. At the 1st and 3rd min postintubation, the fall in DBP from baseline in Group-P was still 7.5%† and 15.5%‡. In contrast the DBP in the Group-E returned to exactly the same as the baseline DBP and at T5 and at T6, it was only 7.4% below the base line.

At 1st and 3rd min after induction, there was a fall in MAP in case of both Group-E and Group-P. The fall in MAP is much sharper for Group-P (24.3%‡ and 28.66%‡) as compared with Group-E (15.87%‡ and 16.6%‡). The stimulus of laryngoscopy and intubation failed to bring the MAP above baseline levels of Group-P (3.2% below baseline) while in case of Group-E there is a 6.9% rise in MAP above baseline

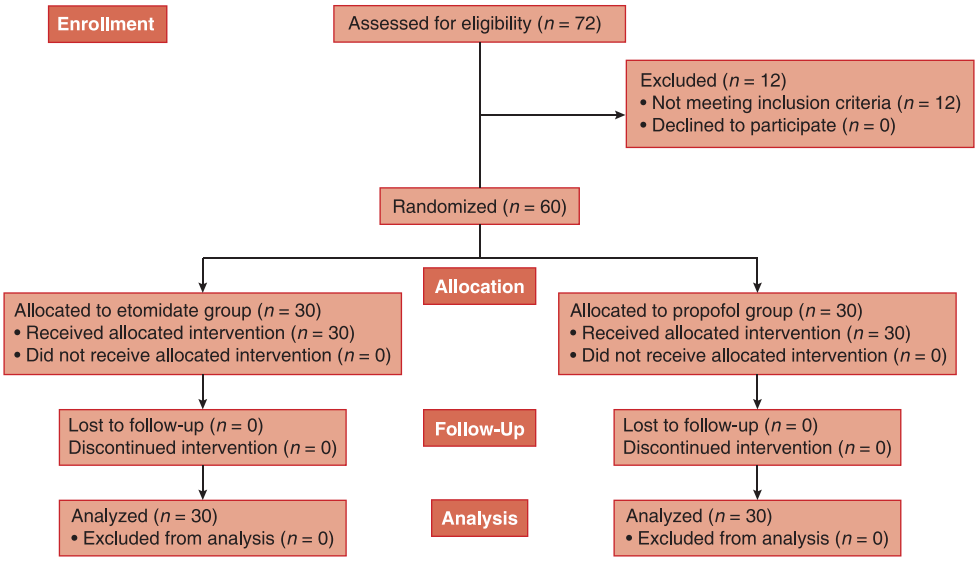

Figure 1: CONSORT 2010 flow diagram of the progress through the phases of a randomized trial (i.e., enrollment, intervention allocation, follow-up, and data analysis)

at T4 (laryngoscopy). The values for MAP at 1st and 3rd min after intubation for Group-P were 9.5%† and 16.3%‡ below the baseline while, for Group-E, MAP values were 0.9% and 8%* below the baseline values [Figure 3 and Table 2].

One patient had myoclonus in the etomidate group despite use of fentanyl. The entropy values were unaffected during myoclonus. Results were analyzed utilizing intention to treat concept.

Etomidate provided hemodynamic stability without the requirement of any rescue drug in 29/30 patients whereas rescue drug ephedrine played a role in maintaining hemodynamic stability in 11/30 of patients employing propofol for induction [Table 3]. In the etomidate group 14 patients required a single topup bolus whereas four patients required two topup boluses of etomidate each. In the propofol group 12 patients required a single topup bolus whereas two patients required two topup boluses of propofol each. The induction doses calculated are inclusive of the amount of drug utilized for topups.

Table 2: Hemodynamic parameters during entropy guided induction and intubation with etomidate and propofol

Hemodynamic parameter	T0	T1	T2	T3	T4	T5	T6
HR (etomidate							
Mean±SD	77.1±10.046	72.23±11.705	80.3±8.819	80.32±8.450	79.53±16.305	78.6±13.037	80.44±11.705
P value		0.052	0.235	0.212	0.312	0.391	0.201
HR (propofol)							
Mean±SD	82.53±11.40	78.30±8.265	87.69±8.054	88.68±7.620	84.96±8.181	85.49±11.02	86.43±8.265
P value		0.078	0.002	0.001	0.298	0.241	0.213
SBP (etomidate)							
Mean±SD	133.23±14.350	118.93±9.255	109.97±9.335	111.6±8.236	137.63±14.929	127.4±10.078	117.23±9.30
P value		0.000	0.000	0.000	0.088	0.007	0.000
SBP (propofol)							
Mean±SD	130.00±10.725	111.70±10.521	90.80±9.796	87.52±9.705	115.17±14.350	114.13±12.261	105.17±13.717
P value		<0.001	<0.001	<0.001	0.001	<0.001	<0.001
DBP(etomidate)							
Mean±SD	78.87±11.749	69.97±7.237	65.20±7.841	67.17±7.580	86.90±9.883	78.87±8.617	72.97±10.842
P value		0.000	0.000	0.000	0.009	1.000	0.022
DBP (propofol)							
Mean±SD	78.93±5.146	68.13±7.272	57.43±9.842	55.97±8.769	75.10±13.306	73.00±10.089	66.60±9.694
P value		<0.001	<0.001	<0.001	0.176	0.004	<0.001
MAP (etomidate)							
Mean±SD	98.03±9.586	87.93±8.940	82.47±8.233	81.77±6.388	104.83±9.067	97.10±.326	90.07±7.320
P value		<0.001	<0.001	<0.001	0.001	0.597	0.001
MAP (propofol)							
Mean±SD	97.43±5.697	84.23±8.067	73.10±9.980	69.24±8.30	91.17±13.094	88.17±9.581	81.63±10.414
P value		0.000	0.000	0.000	0.038	0.000	0.000

SD = Standard deviation, HR = Heart rate, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, MAP = Mean arterial pressure

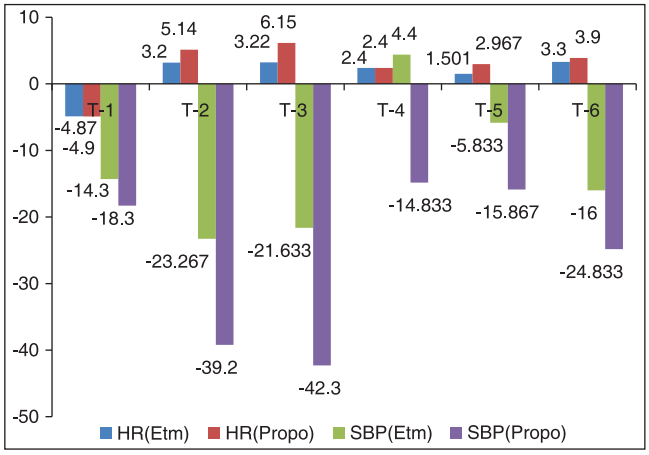

Figure 2: Heart rate and systolic blood pressure variations over time

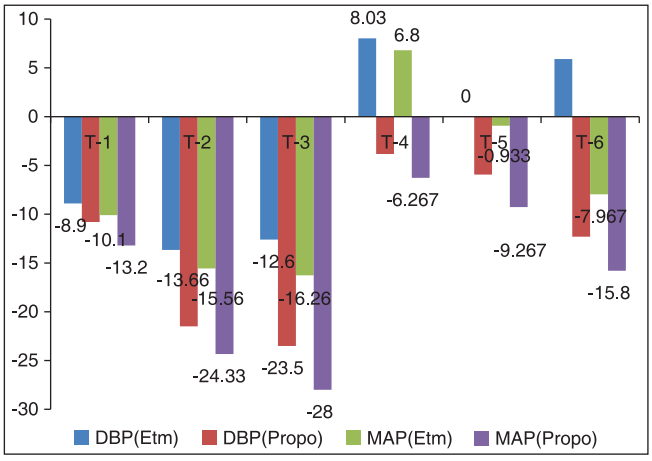

Figure 3: Diastolic blood pressure and mean arterial pressure variations over time

Reduced induction doses 0.15 mg/kg for etomidate and 0.98 mg/kg for propofol respectively, sufficed to give an adequate depth of anesthesia [Figure 4].

Discussion

The magnitude of hypotension is directly proportional to the plasma concentration of the induction agent which in turn depends on many factors such as age, gender, body weight, dose, the infusion rate and cardiac output. There is no agreement regarding the minimum propofol dose and method of administration that minimizes the risk of hypotension. The dose of etomidate utilized by various studies ranges from 0.2 to 0.45 mg/kg. The doses at the higher end of the spectrum (0.4 mg/kg) for etomidate may cause direct myocardial depression.[1] The exact induction dose of etomidate for maintaining hemodynamic stability has not been zeroed upon as yet.

A depth of anesthesia monitor is said to be the "Holy Grail" of anesthesia. Of all the depth of anesthesia monitors, it is the entropy monitor which gives a combined status of inadequate muscle relaxation, inadequate pain suppression and, above all, adequate hypnosis.[7-10]

We, therefore, utilized the entropy monitor to give us a tailor – made induction dose for each patient. It also made the doses of the two induction agents under evaluation comparable.

In our study, we used fentanyl for IV premedication for all cases as it is known to blunt the pharyngolaryngeal reflex on endotracheal intubation and decrease the incidence of myoclonus associated with etomidate.[1,2,6] It also acts synergistically with propofol to reduce the dose required for adequate anesthetic depth.[1]

Table 3: Requirement of rescue drugs

Rescue drug	Group-E (*n* = 30) (%)	Group-P (*n* = 30) (%)
Ephedrine	0	11 (36.6)
Diltiazem	1 (3.3)	0
Esmolol	0	4 (13.3)

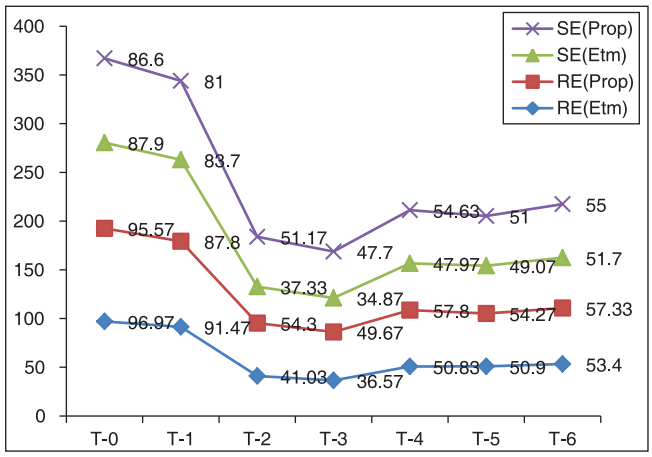

Figure 4: State entropy and response entropy changes over time

As per our results it is evident that propofol causes sustained increase in HR throughout induction and intubation while etomidate keeps the HR stable for the complete duration of induction and intubaton.

The magnitude of variations in SBP, DBP and MAP from baseline was greater when propofol was used as an induction agent versus etomidate in comparable doses. The mechanisms of arterial hypotension following IV anesthetic induction are multifactorial. The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function[1,5] and capacity to bind and stimulate peripheral alpha-2B adrenergic receptors with a subsequent vasoconstriction.[6] Decrease in systemic blood pressure after bolus injection of propofol is dependent on both vasodilation with reduced preload and afterload and myocardial depression (negative inotropic action).[1-4]

Saricaoglu *et al.*[2] after studying the hemodynamic effects of an induction dose of propofol and etomidate found that propofol was associated with significant decreases in SBP and mean blood pressure. They attributed this hypotension to the negative inotropic effect of propofol. Larsen *et al.*[4] examined the effects of propofol upon myocardial function by measuring changes in left ventricle function using transthoracic tissue-Doppler echocardiography and concluded that a decrease in MAP with propofol is secondary to reduce cardiac filling or a consequence of a direct negative inotropic action of propofol. Weisenberg *et al.*[3] concluded that lower doses of propofol (1.3 mg/kg) reduce hemodynamic instability.

This study reveals that at RE of 40, the hemodynamic variations with etomidate were less alpine than propofol throughout the period spanning induction and intubation.

As per the results of our study [Table 4], the mean absolute dose of etomidate required for the complete duration spanning induction and intubation was 9.4 mg or 0.153 mg/kg body weight. This is much less (just 50% of) than the conventional 0.2-0.4 mg/kg body weight dose (average: 0.3 mg/kg).[1,2,5,6] The mean absolute dose of propofol also showed a similar reduction (61.33 mg). The propofol dose per kilogram body weight was 0.98 which again is much less (56% of) than the conventional dose of 1-2.5 mg/kg body weight[1-4] (average: 1.75 mg/kg body weight). We attribute this wholesome dose reduction to the anesthetic - sparing effect of the entropy monitor. Fentanyl (2 μ/kg) and midazolam (0.03 mg/kg)

Table 4: Anesthetic sparing effect of entropy monitor

Name of drug	Etomidate	Propofol
Predicted dose required (mg/kg)	0.3	1.75
Average actual dose (mg/kg)	0.15	0.98
Savings (mg/kg)	0.18	1.02
Cost of drug (Rs./mg)	28.5	1.23
Savings (Rs./kg)	5.13	1.25
Hidden cost	Low	Rescue drugs required

may also have played a role in dose reduction of etomidate and propofol.

Riad *et al.*[7] studied entropy guided propofol induction in 72 elderly patients and found that total dose of propofol and the per kilogram body weight dose were significantly reduced by 37.1% and 31.8%, respectively in the entropy group. They concluded that the use of M-entropy during induction of anesthesia in elderly patients reduces propofol requirements and maintains cardiovascular stability that is consistent with our findings.

To conclude, our induction technique utilizing midazolam, fentanyl and the entropy monitor can be utilized to give greater hemodynamic stability to both induction agents propofol and etomidate by dose reduction effect. On using the entropy monitor the fall in SBP, DBP, and MAP on induction with propofol and etomidate can be reduced whereas the rise in SBP, DBP and MAP during laryngoscopy and intubation with etomidate is also reduced. Dose reduction also resulted in a reduction in the incidence of myoclonus in case of etomidate. Our results highlight the importance of using the entropy monitor to guide hypnosis levels for induction, as it translates into significant dose reductions both for etomidate and propofol. Entropy guided reduced induction doses (0.15 mg/kg for etomidate and 0.98 mg/kg for propofol respectively) result in lesser hemodynamic changes than propofol and etomidate induction with standard per kilogram body weight doses.

Etomidate is more cardiostable than propofol at equipotent dosages.

References

1. Miller RD, Reves JG, Glass PS, Lubarsky DA, McEvoy MD. Intravenous non opioid anaesthetics; Miller's Anaesthesia. 6th ed. Vol. 10. Philadelphia: Elsevier Churchill Livingstone; 2009. p. 318-61.
2. Saricaoglu F, Uzun S, Arun O, Arun F, Aypar U. A clinical comparison of etomidate-lipuro, propofol and admixture at induction. Saudi J Anaesth 2011;5:62-6.
3. Weisenberg M, Sessler DI, Tavdi M, Gleb M, Ezri T, Dalton JE, *et al.* Dose-dependent hemodynamic effects of propofol induction following brotizolam premedication in hypertensive patients taking angiotensin-converting enzyme inhibitors. J Clin Anesth 2010;22:190-5.
4. Larsen JR, Torp P, Norrild K, Sloth E. Propofol reduces tissue-Doppler markers of left ventricle function: A transthoracic echocardiographic study. Br J Anaesth 2007;98:183-8.
5. Sarkar M, Laussen PC, Zurakowski D, Shukla A, Kussman B, Odegard KC. Hemodynamic responses to etomidate on induction of anesthesia in pediatric patients. Anesth Analg 2005;101:645-50.
6. Creagh O, Torres H, Rodríguez N, Gatica SR. Alpha-2B adrenergic receptor mediated hemodynamic profile of etomidate. P R Health Sci J 2010;29:91-5.
7. Riad W, Schreiber M, Saeed AB. Monitoring with EEG entropy decreases propofol requirement and maintains cardiovascular stability during induction of anaesthesia in elderly patients. Eur J Anaesthesiol 2007;24:684-8.
8. Höcker J, Raitschew B, Meybohm P, Broch O, Stapelfeldt C, Gruenewald M, *et al.* Differences between bispectral index and spectral entropy during xenon anaesthesia: A comparison with propofol anaesthesia. Anaesthesia 2010;65:595-600.
9. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectral index for estimating nociception during sevoflurane anaesthesia. Br J Anaesth 2006;96:620-6.
10. Sandhu K, Dash H. Awareness during anaesthesia. Indian J Anaesth 2009;53:148-57.

How to cite this article: Shah SB, Chowdhury I, Bhargava AK, Sabbharwal B. Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels. J Anaesthesiol Clin Pharmacol 2015;31:180-5.
Source of Support: Nil, **Conflict of Interest:** None declared.

Conference Calendar 2015

Name of conference	Dates	Venue	Name of organising secretary with contact details
25th National Conference of Research Society of Anaesthesiology Clinical Pharmacology RSACPCON 2015	October 2nd, 3rd & 4th 2015	SGRD Amritsar	Organising Secretary Dr. Ruchi Gupta Telephone: +91 9814320805 Email: rsacpcon2015@gmail.com Website: http://www.rsacpcon2015.com/
ASA Anesthesiology 2015	October 24-28 2015	San Diego, California 91911, United States	Email: annmtg@asahq.org URL: http://www.asahq.org/Annual-Meeting/Future-Annual-Meetings.aspx