Original Article

A randomised controlled trial to study Bispectral guided induction of general anaesthesia using propofol and etomidate infusion

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ABSTRACT

Background and Aims: The present prospective, randomised study was done to evaluate induction characteristics with bispectral (BIS) index guided infusion of propofol and etomidate. **Materials and Methods:** After institutional ethical committee approval, 70 patients, aged 18–60 years, American Society of Anaesthesiologists (ASA) I and II scheduled for elective surgery were included. Patients were randomly allocated into one of the two groups. In Group E, patients received etomidate infusion at a rate of 0.07 mg kg^{-1} min^{-1} and in Group P, received propofol infusion of 0.7 mg kg^{-1} min^{-1}. Time from start of infusion to loss of palpebral reflex (T_P), loss of verbal command (T_V), BIS to reach 50 (T_{BIS50}), mean induction dose and incremental dose of each drug required to keep $BIS_{50.}$, haemodynamic parameters and adverse effects like pain, myoclonus, apnoea and postoperative nausea and vomiting (PONV) were also noted. **Results:** $T_{P,}$ T_V, and $T_{BIS\ 50}$ was faster in E as compared to *P* group and was statistically significant for all parameters. Mean induction dose of drug required till BIS 50 was 2.68 ± 0.56 mg kg^{-1} and 0.242 ± 0.11 mg kg^{-1} in group *P* and E, respectively. There was a significant difference between the groups with group E requiring incremental dose in a significant proportion of patients ($P = 0.004$). There was a significant decrease in MAP in *P* group as compared to E. In group P, more number of patients experienced pain and had apnoea episode as compared to group E. ($P < 0.001$). Myoclonus was observed in group E only ($P = 0.016$). **Conclusion:** BIS-guided titration of propofol and etomidate infusion for induction did not result in reduction of the dose, haemodynamic variations and other effects.

Key words: Bispectral index, etomidate, infusion, myoclonus, propofol

INTRODUCTION

Induction of general anesthesia by using intravenous anesthetic agents is commonly done because of faster onset and better patient comfort. An ideal intravenous anesthetic agent should produce minimal disturbance of cardiovascular and respiratory functions, should be chemically stable, non-irritant to veins, non-toxic, non-allergenic, easy to administer and have rapid recovery profile.[1]

Propofol and etomidate are two widely used induction agents. Propofol provides faster onset, rapid recovery, better attenuation of airway reflexes, adequate depth of anesthesia and anti-emesis. But the major disadvantage is the dose-dependent rapid fall in blood pressure and pain on injection.[2] Etomidate provides faster onset, rapid recovery, haemodynamic stability and minimal respiratory depression. Use of etomidate was associated with minor side effects like pain on injection, postoperative nausea and vomiting (PONV), dose-dependent myoclonus, and adrenocortical suppression. There were also few reports of adrenocortical suppression in critically ill patients by etomidate infusion.[3] Rediscovery of the beneficial effects of etomidate and lack of new reports

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of adrenocortical suppression lead to a renewed interest in etomidate.[4]

Bispectral index (BIS) is considered a better indicator for depth of anesthesia compared to routine clinical parameters and results in decreased induction dose of anesthetic drug and quick recovery. It is a dimensionless number scaled between 0 and 100, with 100 representing awake patient and 0 represent absence of brain activity or electrical silence. An optimal value for the maintenance of anaesthesia should be between 40 and 60. It is also associated with reduction of the incidence of awareness and recall in adults during general anesthesia.[5]

There are some studies in the literature comparing propofol and etomidate using BIS-guided induction and with different clinical end points, but we did this trial to study induction characteristics using BIS guidance with both the drugs. We hypothesised that the titration of both anaesthetics to an appropriate depth of anesthesia will reduce their required dose and alleviate the dose dependent adverse effects like hypotension and myoclonus. So, the aim of present study was to evaluate the effect of propofol and etomidate infusion with reference to induction dose required and time taken for BIS 50, haemodynamics, myoclonus, pain, apnoea episodes, and PONV.

MATERIALS AND METHODS

After institutional ethical committee approval (IEC/Th/18/Anst09), this prospective, randomised, single center and double blind study was conducted between February 2018 and March 2019 in accordance with the principles of Declaration of Helsinki. 70 patients aged between 18 and 60 years of either sex, belonging to American Society of Anaesthesiology (ASA) physical status I and II scheduled for elective surgery under general anaesthesia were included. Patients having history of uncontrolled hypertension, hypotension, ischemic heart disease, chronic use of alcohol, seizure disorder, allergy to study drugs, steroid therapy, adrenal insufficiency were excluded from the study. Patients were kept fasting for 6 h prior to surgery and premedication in the form of tablet alprazolam 0.25 mg and ranitidine 150 mg was given on the night before and 2 h prior to surgery. The purpose and protocol of study was explained to all patients and an informed and written consent was taken. In the operation theatre (OT), standard monitors like electrocardiogram (ECG), non-invasive blood pressure (NIBP). peripheral oxygen saturation (SpO_2), BIS, and endtidal carbon dioxide ($EtCO_2$) were attached. Intravenous access was established with an appropriate size cannula and fluids were administered @ 2ml kg^{-1} before start of induction. Patients were then allocated into one of the two groups by computer generated sequence of random numbers. In Group E ($n = 35$) patients received etomidate infusion at a rate of 0.07 mg kg^{-1} min^{-1} and in Group *P* ($n = 35$) patients received propofol. The consort flow diagram is shown in Figure 1.

Preoxygenation was done with 100% oxygen for 3 min. The BIS sensor was appropriately applied on left side of forehead with a smoothing rate of 15 s. BIS was activated 1 min before IV fentanyl 2μg kg^{-1} and baseline haemodynamic parameters were recorded. Two minutes after fentanyl administration, induction was started with infusion of study drugs as per group allocation. As BIS reached 50, infusion was stopped and used dose of drug was recorded by an independent anaesthesiologist. IV vecuronium 0.1 mg kg^{-1} was given to facilitate orotracheal intubation. If BIS value was raised above 50 after administering vecuronium and before intubation, then a bolus of 1 ml (propofol 10 mg or etomidate 2 mg) was given in increments till BIS reached 50. Anaesthesia was maintained with sevoflurane 1.5–2.5% in 50% N_2O and 50% $O_2$to keep BIS between 50 and 55. Ventilation was controlled to maintain $EtCO_2$between 30 and 35 mm Hg. At end of surgery, the residual neuromuscular block was reversed using neostigmine 0.05 mg kg^{-1} with glycopyrrolate 0.01 mg kg^{-1} IV.

Demographic variables, time from start of infusion to loss of palpebral reflex (T_p), loss of verbal command (T_V), BIS to reach 50 (T_{BIS50}), dose of drug required for BIS 50, incremental dose of propofol and etomidate required to keep $BIS_{50,}$ and total dose of drug consumed were noted. All these parameters were assessed by the resident who was unaware of the drug being used. Haemodynamic parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), peripheral arterial oxygen saturation (SPO_2) were noted before start of induction (T_b), after induction (T_0), just before intubation (T_i) and 1 (T_1), 3 (T_3), and 5 (T_5) min following intubation. Intraoperative hypotension (blood pressure <20% of baseline), hypertension (blood pressure >20% of baseline), bradycardia (HR <60), tachycardia (HR >100) were recorded and treated accordingly. Adverse effects like pain, myoclonus, apnoea, and PONV were also noted. Pain on injection

was noted using four graded scale: 0- no pain, 1-verbal complaint of pain, 2-withdrawal of arm, 3-both verbal complaint and withdrawal of arm. The incidence of myoclonic movements was graded as: mild- short movement of body segment (a finger or shoulder), moderate- slight movement of two different muscles or muscle groups, severe- intense clonic movements in two or more muscle groups of the body (fast abduction of a limb). These were also assessed by a resident who was unaware of the drug being used.

Our hypothesis was that using BIS 50 as a target for induction will decrease the dose of both drugs and side effects like hypotension and myoclonus. Dose of each drug required and time taken for induction was our primary objective. Changes in haemodynamics during induction and intubation, myoclonus, pain on injection, apnoea, and PONV were taken as secondary objectives.

The sample size was calculated based on time to reach BIS 50. A pilot study was performed consisting of 5 patients in each group reflecting all procedures of the main study where the mean time for BIS to reach 50 in the propofol group was 235.20 s and 179.40 s in etomidate group. Total sample size of 26 per group was calculated to detect the mean difference of 55.8 in time to BIS, at power of 90%,α of 0.05 where standard deviation of two groups was 63.88 and 36.66, respectively. To compensate for dropouts, 35 patients were taken in each group.

All data was compiled and statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS) program for Windows, version 17.0 (SPSS, Chicago, Illinois). Categorical variables were analysed using Chi-square, Student's *t*-test and the quantitative variables in both groups were expressed as mean ± SD. For all statistical tests, a *P* value less than 0.05 was taken as significant.

RESULTS

In the present study, a total of 70 patients with 35 patients in each group were recruited. Both groups were comparable with respect to demographic profile [Table 1]. Time to loss of palpebral reflex (T_p), loss of verbal command (T_V) and BIS50 ($T_{BIS\ 50}$) was faster in E group as compared to *P* group and was statistically significant for all parameters [Table 2]. Mean induction dose of drug required till BIS 50 was 2.68 ± 0.56 mg kg^{-1} in *P* group and 0.242 ± 0.11 mg kg^{-1}

Table 1: Demographic characteristics of the patients

Variable	Group P (*n*=35)	Group E (*n*=35)	*P**
Age (years)	38.03±14.12	42.31±13.37	0.197
Sex M/F	15/20	25/10	0.212
Weight (Kg)	59.89±9.72	56.89±9.24	0.19
ASA grade I/II	35/0	33/2	0.493
MPG I/II/III	8/25/2	7/26/2	0.958

*P<0.05 is significant

Table 2: Induction characteristics between the two groups

Parameter	Group P (*n*=35) (Mean±SD)	Group E (*n*=35) (Mean±SD)	*P**
Loss of palpebral reflex (T_p) (sec)	156.71±33.88	135.00±50.93	0.039*
Loss of verbal command (T_V) (sec)	155.06±32.57	134.26±51.67	0.048*
BIS to reach 50 ($T_{BIS\ 50}$) (sec)	227.97±58.77	174.20±63.72	<0.001*
Dose of drug consumed till BIS 50	2.68±0.56	0.242±0.11	<0.001*
Total dose of drug consumed (mg kg^{-1})	2.76±0.52	0.297±0.12	<0.001*

*P<0.05 is significant

in group E. The total mean anaesthetic dose consumed in group *P* was 2.76 ± 0.52 mg kg^{-1}, while in group E, it was 0.297 ± 0.12 mg kg^{-1} and was statistically significant between the groups ($P < 0.001$). In group P, 60% patients did not require any incremental dose, 22.9% required 1 ml and 17.1% patients required 2 ml incremental dose. In group E, 17.1% patients did not require any incremental dose and 34.3% required 1 ml, 28.6% required 2 ml, 14.3% required 3 ml, 2.9% required 4 ml, 2.9% required 5 ml. There was a significant difference between the two groups with group E requiring incremental dose in a significant proportion of patients ($P = 0.004$) [Figure 2].

Preoperative vitals (HR, SBP, DBP and MAP) were comparable in both groups. There was a decrease in HR in both groups after induction and then there was an increase in HR at 1, 3, and 5 min after intubation as compared to baseline but it was statistically insignificant. It reached at almost baseline level 5 min after intubation. Mean HR was comparable between both groups at all time intervals except for 1 min after intubation. At 1 min after intubation, increase in HR was significantly more in group *P* as compared to group E ($P = 0.041$). There was a significant decrease in MAP in *P* group as compared to baseline after induction and before intubation ($P < 0.001$), at 1, 3, and 5 min after intubation. In group E there was no statistical difference in MAP as compared to baseline till before intubation ($P = 0.110$). It increased at 1 and

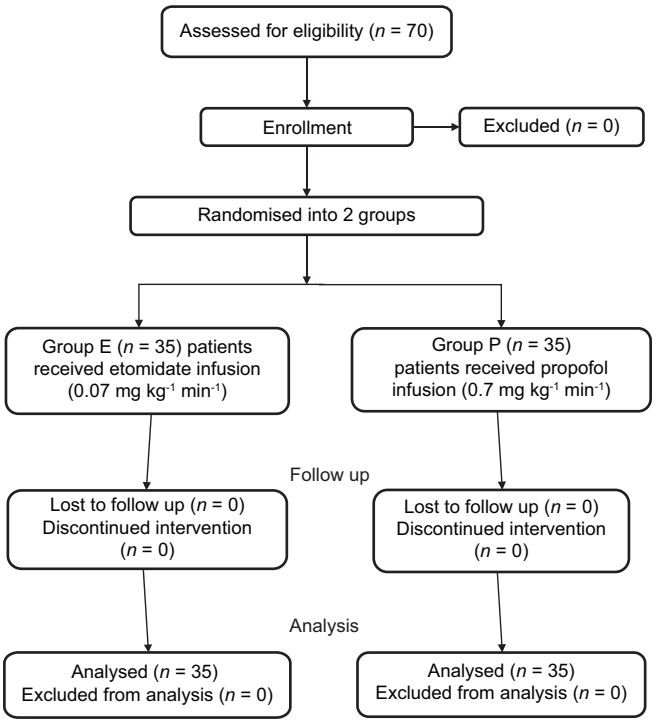

Figure 1: The CONSORT flow diagram

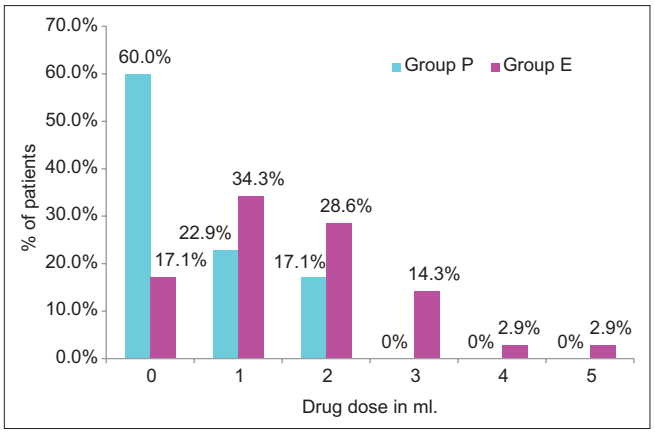

Figure 2: Incremental dose (ml) of drugs required to keep BIS 50 in the two groups

Table 3: Adverse effects between the two groups

	Group P (*n*=35)	Group E (*n*=35)	*P**
Pain	12 (34.3%)	3 (8.6%)	<0.001
Myoclonus	0	25.8%	0.016
Apnoea	29 (82.9%)	10 (28.6%)	<0.001
PONV	0 (0.0%)	2 (5.7%)	0.493
Hypotension	31 (88.6%)	2 (5.7%)	<0.001
Hypertension	1	4	0.114

*P<0.05 is significant

3 min after intubation and reached at almost baseline level 5 min after intubation [Figure 3].

In group P, 12 patients experienced grade 1 pain as compared to only 3 in group E and it was statistically significant ($P < 0.001$). Two patients in group E had PONV while in group *P,* no patient had PONV. In Group P, 29 patients had apnoea episode during induction while in group E only 10 patients had apnoea ($P < 0.001$). Apnoea episodes were transient and not associated with fall in oxygen saturation. Myoclonus was observed only in group E. Based on severity, 8.6% patients had mild, 2.9% had moderate, and 14.3% patients had severe myoclonus episodes ($P = 0.016$) In group P, 31 patients had episode of hypotension, while only 2 patients had hypotension episode in group E. This was found to be statistically significant ($P < 0.001$). Four patients in group E experienced episode of hypertension but no patient in group *P* had any hypertension episode. It was statistically insignificant ($P = 0.114$) [Table 3].

DISCUSSION

We studied etomidate and propofol infusion titrated to a BIS value of 50 to find out the induction dose of either drug, time required for induction, effect on haemodynamic changes and adverse effects if any. The BIS monitor is a well-established monitor for measuring depth of anaesthesia. Our goal was to intubate at a BIS value of 50, which is in the lower third of the recommended range for general anaesthesia (45–60) and reported theoretical time delay of the BIS monitor is 15–30 s. In our study, mean induction dose required till BIS 50 and total consumption of propofol was slightly more than the recommended bolus induction dose (1.5-2.5 mg kg^{-1}) in literature. Similarly, mean induction dose required till BIS 50 and total consumption of etomidate was same as the recommended bolus induction dose (0.15–0.4 mg kg^{-1}). We also wanted to see whether induction times will be comparable with these infusion speeds. But all measured times, that is, T_P, T_V, $T_{BIS\ 50}$ were significantly longer in *P* as compared to E group with the chosen infusion speeds.

Our study results are similar to the study done by Saricaoglu *et al.*, who compared BIS-guided infusion (constant infusion of drug at the rate of 200 ml min^{-1}) of etomidate-lipuro, propofol and admixture at induction in 90 patients. Induction time to reach BIS 40 was significantly faster in etofol group followed by etomidate and propofol group ($P < 0.000$).[6]

Moller *et al.* compared haemodynamic effects of etomidate and propofol infusion for BIS-guided induction in 46 patients undergoing major abdominal

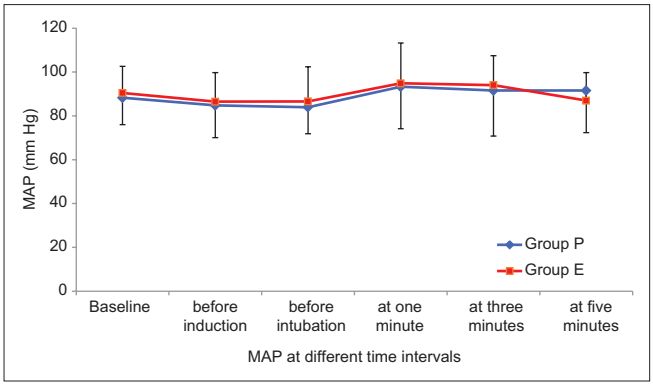

Figure 3: Comparison of MAP between two groups

surgery. They reported that time to loss of palpebral reflex and time until BIS 60 were significantly longer in group E compared with the group P. Mean consumed anaesthetic dose was 1.14 ± 0.33 mg kg^{-1}, 0.15 ± 0.05 mg kg^{-1} for propofol and etomidate respectively and was less as compared to our study. This can be attributed to difference in profile of patients (ASA III) and technique of anesthesia induction. They administered fentanyl 3μg kg^{-1} and midazolam before induction, took depth of anesthesia as BIS60, used different rates of infusion (0.5 mg kg^{-1} for propofol and 0.05 mg kg^{-1} for etomidate) and did not use any incremental dose. Shah *et al*. did comparison of haemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels and observed that reduced doses of etomidate (0.15 mg kg^{-1}) and propofol (0.98 mg kg^{-1}) were sufficient to give an adequate depth using entropy monitors.[7]

Similar to our study, Aggarwal *et al.*, Shah *et al.*, Onkarappa *et al*. noted increase in HR at and after induction and this was statistically significant with propofol as compared to etomidate.[8-10] While Petrun *et al.*, Karki *et al.*, Khare *et al*. did not find any significant change in mean HR between the groups.[7,11,12]

In the present study, there was a significant decrease in MAP in group *P* as compared to group E just after induction and at 1,3, and 5 min after intubation ($P < 0.05$). In group E, MAP remained stable throughout induction and intubation. Many other authors like Aggarwal *et al.*, Onkarappa *et al*. noted a significant decrease in mean arterial blood pressure from baseline at induction in propofol group as compared to etomidate group.[8-10,12,13] On the contrary, Petrun *et al*. observed that MAP showed no change during intubation and remained low as compared to baseline in group P, while in group E MAP increased during intubation and reached approximately baseline value after intubation.[7]

In group P, 31 patients had episode of hypotension, while 2 patients had hypotension and in group E ,4 patients experienced hypertension. But no treatment was required, it responded to IV fluids and increasing the depth of anaesthesia respectively. Petrun *et al*. and Shah *et al*. observed the similar results but treatment was required in the form of ephedrine and diltiazem.[7,9]

In the present study, verbal complaint of pain on injection and episode of apnoea were statistically higher in *P* group as compared to E. This is similar to the study done by Aggarwal *et al.*, Khare *et al.*, Shivanna *et al.*, and Saricaoglu *et al*. In contrast to ours, Onkarappa *et al*. noted that only 2 patients receiving propofol had pain and none had pain with etomidate and it was statistically insignificant. This can be attributed to different technique of induction or premedication. Aggarwal *et al*. noted more episodes of apnoea in propofol than etomidate (76% vs. 66%), but it was statistically insignificant.

In present study, no patient had PONV in group *P* while in group E, 2 patients had PONV. Our study is in contrast to study of Shivanna *et al*. who noted incidence of PONV as 22.9%, and 71.4%, in group *P* and E, respectively ($P < 0.001$). More incidence of PONV in group E can be attributed to different surgical and patient factors.

In present study, 25.8% patients in group E had episode of myoclonus as compared to none in group *P* ($P = 0.016$). Aggarwal *et al.*, Saricaoglu *et al.*, and Onkarappa *et al*. also observed myoclonic movements only in etomidate group. Khare *et al*., Shivanna *et al*. noted myoclonus in 40% patients in etomidate group as compared to 4% in propofol group and it was statistically significant ($P < 0.05$).

We thought that BIS-guided induction will reduce the dose of the drug required for induction and thus decrease the haemodynamic variations and other adverse effects. But dose required for induction and intubation for etomidate was same as recommended for bolus administration and for propofol, it was higher than recommended. When a drug is administered, the amount required to induce anaesthesia depends on several factors: the free concentration of the drug in the plasma; time it takes for the drug to reach its target

organ; time it takes for the drug to enter into the target organ in sufficient concentration; and time it takes to exert its pharmacological action. It is likely that reduction of delivery of a drug to less than a particular rate results in redistribution and elimination of the agent becoming significant factors in determining the rate at which sufficient plasma concentrations are reached, and the overall dose required to achieve induction may even begin to increase.[14] Blum J *et al*. observed that the lowest value for BIS (min), loss of verbal command was achieved in the group with the fastest rate of propofol injection (group 1, 5 s). The highest BISmin was obtained in the group with slowest rate of injection (group 3, 240 s). The haemodynamic parameters were not significantly different among groups.[15]

Our study had a few limitations. BIS systems display a value calculated from the preceding data of last 15–30 s of EEG recording and updated every second. BIS value may lag behind the observed clinical change by approximately 5–10 s. We did not wait for 5–10 s while using incremental dose to keep BIS 50 that might have resulted in greater overall dose, requirement of propofol and etomidate for intubation. Second, we did not have control groups for manual bolus administration and thus to compare with the infusion groups in our study. Third, etomidate and propofol infusion doses were not calculated by equipotency.

To conclude, BIS-guided titration of propofol and etomidate infusion for induction did not result in reduction of the dose of either drug, haemodynamic variations and other effects. However, further studies with larger sample size are required for better statistical significance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jaap V, Elske S, Marije R. Intravenous anesthetics. In: Miller RD, 9th ed. Miller's Anaesthesia. New York: Elsevier Churchill Livingstone; 2019. p. 638-9.
2. Smith I, White PF, Nathanson M. Propofol: An update on its clinical use. Anesthesiology 1994;81:1005-43.
3. Bloomfield R, Noble DW. Etomidate and fatal outcome; even a single bolus dose may be detrimental for some patients. Br J Anaesth 2006;97:116-7.e.
4. Tekwani KL, Watts HF, Rzechula KH, Sweis RT, Kulstad EB. A prospective observational study of the effect of etomidate on septic patient mortality and length of stay. Acad Emerg Med 2009;16:11-4.
5. Galante D, Melchionda M. The introduction of bispectral index (BIS) in anaesthesia. Anaesth Pain Intensive Care 2012;16:23-31.
6. Saricaoglu F, Uzun S, Oguzhan A, Funda A, Ulku A. A clinical comparison of etomidate-lipuro, propofol and admixture at induction. Saudi J Anaesth 2011;5:62-6.
7. Moller PA, Kamenik M. Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate. Br J Anaesth 2013;110:388-96.
8. Aggarwal S, Goyal VK, Chaturvedi SK, Mathur V, Baj B, Kumar A. Comparative study between propofol and etomidate in patients undergoing general anaesthesia. Rev Bras Anesthesiol 2016;66:227-41.
9. Shah SB, Chowdhury I, Bhargava AK, Sabbharwal B. Entropy guided hemodynamics of etomidate versus propofol. J Anaesthesiol Clin Pharmacol 2015;31:180-5.
10. Onkarappa SM, Shetty SM, Kotekar N. Induction properties of propofol and etomidate: Aclinical comparative study. Int J Res Med Sci 2016;4. doi: 10.18203/2320-6012.ijrms20163308.
11. Karki G, Singh V, Barnwal A, Singh L. A Comparative evaluation of hemodynamic characteristics of the three induction agents – Etomidate, thiopentone and propofol. J Evolution Med Den Sci 2014;3:9133-41.
12. Khare A, Tandon B, Samota MK, Mathur V, Singh M. A randomisd clinical study to compare the hemodynamic effects of etomidate with propofol during induction of general anaesthesia. Int J Res Med Sci 2016;4:4593-7.
13. Shivanna DP. Comparison of induction characteristics and hemodynamic parameters of propofol versus etomidate in patients undergoing surgeries under general anaesthesia, a bispectral index guided study. International Journal of Innovative Research in Medical Science 2017;2:1458-67.
14. Berthoud MC, Mclaughlan GA, Broome IJ, Henderson PD, Peacock JE, Reilly CS. Comparison of infusion rates of three i.v. anaesthetic agents for induction in elderly patients. Br J Anaesth 1993;70:423-7.
15. Blum J, Kochs E, Forster N, SchneiderG. The influence of injection rate on the hypnotic effect of propofol during anesthesia: A randomized trial. PLOS Clin Trial 2006;1:e17. doi: 10.1371/journal.pctr.001001.