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

Savita Saini, Mamta Bhardwaj, Asha Sharma, Susheela Taxak
Department of Anaesthesiology and Critical Care, Pt. BD Sharma University of Health Sciences, Rohtak, Haryana, India

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 (Tₚ), loss of verbal command (Tᵥ), BIS to reach 50 (T₅₀), mean induction dose and incremental dose of each drug required to keep BIS₅₀, haemodynamic parameters and adverse effects like pain, myoclonus, apnoea and postoperative nausea and vomiting (PONV) were also noted. Results: Tₚ, Tᵥ, and T₅₀ were 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.[⁴] 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.[⁵] 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.[⁶] 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 (SpO₂), BIS, and endtidal carbon dioxide (EtCO₂) 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% N₂O and 50% O₂ to keep BIS between 50 and 55. Ventilation was controlled to maintain EtCO₂ 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 (T₁), loss of verbal command (T₂), BIS to reach 50 (T₃ₕ₅), dose of drug required for BIS 50, incremental dose of propofol and etomidate required to keep BIS₅₀, 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 (SPO₂) were noted before start of induction (T₁), after induction (T₂), just before intubation (T₃) and 1 (T₄), 3 (T₅), and 5 (T₆) 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 
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%,

\[ \text{sample size} = \frac{(\text{mean difference} / \text{standard deviation})^2 \times \text{power}^2 \times \text{effect size}}{\text{standard deviation}^2} \]

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 (\(T_{\text{BIS 50}}\)) 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\(^{-1}\) 
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

| Table 1: Demographic characteristics of the patients |
|-----------------|-----------------|-----------------|
| **Variable**    | **Group P (n=35)** | **Group E (n=35)** |
| Age (years)     | 38.03±14.12      | 42.31±13.37      |
| Sex M/F         | 15/20            | 25/10            |
| Weight (Kg)     | 59.89±9.72       | 56.89±9.24       |
| ASA grade I/II  | 35/0             | 33/2             |
| MPG I/II/III    | 8/25/2           | 7/26/2           |

*P<0.05 is significant

| Table 2: Induction characteristics between the two groups |
|-----------------|-----------------|-----------------|
| **Parameter**   | **Group P (Mean±SD)** | **Group E (Mean±SD)** |
| Loss of palpebral reflex (T\(_p\)) (sec) | 156.71±33.88 | 135.00±50.93 |
| Loss of verbal command (T\(_v\)) (sec)    | 155.06±32.57 | 134.26±51.67 |
| BIS to reach 50 (T\(_{\text{BIS 50}}\)) (sec) | 227.97±58.77 | 174.20±63.72 |
| Dose of drug consumed till BIS 50 (mg kg\(^{-1}\)) | 2.68±0.56 | 0.242±0.11 |
| Total dose of drug consumed (mg kg\(^{-1}\)) | 2.76±0.52 | 0.297±0.12 |

*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
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.[6-10] 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.[6-10,12,13] 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.\textsuperscript{14} Blum J \textit{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 BIS-min was obtained in the group with slowest rate of injection (group 3, 240 s). The haemodynamic parameters were not significantly different among groups.\textsuperscript{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.

\textbf{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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\textbf{Conflicts of interest}

There are no conflicts of interest.

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