

A Comparison of Haemodynamic Effects of Propofol and Etomidate Induction in Patients Undergoing Lumbar Fixation Surgery Under General Anesthesia

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Abstract

Introduction: Drug induced haemodynamic instability and intubation stress response, are the main anaesthetic hazards during induction of anaesthesia. Wide variation of mean arterial pressure (MAP) is undesirable in neuroanaesthesia to maintain optimum perfusion of brain and spinal cord.

Aims: In a double-blind, randomized trial, we compared the haemodynamic effects of etomidate and propofol infusion for anaesthesia induction in patients undergoing lumbar fixation surgeries.

Methods: Seventy patients were randomly assigned into two groups based on the induction agent for anaesthesia [etomidate (E group) and propofol (P group)] through intravenous infusion with targeted BIS value ≤ 50 . Mean arterial pressure (MAP), cardiac output (CO), heart rate (HR) and BIS values were recorded before giving premedication, before induction, immediately after induction of anaesthesia, at intubation and 1, 3 and 5 min after intubation. The primary outcome of the study was difference in changes of MAP between two groups. Data were analyzed with the IBM SPSS Statistics 18 statistical software and $P < 0.05$ was considered statistically significant.

Results: Before intubation, there was no significant difference in haemodynamics between the two groups. At induction, intubation and up to 5 minutes thereafter, all the haemodynamic parameters were significantly differed from baseline value in both groups ($P < 0.001$). During intergroup comparison, it was noted that in E group the haemodynamic alternation was more pronounced and prolonged than propofol group ($P < 0.01$). At the end of study period, MAP was significantly higher in the E group than P group (105.83 ± 5.512 vs 89.09 ± 5.255 ; $P = 0.000$). CO, HR and BIS values were also higher in E group than P group after intubation.

Conclusion: From this study it is documented that haemodynamic alternations were more pronounced and prolonged with etomidate infusion than propofol infusion during BIS guided induction in lumbar spine fixation surgery under general anaesthesia. So propofol is better induction agent of choice than etomidate during spinal surgery.

Keywords: BIS Guided Induction; Propofol Infusion; Etomidate Infusion; CO Monitoring; Haemodynamic Monitoring

Abbreviations

MAP: Mean Arterial Pressure; BIS: Bispectral index scale; CO: Cardiac Output (CO); HR: Heart Rate

Introduction

Drug induced haemodynamic instability and intubation stress responses, are two main anaesthetic hazards during induction of anaesthesia [1]. Wide variation of mean arterial pressure (MAP) is undesirable in neuroanaesthesia to maintain optimum perfusion of brain and spinal cord [2]. Maintenance of haemodynamic stability, balance between myocardial oxygen demand-supply and amelioration of the stress response to intubation are main considerations in neuroanaesthesia [1]. Nowadays, propofol is widely used as induction agent because of its rapid onset, shorter duration and minimal adverse effects. However, it causes moderate to severe post-induction and pre-intubation hypotension due to marked reduction in systemic vascular resistance [3]. Etomidate, an alternative induction agent, is commonly used in cardiac anaesthesia for its minimal histamine release and stable hemodynamic property [4]. However, till now as an induction agent, etomidate is not so much popular in neuroanaesthesia.

In most of the previous studies, the hemodynamic effects of both agents, were compared in cardiac anaesthesia, not in neurosurgical case [5,6].

In this study we want to explore that whether use of etomidate for induction during lumbar spine surgery has really any advantages over conventional propofol induction.

Aim of the Study

Therefore in this study, we try to evaluate the haemodynamic effects of etomidate in comparison to that of propofol during BIS guided (≤ 50) anaesthesia induction along with cardiac output (CO) monitoring. Differences in MAP between the two groups were compared as primary outcome.

We were also interested to know which agent causes more hypertension and tachycardia at intubation and which causes more hypotension and bradycardia after induction.

Materials and Methods

This prospective randomized, parallel group double blind study was conducted in our neurosurgical unit during the period July 2016 to June 2017. The study protocol was registered at Clinical Trials Registry India (CTRI/2018/03/012447). Following approval of the Institutional Ethical Committee and with written informed consent, seventy adult patients of American Society of Anaesthesiologists (ASA) physical status I and II, aged 18-60 years, posted for elective lumbar spine fixation surgery were included in this study. Patients who were physically dependent on narcotics, allergic to study drugs, valvular heart disease, left ventricular ejection fraction $<50\%$ and with any other organic disease were excluded from this study. Patient with severe hypertension, diabetes mellitus, epilepsy or anticipated difficult airway were also excluded.

Randomization was done on basis of computer generated random number list and it was in custody of senior anaesthesiologists who was not involved in day to day care and monitoring of study participants. This randomization schedule facilitated patient disposition into two equal groups- Group P (propofol = 35) and Group E (etomidate = 35). The list was concealed in opaque sealed envelope that was numbered and opened sequentially after obtaining the patient's consent.

All patients were advised to restrict solid per mouth at least 6 h before surgery along with tablet diazepam (5 mg) and ranitidine (150 mg) on the night before surgery. On arrival to the operating room, an intravenous (IV) Ringer's solution (10 ml/kg) was started. An arterial line was placed into the radial artery and Edward CO sensor in cardiac monitor EV1000 was attached for measuring mean arterial pressure (MAP) and CO. BIS electrodes were placed and attached with Aspect 2000 BIS monitor XP platform. All the preoperative baseline parameters were recorded. The perfusor with the anaesthetic agent for induction was prepared by an independent contributor who was not involved in any other part of study. Fentanyl 2 $\mu\text{g}/\text{kg}$ was administered intravenously just before induction. After preoxygenation with

100% oxygen for 3 minutes, P group received propofol at the infusion speed 0.5 mg/kg/min and E group received etomidate at the infusion speed of 0.05 mg/kg/min. Both the drugs are administered through identical 20 ml syringe and the external appearance of both drug were identical which could not be differentiated by third person (both were white in colour). As soon as the target BIS \leq 50 was reached, IV rocuronium 0.6 mg/kg was administered and the patient was orotracheally intubated by the main examiner (when TOF count 0). The main examiner was unaware about the type of induction agent. After intubation, the patient was mechanically ventilated with a mixture of oxygen and N₂O (1:1) with addition of sevoflurane 1 vol% which was included into the gas mixture immediately after intubation and reached 1 vol% in the gas mixture ~10 minutes after intubation. The tidal volume was 6 ml/kg, the breathing frequency was 12/min and fresh gas flow was 2 litre/min with maintaining end tidal CO₂ value 35 - 40 mmHg. No surgical intervention was allowed until 10 minutes after induction.

HR, MAP, CO and BIS values all were recorded before premedication, immediately before and after induction of anesthesia, at intubation and 1, 3, and 5 min after intubation. The study was ended at that point and thereafter all the vitals were monitored throughout the surgery. Data were stored in an IBM-compatible computer.

The primary outcome of the study was to evaluate the haemodynamic effects of etomidate in comparison to that of propofol during induction reflected by difference in changes of MAP between two groups. Secondary outcomes were measured by comparing HR, changes in BIS values and CO during the study period.

Any adverse effect like bradycardia, hypotension, pain on injection cough, laryngospasm, bronchospasm, apnoea and any involuntary movement was also noted.

Injection Atracurium at a dosage of 0.1 mg/kg was repeated accordingly to maintain relaxation as and when necessary (when TOF \geq 2). IV tramadol 2 mg/kg was administered as analgesic just before incision. Nitrous oxide was stopped before reversal with IV neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). After oropharyngeal suctioning, extubation was done and 100% oxygen was given through face mask. All the patients were sent to the recovery room in fully conscious state.

All complications were treated after 1 min of their duration. Hypotension (MAP \leq 55 mm Hg) was treated with IV phenylephrine infusion until the desired clinical effect was achieved. Hypertension (MAP \geq 100 mm Hg) was treated with fentanyl 1 μ g/kg up to three times and afterwards with a nitroglycerine infusion (10 - 100 μ g/min). Bradycardia (HR \leq 40/min) was treated with atropine 0.3 mg. Tachycardia (HR \geq 90/min) was treated with fentanyl 1 μ g/kg.

Data were analyzed with the IBM SPSS Statistics 18 statistical software. Data were summarized by routine descriptive statistics namely mean and standard deviation (SD) for numerical variables and counts and percentages for categorical variables. Numerical data were compared between groups by Student's independent t-test if normally distributed or by Mann-Whitney-U Test if skewed. The Chi-square test or Fisher's Exact Test were employed for intergroup comparison of categorical variables. Changes in haemodynamic variables over time were assessed for statistical significance by repeated measures ANOVA (Analysis of Variance) followed by the Tukey's Test for post hoc comparison. All analysis were two tailed and $p < 0.05$ were considered statistically significant.

Sample size was calculated on the basis of MAP as the primary outcome measure. It was estimated that 35 subjects would be required per group in order to detect a difference of 10mm of Hg BP in the groups with 80% power and 5% probability of type I error. This calculation assumed a SD of 15mm of Hg for MAP in both propofol and etomidate groups on the basis of previous study [7]. Sample size calculation was done with the help of nMaster 2.0 (Dept. of Biostatistics, CMC, Vellore) software.

Result

In this study total 80 patients were screened for elective spinal fixation under general anesthesia (GA). Out of them, 10 patients were not included because of unwillingness and did not meet the inclusion criteria. Ultimately seventy patients were randomized for assessment and none of the patients were lost during follow-up (Figure 1). All the demographic characteristics like age, sex, height and body

weight were comparable between two groups (Table 1). Baseline haemodynamic parameters in both groups were also comparable ($P > 0.05$). Each intubation was successful at the first attempt and took < 20 s.

Parameter	Propofol	Etomidate	P Value
Age (yr)	40.26 ± 9.912	41.74 ± 10.961	0.554
Height (inches)	59.26 ± 6.279	61.74 ± 5.249	0.077
Weight (kg)	63.11 ± 2.374	63.34 ± 2.014	0.665
BSA (m ²)	1.65 ± 0.128	1.68 ± 0.111	0.281

Table 1: Basic demographic characteristics. Values in mean (SD). BSA=body surface area.

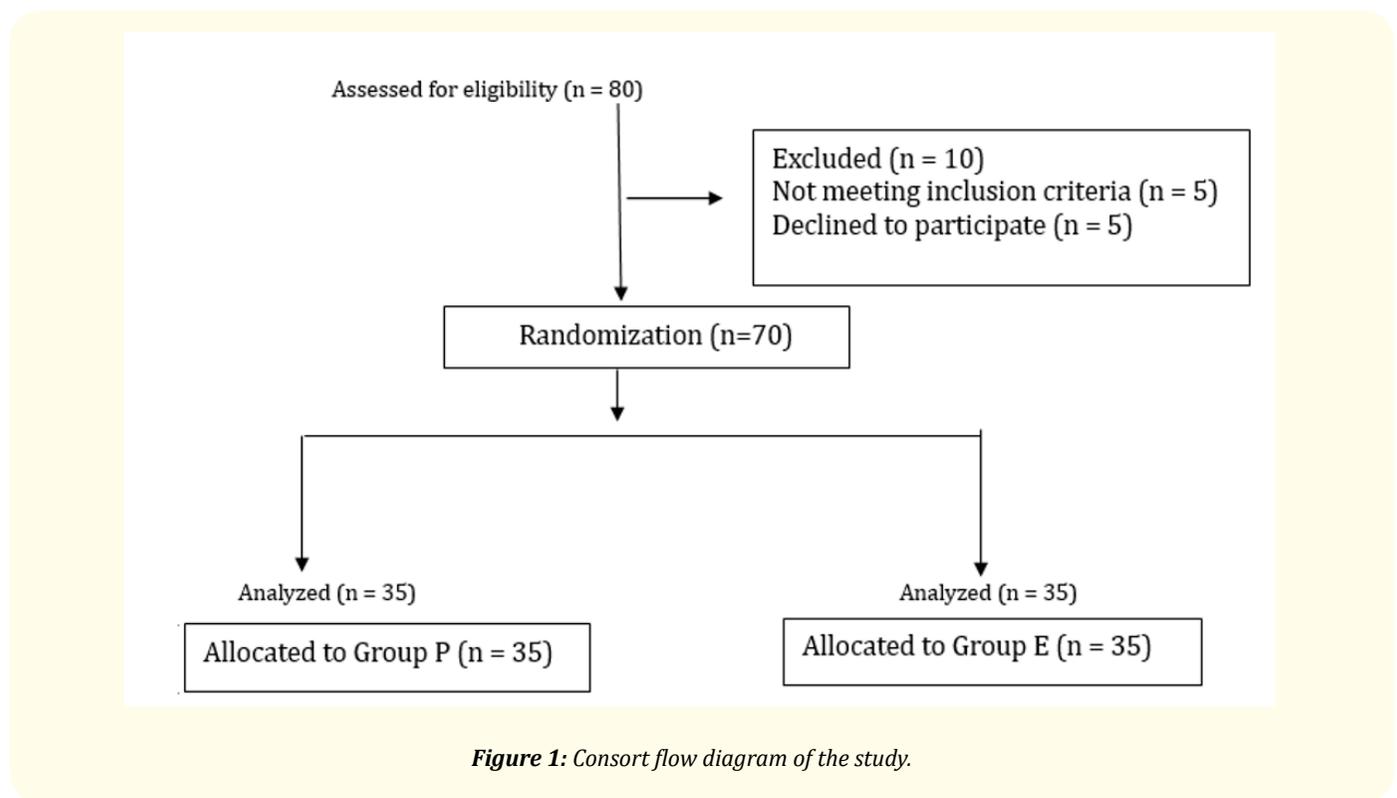


Figure 1: Consort flow diagram of the study.

In Pgroup, immediately after induction MAP was gradually decreased (93.37 ± 5.558) from baseline value (101.4 ± 7.582) upto intubation. Just after intubation, MAP was increased transiently (97.69 ± 5.212) and then it again gradually came down to basal level at the end of study (89.09 ± 5.255). Whereas, in E group after induction MAP was decreased to some extent (95.80 ± 6.443) from baseline value (99.80 ± 6.118), but it was sharply increased after intubation (109.86 ± 6.103) and remained in higher level upto to the end of study period (105.83 ± 5.512). After induction, in both the groups MAP significantly differed from base line value during intragroup comparison at all time intervals ($p < 0.01$). During intubation, MAP did not significantly differ in two groups. During intergroup comparison, MAP was significantly higher in E group than P group at 1, 3 and 5 minutes after intubation ($p = 0.000$) (Table 2). 3 out of 35 patients in E group required rescue IV fentanyl (2 mcg/kg) and infusion nitroglycerine (10 - 100 mcg/kg/min) to control BP.

Parameter	Propofol (P)	Etomidate (E)	P value
PreOp Baseline	101.4 ± 7.582	99.80 ± 6.118	0.350
Premed	99.97 ± 6.702	98.14 ± 6.481	0.250
Induction	97.14 ± 6.372	96.66 ± 5.466	0.733
Intubation	93.37 ± 5.558	95.80 ± 6.443	0.096
After 1 min	97.69 ± 5.212	109.86 ± 6.103	0.000
After 3 min	92.71 ± 5.211	107.54 ± 5.332	0.000
After 5 min	89.09 ± 5.255	105.83 ± 5.512	0.000

Table 2: Comparison of effect of propofol and etomidate on mean arterial pressure (mmHg). Values in mean (SD).

Similar to MAP, HR, CO and BIS all parameters were decreased from their baseline value just after induction in both the groups and increased transiently just after intubation. During intubation, HR, CO and BIS was not significantly different between two groups. HR, CO and BIS values came down to its baseline value in P group at end of study, but in E group their value remained significantly at higher level than baseline value. During intragroup comparison parameters were significantly differ from their baseline values ($p < 0.01$). During intergroup comparison their values were significantly higher in E group than P group at 1, 3 and 5 min after intubation ($p = 0.000$) (Table 3-5).

HR	Propofol (P)	Etomidate (E)	P value
PreOp Baseline	91.51 ± 9.769	90.26 ± 9.639	0.590
Premed	91.97 ± 7.778	93.37 ± 8.964	0.488
Induction	88.29 ± 7.653	91.26 ± 8.665	0.133
Intubation	87.54 ± 6.955	88.46 ± 7.939	0.610
After 1 min	95.51 ± 7.808	103.17 ± 9.963	0.001
After 3 min	88.26 ± 6.980	101.31 ± 9.860	0.000
After 5 min	82.43 ± 7.192	99.00 ± 10.27	0.000

Table 3: Comparison of effects of propofol and etomidate on heart rate (HR). Values in mean (SD).

	Propofol (P)	Etomidate (E)	P value
PreOp Baseline	5.47 ± 0.368	5.33 ± 0.240	0.059
Premed	5.53 ± 0.333	5.39 ± 0.234	0.050
Induction	4.41 ± 0.305	5.33 ± 0.285	0.260
Intubation	5.28 ± 0.364	5.250 ± 0.285	0.689
After 1 min	5.57 ± 0.398	5.63 ± 0.289	0.452
After 3 min	5.31 ± 0.303	5.57 ± 0.275	0.000
After 5 min	5.20 ± 0.302	5.49 ± 0.274	0.000

Table 4: Comparison of effects of etomidate and propofol on cardiac output (CO). Values in mean (SD).

	Propofol (P)	Etomidate (E)	P value
Premed	98.34 ± 1.305	98.80 ± 1.167	0.087
Induction	55.80 ± 4.645	53.29 ± 6.215	0.059
Intubation	47.34 ± 3.378	49.03 ± 5.205	0.113
After 1 min	52.20 ± 3.833	55.77 ± 4.413	0.001
After 3 min	52.34 ± 3.903	59.89 ± 4.315	0.000
After 5 min	50.89 ± 4.639	62.80 ± 4.283	0.000

Table 5: Comparison of effects of propofol and etomidate on bispectral index. Values in mean (SD).

During the study period, there was no pain on injection, cough, laryngospasm, bronchospasm, apnoea and any involuntary movements in either group of patients without any hypotension or bradycardia.

Discussion

In this study, we compared the haemodynamic effects of propofol and etomidate during induction, intubation and 5 minutes thereafter in patients undergoing lumbar fixation surgeries under general anaesthesia. It was found that in both group hypertension and tachycardia occurred during intubation, but the degree and duration of haemodynamic alternation (hypertension and tachycardia) were more in etomidate than propofol group. It was also shown that, during BIS-guided induction, propofol did not cause significant hypotension.

Anaesthetic induction, is associate with significant haemodynamic suppression due to peripheral vasodilatation, reduction in preload and venous return and to a lesser extent, decreased myocardial contractility [8]. On the other hand, stress response during laryngoscopy and intubation leads to various haemodynamic changes like hypertension, tachycardia, dysrrhythmia, myocardial infarction and increase in intracranial and intraocular pressure. These changes are due to increase in plasma concentrations of epinephrine, norepinephrine and vasopressin [9]. The undesirable haemodynamic effects of laryngoscopy and tracheal intubation, are not only detrimental for intraoperative safety, but also prudent in post-operative recovery, long term survival and health care costs [10]. Maintaining adequate depth of anaesthesia is essential for stable hemodynamics during induction and intubation. it is a challenging task for anaesthesiologist.

The BIS is a well-established monitor for measuring the depth of anaesthesia. Our goal was to intubate at BIS ≤ 50, which is in the lower third of the recommended range for general anaesthesia (BIS 45 - 60) [11].

In spinal surgery, acute alternation of MAP is detrimental, as sudden hypotension during induction may hamper spinal cord perfusion and on the other hand marked hypertension during intubation may lead to massive intraoperative haemorrhage. So tight control of MAP is very essential during spine surgery [2].

Invasive haemodynamic monitoring, especially beat to beat measurements of arterial blood pressure and cardiac output, are useful for accurate monitoring and management of perioperative haemodynamic changes. Monitoring of Cardiac Output (CO), is also essential to ensure adequate tissue perfusion in the perioperative period [12]. There was no study in the available literature which compares the haemodynamic of effects propofol and etomidate on cardiac output before and after intubation in neuroanaesthesia .We decided to use Edward CO sensor in our study because it only requires a standard radial arterial line and we were interested in trends of CO rather than the absolute values.

In our study, it was found that after induction HR, MAP and CO all were decreased from baseline value in both groups, but 1 minute after intubation they were increased. These increases in MAP, HR and CO were more pronounced in E Group. At the end of study period, in P group MAP, HR and CO, all the parameters reached to their basal level, but in E group their values remained in higher level. In P group BIS

value was maintained around target level throughout the study period (50.89 ± 4.639), whereas after intubation in E group BIS value was maintained at higher rang (62.80 ± 4.283). After intubation, sevoflurane which was introduced with a slow wash-in technique to delay its haemodynamic effects (baroreflex depression, depression of the contractility of the heart) and could also have had synergistic depressant haemodynamic effects in both groups.

In one study, Larsen and colleagues compared the haemodynamic effects of propofol and etomidate induction in geriatric patients undergoing major upper abdominal surgery [13]. Similar to our study, they found that after induction MAP and HR were decreased in both groups to the same extent, but at intubation the haemodynamic stress response was more prominent in etomidate group.

In another study, Kaushal RP, *et al.* observed the effect of propofol and etomidate induction in patients undergoing CABG or mitral/aortic valve replacement under CPB. They found that after induction decrease in HR from baseline values in P group, but not in E group. After intubation HR raised in both P and E group, but after 5 minutes HR became normal in P group, but in E group it remained at higher level [14].

In another study, Singh and colleagues compared the induction effect of etomidate (0.2 mg/kg) and propofol (1.5/mg kg) in patients with coronary artery disease and left ventricular dysfunction [15]. They found that MAP, cardiac index (CI) and HR were significantly decreased after induction and increased after intubation in comparison with the baseline with no significant differences between the groups.

In contrary to our study, Haessler and colleagues found that propofol induced severe hypotension predominantly in patients with severe three-vessel disease. This hypotension was mainly due to excess propofol dose as induction was not guided by BIS [16]. Similarly, McCollum JSC and Dundee JW, when compared the efficacy of IV boluses propofol and etomidate as induction agent in elective surgeries under GA, they found that hypotension was more with propofol 2.0 and 2.5 mg/kg than etomidate 0.3 mg/kg [17]. In our study, as both the induction agent was administered through infusion pump, no such haemodynamic alternation was occurred.

In another study, Bendel and colleagues compared the haemodynamic effects of propofol and etomidate after slow bolus administration (titrating to BIS 60 or less) in patients with aortic stenosis [18]. They found that propofol is more likely to cause hypotension than etomidate, which is due to aortic stenosis. Shivanna S., *et al.* in 2015 conducted a study to compare haemodynamic stability of propofol and etomidate in patients undergoing CABG with CPB. They observed that after induction, mean MAP reduced by 30% in group P and 22% in group E [19].

In a another study by Shah SB., *et al.* in cardiac surgery (2017), they used State and Response Entropy for induction and intubation. The fall in MAP was much sharper for Group-P (24.3% and 28.66%) as compared with Group-E (15.87% and 16.6%) [20]. The above studies were differing from our study in respect to cardiac compromise patients. In our study on patient undergoing lumbar spine surgery, the haemodynamic variation was more pronounced and prolonged in etomidate group than p group. In some recent studies the same haemodynamic variations like our study were noted with etomidate induction [21-23].

The other important conflicting factor regarding use of etomidate over other induction agent and its safety in this population is a matter of strong debate in the critical care community as the drug is associated with suppression of adrenal steroidogenesis, which can last up to 72 hours after a single dose, primarily through potent inhibition of the 11β -hydroxylase enzyme [24,25].

The study had its limitations. Firstly, it was a single centre study with small sample size. Secondly, haemodynamic monitoring was not continued beyond intraoperative period to assess any probable residual effect of either of the study drugs. Thirdly, serum cortisol level could not be measured in our study. To evaluate the haemodynamic effects of both drugs in higher risk group like in elderly and debilitated patients, further studies are needed.

Conclusion

From this study it can be documented that though etomidate is a popular induction agent in cardiac surgery, propofol induction is more ideal for spine surgery, as better haemodynamic is maintained with less hypertension and tachycardia at and after intubation. On the other hand, in neuroanesthesia, use of etomidate was not associated with stable haemodynamics because of its inability to prevent an increase in HR and blood pressure at and after intubation.

Conflict of Interest

There is no any financial interest or any conflict of interest.

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