Comparison of the Haemodynamic Response to Laryngoscopy and Endotracheal Intubation with Etomidate versus Propofol-Ketamine and Thiopentone-Ketamine in Lumber Spine associated Surgery: A Randomized Interventional Study

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Abstract

Background: Laryngoscopy and endotracheal intubation is commonly used for securing airway during general anaesthesia but it's associated with stress response induced hemodynamic disturbances. We aimed to determine the difference in haemodynamic variables during laryngoscopy and endotracheal intubation with Etomidate versus Propofol-ketamine and thiopentone-ketamine as induction agent in elective lumber spine associated surgery. **Material and Methods:** It was a Prospective randomized comparative interventional study on total 111 patients, aged 25-60 years of either sex with ASA physical status I and II who were randomly allocated into three groups (37in each group). **Group A**: Received inj**.** Etomidate 0.3 mg/kg IV**, Group B** received inj. Propofol 1.5 mg/kg IV + inj. Ketamine 0.5 mg/kg IV**, Group C** received inj. Thiopentone 3 mg/kg + inj. Ketamine 0.5 mg/kg IV; at induction of anaesthaesia. Haemodynamic parameters (SBP, DBP, MAP, and HR) were noted at baseline, after induction, just before intubation, and 1, 3, 5, 10 and 15 min after intubation. Side effects like myoclonus, post-operative nausea and vomiting (PONV) and hallucinations were also noted. Statistical analysis was performed using ANOVA test and chi-square test ($P \leq 0.05$ significant). **Results**: Hemodynamic parameters were increased in all groups after intubation and was minimum in Group B compared to Group A and C at one min post intubation. Myoclonus and PONV were observed more in Group A than Group B and C (statistically nonsignificant in all three groups). **Conclusion**: Propofol-ketamine combination is a safe and effective induction agent with better hemodynamic stability as compared to Etomidate and thiopental-ketamine in general anaesthesia.

Keywords: Myoclonus, Post-Operative Nausea and Vomiting, Hallucination, Airway

Introduction

Securing the airway with laryngoscopy and endotracheal intubation is commonly required to conduct surgery under general anaesthesia. Endotracheal intubation causes a reflex increase in sympathetic activity that may result in hypertension, tachycardia and arrhythmias; if no specific measures are taken to blunt the hemodynamic response to laryngoscopy. Various intravenous anaesthetic agents are used as

induction agents like Etomidate, Thiopentone, Ketamine and Propofol with variable hemodynamic changes during laryngoscopy and intubation, but each drug has its limitations.

Etomidate is a potent, short-acting anaesthetic agent that causes minimal histamine release and provides stable hemodynamics. The common side effects of this drug are pain on injection, excitatory events, and myoclonus.[1] Due to its fast action and short duration of action, propofol is the most common induction agent, but anaesthesia using Propofol as an induction agent leads to hypotension and bradycardia.[2-3] It causes dose-dependent hypotension and respiratory depression.[4] Ketamine is a short-acting induction agent with distinct cardiovascular effects. Unlike many anaesthetics, it stimulates the cardiovascular system, causing an increase in heart rate, blood pressure and cardiac output.[5] Thiopentone is an ultra-short-acting barbiturate that is widely used as an induction agent for general anaesthesia. It causes a dose-dependent decrease in systemic vascular resistance, stroke volume and cardiac output, leading to compensatory tachycardia.[6]

Simultaneous use of two or more induction agents in combination (co-induction) for general anaesthesia has various advantages over mono-induction therapy with few side effects that may be due to balancing of opposing haemodynamic effects. Our study aimed to evaluate and compare hemodynamic changes during induction with Etomidate versus Propofol-Ketamine and Thiopentone-Ketamine to find a suitable combination of drugs having more stable hemodynamic properties with fewer side effects.

Material and Method

This was a hospital-based, prospective, randomized, comparative interventional study conducted after obtaining approval from the institutional review board and ethics committee (257/MC/EC/2019) of SMS Medical College Jaipur from May 2019 to December 2019 and after obtaining informed consent from patients. We enrolled a total of 111 patients (37 in each group), aged 25 to 60 years of either sex, weighing 40–70 kg, with ASA physical status I- II, posted for elective lumber spine surgery under general anaesthesia. Patients with anticipated difficult intubation, allergy to anaesthetic agents used in the study, history of receiving medications that can affect heart rate and blood pressure, history of adrenal insufficiency, asthma, hypertension, psychiatric and endocrine illness were excluded from the study. Pre anaesthesia check-up was done a day prior to surgery in all patients. After explaining the procedure and instructing the patients to stay nil by mouth for 6 hours before surgery, informed consent was obtained. Randomization was done by a computer-generated random number table and the random numbers were kept in sealed envelopes. All outcome variables were objective, so blinding was not required. In the operation theatre, all standard monitors were attached and baseline parameters like SpO_2, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded. Two intravenous lines were secured with 18G/20G cannula and intravenous fluids were started at a rate of 10ml/kg/hour. All patients were pre-medicated with Inj. Ranitidine 50 mg i.v., inj. metoclopramide 10 mg i.v., inj. Glycopyrrolate 4 µg/kg i.v., inj. Midazolam 0.01 mg/kg i.v., and inj. Fentanyl 2 µg/kg i.v. 5 minutes before induction of anaesthesia. All patients were pre-oxygenated with 100% oxygen for 5 minutes. Hemodynamic parameters were noted 5 minutes after premedication (just before injection of the study drug). Study drug was administered according to group allocation, group-A received inj. Etomidate 0.3 mg/kg i.v., group-B received inj. Propofol 1.5 mg/kg + inj. Ketamine 0.5 mg/kg i.v. and group-C received inj. Thiopentone 3 mg/kg+ inj. Ketamine 0.5 mg/kg i.v. After confirmation of bag and mask ventilation, rocuronium (0.9 mg/kg) was given as a muscle relaxant to facilitate endotracheal intubation. Patients were ventilated with 100% oxygen for 90 seconds before performing direct laryngoscopy and oral endotracheal intubation with an appropriate size endotracheal tube. Hemodynamic parameters were noted after induction, just before intubation, and after intubation at 1, 3, 5, 10 and 15 mins. After that, all patients were placed in prone position and surgery was started with aseptic precautions. Anaesthesia was maintained with 60% Nitrous Oxide and 40% Oxygen, 1% Sevoflurane and inj. Atracurium 0.1 mg/kg i.v. and inj. Fentanyl 30 mcg was given to maintain hemodynamic variables within 20% of the baseline value intra-operatively. At the end of the surgery,

patients were reversed with inj. Neostigmine (0.05 mg/kg i.v.) and inj. Glycopyrrolate (0.008 mg/kg i.v.). Extubation was done, when the patient was fully awake and obeying verbal commands. Postoperatively, patients were observed for side effects for one hour.

Statistical analysis: The sample size calculated was 37 in each group at an alpha error of 0.05 and power of 80% to verify the minimum expected difference of 1.50±2.1 mm of Hg in mean diastolic blood pressure of all three groups as per seed article.[7] This sample size is large enough to include all other variables in this study. So, for the study purpose, 37 patients were taken in each of the three groups. SPSS version 21 for Windows statistical software package (SPSS inc., Chicago, Illinois, USA) was used for statistical analysis. Continuous data were summarized in form of Mean ± SD. Difference in mean was analyzed using ANOVA Test. Chi sqaure test was employed for comparison of side effects between the three groups. Levels of significance and α-error were kept at 95% and 5% respectively, for all statistical analysis. Probability (P value) was considered to be statistically significant if P value was ≤0.05.

Results

A total of 111 patients were enrolled in the study and randomly allocated into three groups, as presented in the consort flow chart (Figure 1). All three groups were comparable with respect to demographic and clinical characteristics (age, gender, weight) of patients (table 1).

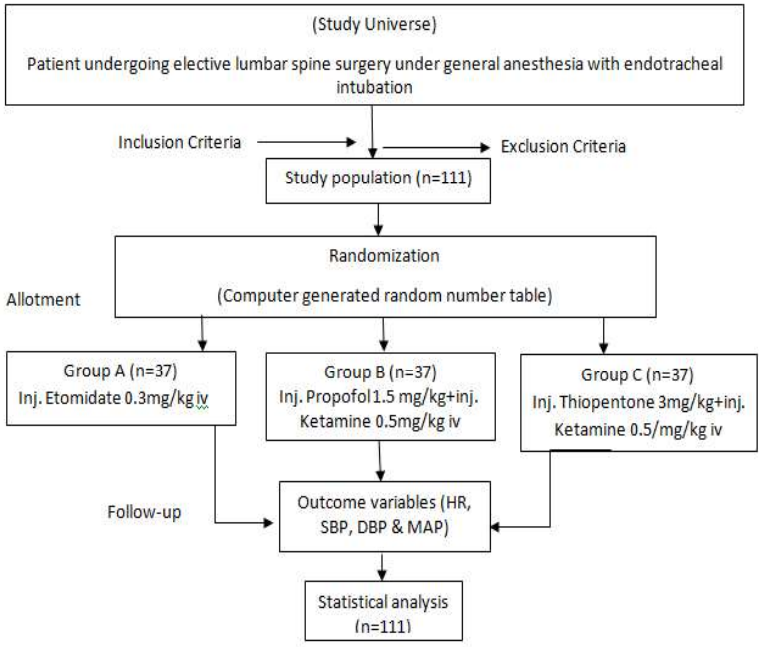

Fig. 1 Consort flow chart

Table 1 Demographic and other characteristics of patients in three groups

Variables	Group A	Group B	Group C	P-value
Age (yr)[a]	42.54±12.13	40.24±12.79	37.32±10.04	0.163
Weight(kg)[b]	62.41±6.72	60.68±5.71	60.11±7.59	0.312
Gender[c]				0.523
Male	26(70.27%)	26(70.27%)	22(59.46%)	
Female	11(29.73%)	11(29.73%)	15(40.54%)	

a, b - ANOVA Test Used, c – Chi-square test used

Figure 2. Comparison of Mean Heart Rate (bpm) at different time intervals among the groups from baseline using ANOVA test

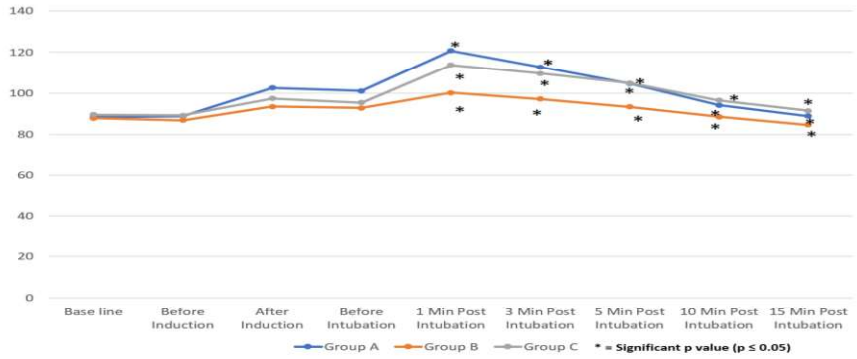

Figure 2.
Comparison of mean heart rate (bpm) at different time intervals among the group from baseline (ANOVA test used)

Figure 3. Comparison of Mean Systolic Blood Pressure at different time intervals among the groups from baseline using ANOVA test

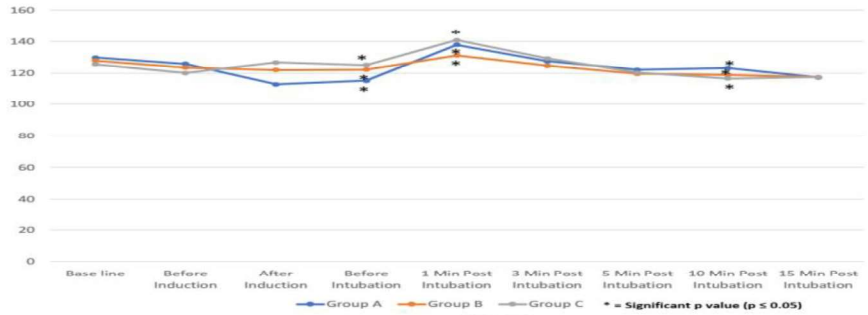

Figure 3.
Comparison of systolic blood pressure (mm of hg) at different time intervals among the groups from baseline (ANOVA test used)

Figure 4. Comparison of Mean Diastolic Blood Pressure at different time intervals among the groups from baseline using ANOVA test

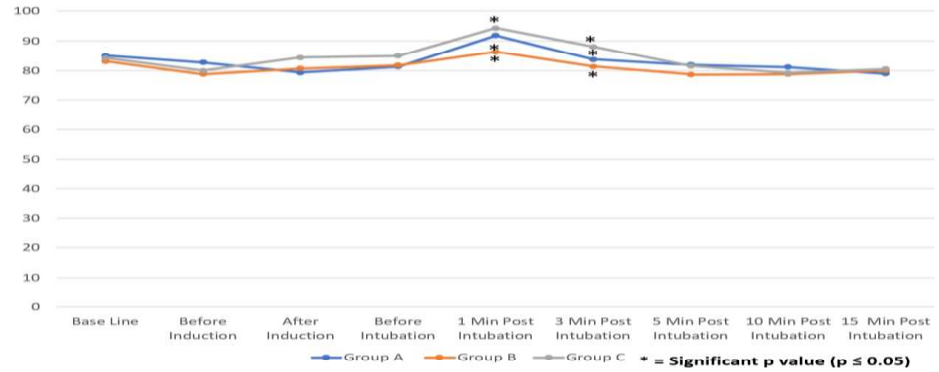

Figure 4.
Comparison of diastolic blood pressure at different time intervals among the groups from baseline (ANOVA test used)

Figure 5. Comparison of Mean Arterial Pressure (MAP) at different time intervals among the groups from baseline using ANOVA test

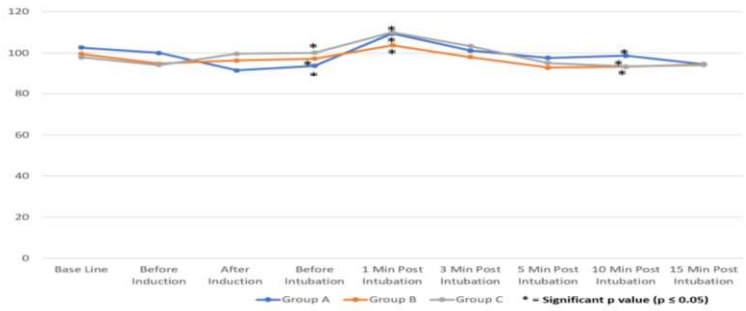

Figure 5.
Comparison of mean arterial pressure (mm of hg) at different time intervals among the groups from baseline (ANOVA test used)

Figs. 2, 3, 4, and 5 depict the comparison and changes in mean heart rate, SBP, DBP and MAP, respectively, at different time intervals among the groups from baseline. Data are Mean & SD.* P ≤0.05 was considered to be statistically significant value.

Baseline haemodynamic parameters were comparable among all three groups, with no statistically significant difference until intubation was observed. At 1 minute post intubation, all three study groups had statistically significant differences in mean SBP, DBP, MAP and HR from baseline. Changes in mean heart rate were significant with differences observed from 1 min to 15 min post intubation in all three groups (fig.2).Changes in Mean SBP and MAP were significant only at 1 min post intubation (fig. 3, 4). Changes in Mean DBP were significant at 1 and 3 min post intubation (fig. 5). Changes in mean of haemodynamic parameters (HR, SBP, DBP and MAP) were significantly lower in Group B as compared to Group A and C at one min post intubation (P<0.001, P<0.009, P<0.002, P<0.022 respectively) . Myoclonus was observed in 3 patients (8.11%) of Group A and 2 patients (5.41%) of Group C. PONV was observed only in 1 patient (2.7 %) of Group A. Hallucinations were observed in 2 patients (5.41%) of Group C. Adverse drug reactions were not observed in Group B. No statistically significant difference with regards to side effects or complications (myoclonus, postoperative nausea and vomiting, hallucination) were found in the study groups.

Discussion

Cardiovascular response to laryngoscopy and endotracheal intubation in the form of hypertension, tachycardia, and arrhythmias has always been a challenge for anaesthesiologist. These effects may prove disastrous in patients who have hypertension, myocardial insufficiency, cerebral haemorrhage or coronary artery disease.[8] There are many factors influencing haemodynamic responses during laryngoscopy and intubation in general anaesthesia. Various drugs and techniques have been used to attenuate this hemodynamic response to laryngoscopy and tracheal intubation.

Currently, various anaesthetic agents have been used in combination for induction of anaesthesia, and these combinations offer separate beneficial sedative, amnestic and hypnotic effects. Considering the opposing effects of propofol and ketamine on hemodynamic parameters, it appears that a combination of these agents can decrease the overall side effects of either agent, and this has also been confirmed in our study.

We compared the effects of Etomidate versus Propofol-Ketamine and Thiopentone-Ketamine on hemodynamic responses to laryngoscopy and endotracheal intubation. Demographic data (Age, Weight, and Gender) among the study groups were comparable and difference observed was statistically non significant in all three study groups. Statistically significant difference was observed in haemodynamic variables (HR, SBP, DBP, MAP) at different time intervals, which was maximum in thiopentone-ketamine and minimum in propofol-ketamine group. This shows that group B (Propofol-Ketamine) was

comparatively better at maintaining hemodynamic stability after induction as compared to group A (Etomidate) and group C (Thiopentone-Ketamine).

Studies conducted by Kelkar VP et al,[9] Singh R et al,[10] and Ramakrishna S et al[11] found that Propofol with ketamine combination was better than Etomidate alone in terms of haemodynamic stability during laryngoscopy and intubation.

Results of our study are comparable with the studies carried by Saleem S et al,[12] Vora KS et al,[13] and Jamuna T et al.[14] They observed that Propofol–ketamine combination was better for hemodynamic stability as compared to Propofol–Thiopentone combination. Our results also coincide with the study by Bardari GA et al[7] showing that the combination of Ketamine-Propofol is an effective and safe induction agent for attenuating hemodynamic response to laryngoscopy and intubation with better hemodynamic stability as compared to Etomidate and Thiopentone-Ketamine combination.

Smischney NJ et al[15] observed that the combination of ketamine and propofol provides better hemodynamic stability during the first 10 minutes after induction as compared to propofol used alone. Similarly, Rim JC et al[16] showed that the combination of Ketamine and Propofol was a better alternative to Propofol in maintaining hemodynamic stability after induction. A study by Habibi MR et al[17] found no difference in haemodynamic variables after induction of anaesthesia and intubation with Etomidate vs. Ketamine-Thiopentone combination. They concluded that the ketamine-thiopentone combination is safe in CABG surgery patients with low ejection fraction during induction of anaesthesia as compared to etomidate alone.

When we observed side effects, it was found that none of the patient in the Propofol-ketamine and Thiopentone-ketamine groups had PONV, whereas only 2% of patients reported PONV in the Etomidate group. A study by Sümer C et al[18] showed that etomidate causes more PONV compared to propofol. It may be attributed to the antiemetic property of propofol, either due to its sedative effect or its property to modulate the subcortical pathway.

The other finding was that 8% of patients in the etomidate group and 5% of patients in the thiopentone-ketamine group developed myoclonus. The incidence of myoclonus in our study was lower as compared to the study conducted by Bardari GA et al.[7] This may be attributed to the use of inj. rocuronium in place of succinylcholine for intubation. In another study, Hwang JY et al[19] showed that midazolam is probably a better choice than remifentanil for reducing etomidate-induced myoclonus during anaesthesia induction because it inhibits subcortical neuronal activity and decreases the incidence of myoclonus. This study supports our findings. With all these studies, the result of our study also showed that the combination of Thiopentone-ketamine is better at maintaining hemodynamic stability as compared to Etomidate, but the combination of Propofol-ketamine resulted in significantly better hemodynamic stability compared to Etomidate and Thiopentone-ketamine combination, with no significant side effects or complications.

Limitation: All patients in three groups received the same premedication with inj. midazolam 0.01 mg/kg and inj. fentanyl 2 µg/kg at a fixed dose according to per kg body weight, which may have been unequally distributed in all groups and could have influenced the hemodynamic parameters. Dosage of these premedication drugs may be a confounding variable.

Conclusion

Propofol-ketamine combination is a safe and effective induction agent with better hemodynamic stability as compared to Etomidate and the combination of thiopental and ketamine in patients undergoing lumber spine surgery in general anaesthesia.

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