

A Comparative Study of Propofol, Etomidate and 50% Admixture of Etomidate and Propofol for Induction in General Anaesthesia.

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Abstract

Prospective randomized double-blind controlled study in which patients was randomized into three groups by using online Research Randomizer software (Research Randomizer (Version 3.0) [Computer software] by computer generated number into three groups of 30 each. We compared groups for hemodynamic parameters and incidence of myoclonus, pain on injection, postoperative nausea vomiting upon induction with intravenous injection of propofol (P), etomidate (E) and 50% admixture of etomidate and propofol (PE). Incidence of myoclonus statistically significant ($P < 0.001$) in group E as compared to Group P, significantly reduced from 76.6% in group E to 6.6% in group PE. Statistically significantly ($P < 0.001$) reduction of incidence of pain on injection in group PE and statistically significant fall in systolic, diastolic blood pressure and mean arterial blood pressure in group P at 1 min after induction. Incidence of myoclonus reduced in Group PE as compared to group E, reduced incidence pain on injection and no fall of systolic, diastolic and mean arterial BP in Group PE as compared to Group P.

Introduction

General anaesthesia is commonly produced by a combination of intravenous drugs and inhaled gases, with the overall aim of ensuring sleep, amnesia, analgesia, relaxation of skeletal muscles, and loss of reflexes of the autonomic nervous system. Etomidate [R-1-(1-ethylphenyl) imidazole-5-ethyl ester] is a carboxylate imidazole-containing compound characterized by haemodynamic stability, minimal respiratory depression and cerebral protective effects [1] Propofol [2, 6-diisopropylphenol] is an alkylated phenol. Propofol decreases blood pressure, cardiac output and systemic vascular resistance due to inhibition of sympathetic vasoconstriction and impairment of baroreceptor reflex regulatory system [2,3]. Etomidate and propofol combination in the ratio of 1:1 can be used for induction in general anesthesia. Combination of etomidate with propofol would decrease the required dose of both the medications. The combination also provide the benefits of both agents including more stable hemodynamic. Etomidate + propofol is effective in maintaining

hemodynamic stability and preventing hemodynamic changes that occur due to propofol administration. The use of etomidate and propofol 1:1 admixture for induction of anaesthesia is associated with no injection pain, very low rate of myoclonus and significantly faster induction time compared to propofol and etomidate along with hemodynamic stability.

Materials and Methods

Study Design

After ethical committee approval of the hospital, single center comparative, prospective randomized double blind controlled study was conducted to compare the effects of induction agent propofol, etomidate and 50% admixture of etomidate and propofol on hemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation and there side effect such as pain on injection, myoclonus and post operative nausea and vomiting.

Study Area

This study was conducted in an 1100 bedded tertiary care super specialty teaching hospital between April 2014 and September 2015.

Study Population

The study was conducted on 90 patients of ASA physical

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status I and II in the age group of 18 years to 60 years, of either sex, posted for elective surgery under general anaesthesia.

Sample Size

Sample size was calculated keeping in view at most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). After considering which the past data, which gives idea of variation in variable, play important role in calculating the sample size. Sample size should be 30 in each group for safer side and normality of the data. The groups received the drugs as follows:

- Group “P”** – Propofol 2.5 mg/kg
Group “E” – Etomidate 0.3mg/kg
Group “PE” – 50% admixture of etomidate (0.2mg/kg) and propofol (1mg/kg)

Inclusion Criteria

1. Patients aged 18 to 60 years of either sex scheduled for elective surgeries.
2. Physical Status American Society of Anaesthesiologist (ASA) I and II

Exclusion Criteria

- 1.) ASA grade >II
- 2.) Age less than 18 years and more than 60 years
- 3.) Patient with seizure disorder
- 4.) Presence of known primary and secondary adrenal insufficiency or on any steroid medication
- 5.) Pregnancy.
- 6.) Cardiac surgery
- 7.) Neurosurgery
- 8.) Thoracic surgery
- 9.) Renal dysfunction
- 10.) Hepatic disease
- 11.) Known allergy to study drugs

Methodology

This study was conducted at a tertiary care service hospital between Apr 2014 and Sep 2015. During this period 90 patients of ASA physical status I and II in the age group of 18 years to 60 years, of either sex, posted for elective surgery under general anaesthesia were recruited in the study after obtaining written informed consent to assess the haemodynamic responses before and after tracheal intubation following induction of anaesthesia with all the study induction agent.

Pre-operative

All patients will be kept fasting overnight. All standard ASA monitoring like ECG, NIBP, HR, RR, SPO₂ were attached and all basal parameters were recorded. Intravenous line was secured. Patients was premedicated with injection Glycopyrrolate 0.2 mg I.V, injection Ondansetron 4 mg I.V, injection Fentanyl 1 microgram/kg body weight.

Peri-operative

In each group patients was induced with respective drugs. Heart rate, % of oxygen saturation (SpO₂), blood pressure, subjective pain on injection will follow during induction, myoclonus will be recorded as per myoclonus grading during induction. Subjective Pain on injection will be recording as per pain grading scale

- Grade 0** No pain communicated
Grade 1 Complains of pain
Grade 2 Withdrawal to pain
Grade 3 Both verbal complain and withdrawal of arm

Myoclonus was recorded as per myoclonus scale:

	Severity	Sign
Grade 0	No	No Myoclonus
Grade 1	Minor	Exhibit jerks of one or both hands and feet
Grade 2	Moderate	Exhibit jerks of one or both arms or leg.
Grade 3	Severe	Hypertonia of neck or trunk

To ensure blinding, anaesthesia was induced by an anaesthesiologist who didn't involve in the study.

- Group “P”** – Propofol 2.5 mg/kg
Group “E” – Etomidate 0.3mg/kg
Group “PE”– 50% admixture of etomidate and propofol

Tracheal intubation was facilitated by using injection Vecuronium 0.1 mg/kg and General anaesthesia was maintained with O₂, N₂O and sevoflurane. Monitoring of heart rate, blood pressure (systolic, diastolic, MAP) and oxygen saturation would be done baseline and at 1min after the study drug, 1 min after intubation and then 3,5,10,20,30,40 min after intubation at the end of surgery. Residual neuromuscular blockade was reversed with injection Neostigmine 0.05mg/kg and injection Glycopyrrolate 0.008mg/kg. Patient were extubated after adequate recovery of muscle power and patient will be

monitored post operatively for nausea and vomiting as per verbal rating scale (VRS).

For Nausea

	Severity
Grade 0	No
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe

For Vomiting

Severity	Episodes
Nil	0
Mild	1
Moderate	2 /3

Statistical Analysis

The data was analyzed using Statistical Package for Social Science (SPSS version 16.0). Sample size was calculated keeping in view at most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). After considering which the past data, which gives idea of variation in variable, play important role in calculating the sample size. Sample size should be 30 in each group for safer side and normality of the data.

Data was expressed as means, standard deviation (S.D), medians, frequency and percentages. Categorical data are described as number of patient (n) and compared using oneway analysis. Physical characteristics, SBP, DBP,MAP, HR values, all time intervals are compared using ANOVA, was followed by suitable post hoc test for multiple comparison(Tukey HSD). All differences were considered significant at $P < 0.05$.

Results

There were no significant differences among patients in all three groups regarding age, sex, weight, ASA physical status.

Incidence of myoclonus in group E is 76.6% as compared to 6.6% mild grade of myoclonus in group PE and nil in group P.

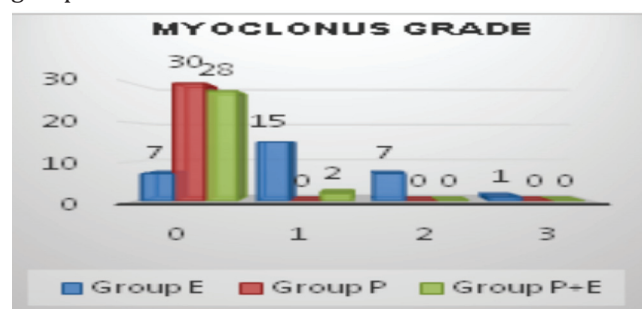
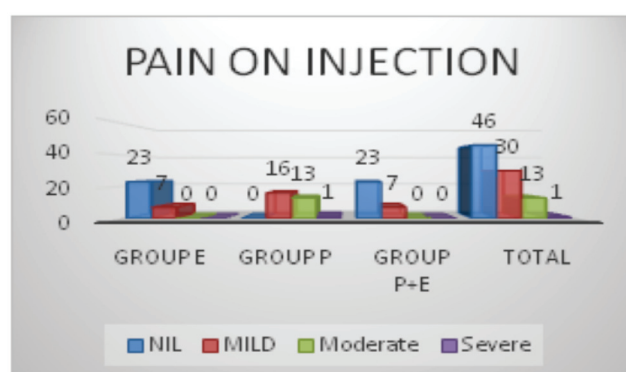


Fig. 1: Incidence of myoclonus between groups

Myoclonus Grade	Group E	Group P	Group P+E	Total
0	7	30	28	65
1	15	0	2	17
2	7	0	0	7
3	1	0	0	1
Total	30	30	30	90

Pearson Chi-Square 54.396 p-value <0.001

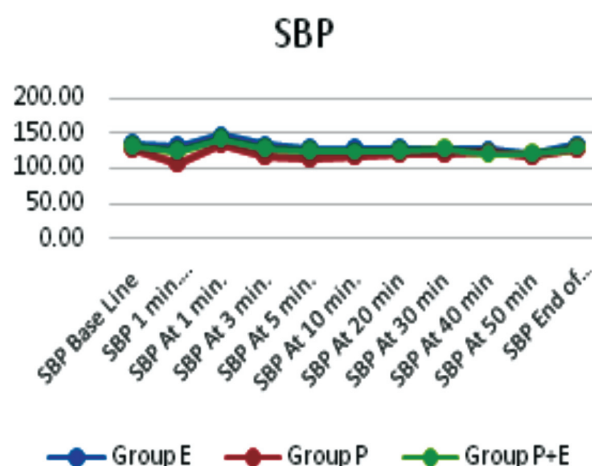
Reduction of incidence of pain on injection Statistically significantly ($p < 0.001$) in group PE in comparison to group P.



Pain on Injection	Group E	Group P	Group P+E	Total
Nil	23	0	23	46
Mild	7	16	7	30
Moderate	0	13	0	13
Severe	0	1	0	1
Total	30	30	30	90

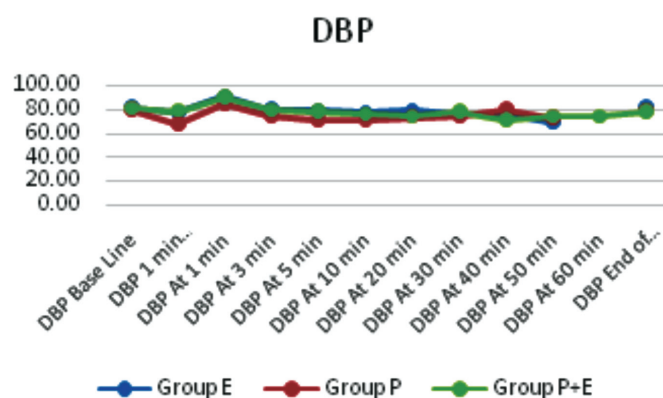
Pearson Chi-Square: 56.4 p-value: <0.001

There was significant decrease in SBP, MAP, DBP from baseline in Group P after induction dose as comparison to Group E and Group PE.

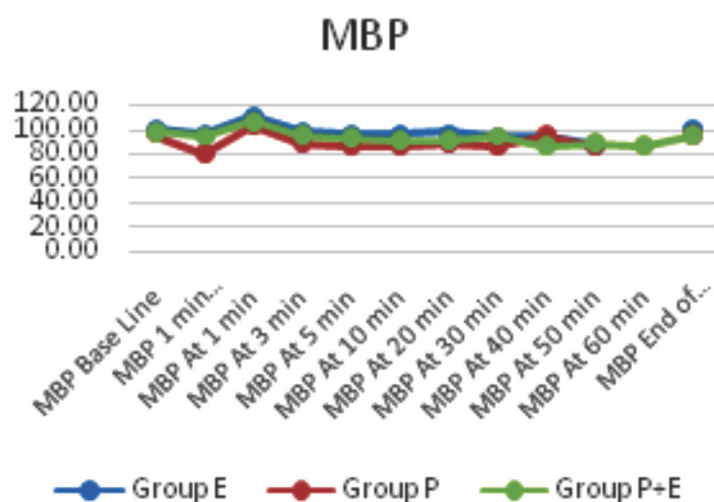


		Mean	Std. Deviation	F-value	p-value	Multiple comparisons	p-value
SBP Base Line	Group E	136.23	11.50	3.651	0.03	Group E vs P	0.023
	Group P	128.10	10.98			Group E vs P+E	0.44
	Group P+E	132.53	12.49			Group P vs P+E	0.31
	Total	132.29	12.02				
SBP 1 min. after study drug	Group E	132.53	11.78	38.031	<0.001	Group E vs P	<0.001
	Group P	107.67	10.41			Group E vs P+E	0.058
	Group P+E	125.70	11.98			Group P vs P+E	<0.001
	Total	121.97	15.44				
SBP At 1 min.	Group E	148.40	12.02	7.402	0.001	Group E vs P	0.001
	Group P	135.77	13.25			Group E vs P+E	0.218
	Group P+E	142.87	12.94			Group P vs P+E	0.085
	Total	142.34	13.64				
SBP At 3 min.	Group E	133.40	13.07	9.369	<0.001	Group E vs P	<0.001
	Group P	118.30	13.08			Group E vs P+E	0.47
	Group P+E	129.17	15.52			Group P vs P+E	0.009
	Total	126.96	15.19				

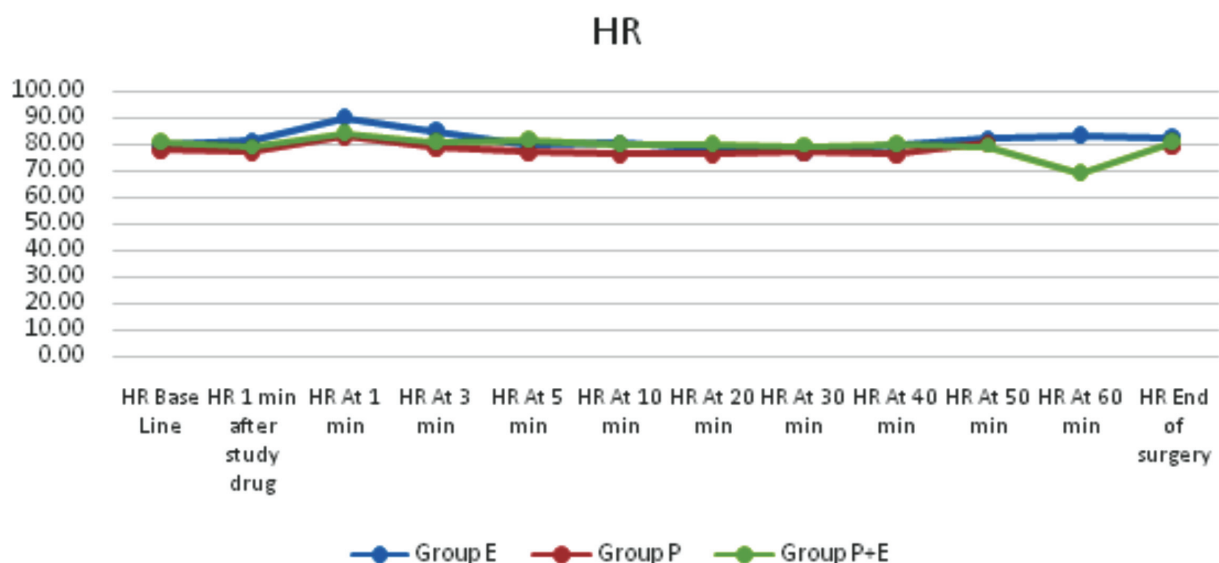
		Mean	Std. Deviation	F-value	p-value	Multiple comparisons	p-value
DBP Base Line	Group E	81.77	7.54	0.217	0.805	Group E vs P	0.791
	Group P	80.20	11.47			Group E vs P+E	0.914
	Group P+E	80.80	8.39			Group P vs P+E	0.966
	Total	80.92	9.20				
DBP 1 min after study drug	Group E	77.97	10.45	9.2	<0.001	Group E vs P	0.002
	Group P	67.97	12.60			Group E vs P+E	0.956
	Group P+E	78.77	9.29			Group P vs P+E	0.001
	Total	74.90	11.83				
DBP At 1 min	Group E	91.07	11.11	2.581	0.081	Group E vs P	0.099
	Group P	85.03	11.52			Group E vs P+E	0.962
	Group P+E	90.30	10.96			Group P vs P+E	0.169
	Total	88.80	11.40				
DBP At 3 min	Group E	80.30	9.26	1.723	0.185	Group E vs P	0.178
	Group P	74.83	12.95			Group E vs P+E	0.88
	Group P+E	78.83	12.84			Group P vs P+E	0.392
	Total	77.99	11.90				



		Mean	Std. Deviation	F-value	p-value	Multiple comparisons	p-value
MBP Base Line	Group E	99.77	7.08	1.312	0.274	Group E vs P	0.249
	Group P	96.17	10.31			Group E vs P+E	0.816
	Group P+E	98.40	8.37			Group P vs P+E	0.582
	Total	98.11	8.72				
MBP 1 min after study drug	Group E	96.07	9.79	24.452	<0.001	Group E vs P	<0.001
	Group P	80.60	9.26			Group E vs P+E	0.85
	Group P+E	94.73	9.42			Group P vs P+E	<0.001
	Total	90.47	11.73				
MBP At 1 min	Group E	110.60	9.90	2.949	0.058	Group E vs P	0.045
	Group P	103.57	12.44			Group E vs P+E	0.412
	Group P+E	106.90	11.18			Group P vs P+E	0.486
	Total	107.02	11.46				
MBP At 3 min	Group E	98.10	9.07	4.9	0.01	Group E vs P	0.01
	Group P	89.23	12.35			Group E vs P+E	0.737
	Group P+E	95.90	12.52			Group P vs P+E	0.067
	Total	94.41	11.91				



		Mean	Std. Deviation	F-value	p-value	Multiple comparisons	p-value
HR Base Line	Group E	79.90	10.80	0.553	0.577	Group E vs P	0.829
	Group P	78.43	9.00			Group E vs P+E	0.888
	Group P+E	81.07	9.25			Group P vs P+E	0.548
	Total	79.80	9.67				
HR 1 min after study drug	Group E	81.40	12.95	1.064	0.349	Group E vs P	0.32
	Group P	77.23	9.14			Group E vs P+E	0.667
	Group P+E	78.93	10.95			Group P vs P+E	0.825
	Total	79.19	11.13				
HR At 1 min	Group E	90.10	15.45	2.234	0.113	Group E vs P	0.126
	Group P	83.37	11.52			Group E vs P+E	0.231
	Group P+E	84.47	12.42			Group P vs P+E	0.945
	Total	85.98	13.42				
HR At 3 min	Group E	85.07	14.35	2.354	0.101	Group E vs P	0.091
	Group P	78.80	9.45			Group E vs P+E	0.317
	Group P+E	80.77	9.87			Group P vs P+E	0.784
	Total	81.54	11.61				
HR At 5 min	Group E	80.13	14.08	1.179	0.313	Group E vs P	0.642
	Group P	77.60	8.35			Group E vs P+E	0.805
	Group P+E	81.90	9.43			Group P vs P+E	0.283
	Total	79.88	10.93				



In all groups the pre-induction heart rate was comparable and was statistically insignificant in inter groups ($P > 0.05$). Mean pre -induction heart rate in group E, P and PE were 79.9/min, 78.4/min and 81.0/min respectively. Mean Heart rate after 1 min of giving study drug, 1min, 3min and 5 min after intubation were as 81.4/min, 90.10/min, 85.07/min and 80.13/min respectively in group E, 77.23/min, 83.37/min, 78.80/min and 77.6/min respectively in group P and 78.93/min, 84.37/min, 80.77/min and 81.9/min respectively in group PE. There was increase in mean heart rate in group E and decrease in both group P and PE with no significant difference. Then throughout the procedure heart rate remained near stable in all three groups.

Discussion

Propofol and etomidate are two commonly used intravenous induction agents. Hypotension is known to occur with propofol induction due to reduction of sympathetic activity causing vasodilatation [4]. The haemodynamic stability observed with etomidate may be due partly to its unique lack of effect on the sympathetic nervous system and on baroreceptor function [1]. This study was carried out to compare etomidate, propofol and 50% admixture of etomidate and propofol on the haemodynamic responses prior and following tracheal intubation.

Fatma S. et al. [5] compared etomidate, propofol and admixture of etomidate and propofol as induction agent and noted hemodynamic stability and side effects with each agent and admixture. They concluded that mean and systolic blood pressures were significantly decreased in propofol group compared to etomidate and etofol group. The incidence of injection pain was significantly lower in Etofol group, no injection pain in group PE higher incidence of myoclonic activity was seen in etomidate group compared with propofol and etofol groups. In our study pain on injection with admixture group is significantly lower than propofol and etomidate group and incidence of myoclonus and hemodynamic parameters are consistent with above study.

Hashaam B G et al. [6] compared hemodynamic stability with etomidate and propofol induction in LMA insertion and concluded no statistically significant difference heart rate between the two groups. In our study no significant difference in heart rate in all group, Hosseienzadeh H. et al. [7] compared hemodynamic changes following Induction with Propofol, Etomidate and Propofol + Etomidate for LMA Insertion. They concluded systolic blood pressure, MAP are significantly low in Group P as compared to Group P+E and Group E. Shivaprakash S. et al. [8] compared hemodynamic effects of propofol and

etomidate as induction agent in coronary artery surgery. MAP reduced by 30% in group P ($p < 0.001$) and 22% in group E ($p < 0.001$), our results are comparable. Supriya Aggarwal et al. [9] compared induction with propofol and etomidate. Decrease in MAP and increase in heart rate was more from baseline in propofol group than etomidate group at induction ($p > 0.05$) and concluded etomidate is better with hemodynamic stability over propofol along with less incidence of pain on injection high incidence of myoclonus. Yogesh Kumar [10] compared etomidate and propofol in patients under general anaesthesia shows etomidate is better induction than propofol in hemodynamic stability and less pain on injection. Kavita Meena [11] compared propofol, etomidate and etomidate plus propofol and concluded combination is better than hemodynamic stability etomidate and propofol alone. In our study we found that induction with admixture of propofol, etomidate and etomidate is more hemodynamic stability than propofol and other side effects of propofol and etomidate is reduced in admixture of etomidate and propofol group.

Conclusion

We conclude the admixture (50%) of etomidate and propofol used as a induction agent in general anaesthesia reduced the side effects of both the drugs such as pain on injection in propofol group and post operative nausea vomiting and myoclonus in etomidate group.

Admixture (50%) of propofol and etomidate is also safe for use as induction agent as it provide better hemodynamic stability.

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Guarantor:	Dr. Amit Sharma will act as guarantor of this article on behalf of all co-authors.

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