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Clinical Analysis of Propofol, Etomidate and an Admixture of Etomidate and Propofol for Induction of General Anaesthesia

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Abstract

Objective: To compare the clinical outcome following induction of general anaesthesia with intravenous (IV) injection of propofol (P), etomidate (E) or a 50% admixture of propofol and etomidate (PE).

Methods: In this prospective, randomised, double-blind controlled study, patients 18–60 years of age who were undergoing elective surgery with general anaesthesia were randomised to receive either propofol 2.5 mg kg^{-1} IV (group P; n=30), etomidate 0.3 mg kg^{-1} IV (group E; n=30) or an admixture of etomidate 0.2 mg kg^{-1} IV and propofol 1 mg kg^{-1} IV (group PE; n=30) as the induction agent. The haemodynamic response was first recorded at baseline, then at 1 minute following administration the study drug, and 1, 3, 5, 10, 20, 30 and 40 minutes following intubation. Perioperative symptoms such as myoclonus, pain upon injection and/or vomiting upon induction as well as postoperative nausea were recorded.

Results: We observed a decrease in systemic haemodynamics from baseline following induction in group P compared to groups E and PE ($p<0.05$). Incidence of myoclonus was reduced from 76.6% in group E to 6.6% in group PE ($p<0.001$). There was also a reduction in reported pain upon injection in group PE compared to group P ($p<0.001$). Although we found no statistically significant difference between the three groups when assessing postoperative nausea and vomiting, these symptoms were more prevalent in groups E and PE than in group P.

Conclusion: Using an admixture of etomidate and propofol as the induction agent reduced the incidence of side effects observed with use of either drug alone such as pain upon injection, myoclonus and haemodynamic instability.

Keywords: Etomidate, haemodynamic, propofol

Introduction

Since the establishment of induction agents for general anaesthesia (GA), no flawless induction agent has yet been produced in terms of providing haemodynamic stability during endotracheal intubation. GA is accomplished by administering 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 is a carboxylate imidazole-containing compound known to support haemodynamic stability with minimal respiratory depression, and has also been shown to have cerebral protective effects; making it a drug of choice in haemodynamically unstable patients. Some side effects associated with etomidate include nausea and vomiting, burning sensation upon IV Injection, thrombophlebitis, myoclonus and suppression of steroid production (1, 2). Propofol is an alkylated phenol provides faster onset of action, potent attenuation of airway reflexes, adequate depth of anaesthesia during intubation, anti-emesis and rapid recovery (1). Additional drawbacks associated with the use of propofol are

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dose dependent depression of ventilation, hypotension and pain upon injection (3).

The combination of etomidate and propofol combination in a 1:1 ratio can be used for induction of GA. In the past, many studies have compared both induction agents individually, but very few studies assessed the use of propofol and etomidate (PE) in combination. Combining PE would not only decrease the required dose of either medication and provide the known benefits of both agents, it may prevent the haemodynamic changes that occur due to propofol administration alone. We hypothesise that use of 1:1 admixture of PE will be associated with reduced injection pain, a very low rate of myoclonus as well as increased haemodynamic stability compared to the use of propofol or etomidate alone.

Methods

This study was conducted in an 1100 bed tertiary care super specialty hospital in India. Following approval from the Institutional Ethics Committee, written informed consent was obtained from the patients prior to their procedures. Out of 1206 patients admitted for GA in the operation theatre during the study period (April 2014 to September 2015), a total of 90 patients of ASA physical status I and II, in the age group of 18-60 years, of either sex, who were scheduled for elective surgery under GA were enrolled for this prospective, randomised double blind study. Patients with a history of cardio-respiratory disorders, renal dysfunction, hepatic disease, seizure disorder, adrenal insufficiency or who were pregnant at the time were excluded from the study. Patients on any steroid medication or with a known allergy to study drugs were also excluded from the study. Of the excluded patients, 1105 patients did not meet the inclusion criteria and 11 were omitted due to unavailability of investigator.

According to a computer-generated randomisation chart, the patients were assigned to one of the three treatment groups. To ensure blinding, anaesthesia was induced by an anaesthesiologist not involved in the study. Patients in group P received propofol 2.5 mg kg^{-1} IV, patients in group E received etomidate 0.3 mg kg^{-1} IV, and patients in group PE received an admixture of etomidate 0.2 mg kg^{-1} IV and propofol 1 mg kg^{-1} IV as the induction agent. Each test drug was prepared blind in a 20 mL syringe and labelled as 'TEST DRUG' and administered by a nurse who was also blinded to group assignments. Vitals were recorded by a treating clinician who was also blinded to group assignments. All standard ASA monitors were attached and all basal parameters were recorded. The intravenous line was secured as standard with a 20 gauge cannula on the dorsum of the hand. Patients were premedicated with injections of glycopyrrolate 0.2 mg IV and fentanyl 1 µ kg^{-1} IV. Tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1} IV and GA was maintained with O_2, N_2O and sevoflurane. Subjective pain and myoclonus assessment will follow during induction as per grading scale. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and oxygen saturation (SpO_2) were measured at baseline and 1 minute following injection of the study drug, then 1, 3, 5, 10, 20, 30 and 40 minutes following intubation. All patients were given ondansetron 0.15 mg kg^{-1} IV 30 min prior to extubation. Residual neuromuscular blockade was reversed with neostigmine 0.05 mg kg^{-1} IV and glycopyrrolate 0.008 mg kg^{-1} IV. Patients were extubated following adequate recovery of muscle control and were closely monitored post operatively for nausea and vomiting as per verbal rating scale.

For assessment of pain during induction, patients were subjectively assessed on a 4-point grading scale (0=no pain communicated, 1=complains of pain, 2=withdrawal to pain, 3=both verbal complaint and withdrawal of arm). Myoclonus was recorded as per 4-point of myoclonus grading scale (0=no myoclonus, 1=exhibit jerks of one or both hands and feet, 2=exhibit jerks of one or both arms or leg, 3=hypertonia of neck or trunk). Postoperative nausea was recorded as grade 0, 1, 2 and 3 as no, mild, moderate and severe nausea, respectively. Postoperative vomiting was subjectively assessed on a moderate (1 episode) and severe (2 or 3 episodes) grade scale.

Statistical analysis

The data was analysed using Statistical Package for Social Science version 16.0 (SPSS Inc.; Chicago, IL, USA). Sample size was calculated keeping in view at most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). In calculating desired sample size, we considered past data, which gave us an idea of expected variation. We determined that sample size should be 30 in each group for appropriate reproducibility and interpretation of the data. Data was expressed as means, standard deviation, medians, frequency and percentages. Categorical data are described as number of patients (n) and compared using one-way analysis. Physical characteristics, SBP, DBP, MBP, HR values and all time intervals are compared using one way ANOVA, followed by suitable post-hoc test for multiple comparisons (Tukey HSD). All differences were considered significant at $p<0.05$.

Results

Demographic parameters and clinical characteristics were comparable between the groups, although a majority of the patients were females under the age of thirty. Most of patients were in ASA grade I (Table 1).

The baseline haemodynamic (HR, MBP) parameters were normal and comparable between the groups (Table 2). We ob-

Table 1. Demographic profile and baseline clinical characteristics of patients in groups

Baseline characteristics	Group P (n=30)	Group E (n=30)	Group PE (n=30)	p
Age (years)	41.2±10.4	38.8±10.8	42.5±11.2	0.75
Gender (male/female)	7/23	9/21	11/19	0.53
ASA I/II	25/5	17/13	20/10	0.07
Body weight (kgs)	60.2±6.8	59.3±8.2	62.9±7.6	0.63

P: propofol; E: etomidate; PE: propofol and etomidate; ASA: American society of anaesthesiology

Table 2. Systemic haemodynamic parameters (values expressed as mean±SD or number) at various time points in groups

	Group	Mean±SD	F-value	p	Multiple comparisons	p
MBP Baseline	E	99.7±7	1.31	0.27	E vs. P	0.25
	P	96.2±10.3			E vs. PE	0.81
	PE	98.4±8.4			P vs. PE	0.58
MBP 1 min after study drug	E	96±9.8	24.45	0.001	E vs. P	0.001
	P	80.6±9.3			E vs. PE	0.85
	PE	94.7±9.4			P vs. PE	0.001
MBP At 1 min	E	110.6±10	2.94	0.05	E vs. P	0.04
	P	103.5±12.5			E vs. PE	0.41
	PE	106±11.2			P vs. PE	0.48
MBP At 3 min	E	98±9	4.9	0.01	E vs. P	0.01
	P	89.2±12.3			E vs. PE	0.73
	PE	95.9±12.5			P vs. PE	0.06
MBP At 5 min	E	96.3±11.3	6.75	0.002	E vs. P	0.002
	P	86.4±11.2			E vs. PE	0.57
	PE	93.5±9.7			P vs. PE	0.032
HR Baseline	E	79.9±10.8	0.55	0.57	E vs. P	0.83
	P	78.4±9			E vs. PE	0.88
	PE	81±9.2			P vs. PE	0.54
HR 1 min after study drug	E	81.4±13	1.06	0.35	E vs. P	0.32
	P	77.2±9			E vs. PE	0.66
	PE	78.9±11			P vs. PE	0.82
HR At 1 min	E	90.1±15.4	2.23	0.11	E vs. P	0.12
	P	83.4±11.5			E vs. PE	0.23
	PE	84.4±12.4			P vs. PE	0.94
HR At 3 min	E	85±14.3	2.35	0.10	E vs. P	0.09
	P	78.8±9.4			E vs. PE	0.31
	PE	80.7±10			P vs. PE	0.78
HR At 5 min	E	80.1±14	1.17	0.31	E vs. P	0.64
	P	77.6±8.3			E vs. PE	0.80
	PE	81±9.4			P vs. PE	0.28

P: propofol; E: etomidate; PE: propofol and etomidate; MBP: mean arterial pressure; HR: heart rate; SD: standard deviation

served an increase in HR in group E and decrease in groups P and PE at 1 min following administration of the study drug. Throughout the procedures, patient HR remained near stable in all three groups. There was a significant decrease in MBP from baseline in group P after induction dose as compared to groups E and PE (Figure 1). There was no significant fall in SBP or MBP in groups E and PE. There was a significant decrease in DBP from baseline in group P following induction dose as compared to groups E and PE, but no statistical difference following tracheal intubation. Comparison of baseline

Table 3. Myoclonus, pain upon injection and incidence of nausea and vomiting grades (values expressed as mean±SD or number) at various time points in the groups

		Group P	Group E	Group PE	Pearson Chi-Square	p
Myoclonus Grade	0	30	07	28	54.39	0.001
	1	0	15	02		
	2	0	07	00		
	3	0	01	00		
Pain on injection	Nil	0	23	23	56.4	0.001
	Mild	16	7	7		
	Moderate	13	0	0		
	Severe	1	0	0		
Nausea	Nil	23	16	21	5.86	0.21
	Mild	5	13	7		
	Moderate	2	1	2		
Vomiting	Nil	23	16	21	5.86	0.21
	Mild	5	13	7		
	Moderate	2	1	2		

P: propofol; E: etomidate; PE: propofol and etomidate

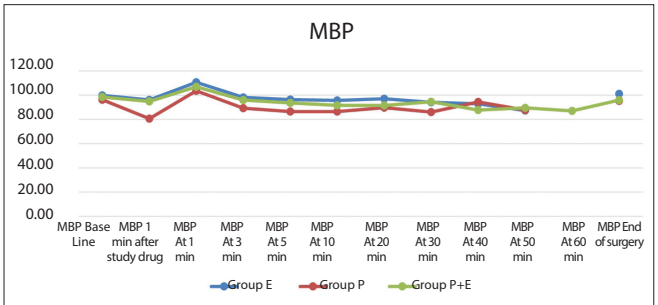

Figure 1. Comparison of mean arterial blood pressure between the groups
P: propofol; E: etomidate; PE: propofol and etomidate; MBP: mean arterial pressure

vs end of surgery haemodynamic parameters was normal within every group (Table 2).

Incidence of myoclonus was reduced from 76.6% in group E to 6.6% in group PE ($p<0.001$) (Table 3). There was also a reduction in incidence of pain upon injection in group PE compared to group P ($p<0.001$) (Table 3). There was no significant difference between all three groups for postoperative nausea and vomiting, but incidence was higher in groups E and PE than P (Table 3). SpO_2 was 100% throughout the study period in all 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 a 50% admixture of etomidate and propofol on the haemodynamic responses prior to, and following, tracheal intubation.

Fatma et al. (5) compared etomidate, propofol and an admixture of etomidate and propofol (PE) as induction agents and noted haemodynamic stability and side effects with each agent and admixture. They concluded that mean and SBP were significantly decreased in the propofol group compared to the etomidate and PE groups. The incidence of injection pain was significantly lower in the PE group, although higher incidence of myoclonus activity was seen in etomidate group compared with propofol and PE groups. In our study, pain upon injection with the admixture group was significantly lower than PE alone, and the incidence of myoclonus and changes in haemodynamic parameters were consistent with above study.

Ghafoor et al. (6) compared haemodynamic stability with etomidate or propofol induction in laryngeal mask airway (LMA) insertion and concluded no statistically significant difference in HR between the two groups. In our study, no significant difference was observed in HR rate between any group. Hosseinzadeh et al. (7) compared haemodynamic changes following induction with propofol, etomidate or propofol+etomidate (PE)

for LMA Insertion .They concluded SBP, MBP were significantly low in the propofol group as compared to the etomidate or PE groups. Shivaprakash et al. (8) compared haemodynamic effects of PE as induction agents in coronary artery surgery. In this study, MBP was reduced by 30% in the propofol group ($p<0.001$) and 22% in the etomidate group ($p<0.001$) which is comparable to our results. Supriya et al. (9) compared induction with propofol or etomidate. They observed a decrease in MBP and increase in HR from baseline in the propofol group compared to the etomidate group at induction ($p>0.05$), and concluded that etomidate had better haemodynamic stability over propofol along with less incidence of pain upon injection, but with a high incidence of myoclonus. Kumar (10) compared etomidate and propofol in patients under GA and observed that etomidate was better for induction than propofol in regards to haemodynamic stability and resulted in less pain upon injection. Kavita et al. (11) also compared propofol, etomidate and etomidate plus propofol and concluded that the combination results in better haemodynamic stability than etomidate or propofol alone. In our study, we found that induction with an admixture of PE was associated with greater haemodynamic stability than Propofol alone, and that the side effects of PE were reduced in admixture of PE group.

Conclusion

We conclude that an admixture of etomidate and propofol used as an induction agent for GA reduced the side effects of both the drugs such as pain upon injection and myoclonus, and was also found to ensure better haemodynamic stability.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institutional Ethics Committee Base Hospital Delhi Cantt (Date: 01.02.2016).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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