HAEMODYNAMIC EFFECTS OF ETOMIDATE AND PROPOFOL ON INDUCTION OF GENERAL ANAESTHESIA AND ENDOTRACHEAL INTUBATION- A CLINICAL COMPARISON

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ABSTRACT

BACKGROUND

An ideal induction agent for general anaesthesia should have haemodynamic stability, minimal respiratory side effects and rapid clearance. Sudden hypotension has a deleterious effects on maintaining the circulation to vital organs. Presently, etomidate and propofol are popular rapid acting inducing agents. Hence, this study was conducted to compare the haemodynamic effects of etomidate and propofol.

MATERIALS AND METHODS

Double-blind randomised study was conducted on sixty patients after informed consent comprising of thirty patients each (Group E for etomidate and group P for propofol). Patients were premedicated with Inj. Glycopyrrolate 0.2 mg IV, Inj. Butorphanol 0.03 mg/kg IV, Inj. Midazolam 0.3 mg/kg IV followed by etomidate 0.3 mg/kg given slowly over 45 seconds in the group E and propofol 2 mg/kg for induction of anaesthesia in the group P. Heart rate and blood pressure were measured before induction and every minute for 3 minute after induction.

RESULTS

When compared to etomidate group, there was a significant fall in blood pressure in propofol group. There was no significant change in hearts rate in all three groups.

CONCLUSION

When etomidate is used as an induction agent during general anaesthesia, there is a better haemodynamic stability in comparison to propofol.

KEYWORDS

Etomidate, Propofol, General Anaesthesia, Haemodynamic Effects.

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BACKGROUND

Since the successful demonstration of painless surgery by using Ether in 1946, anaesthesia traditionally has been all about using various inhalational agents to make the patient unconscious and pain-free to facilitate surgery. Exhalation being the primary mode of reversal of anaesthesia with these gaseous agents, concerns have been raised regarding the contribution of the inhalational anaesthetic agents towards global warming, depletion of the ozone layer of the atmosphere as well as the effects of waste anaesthetic gases on the health of anaesthesiologists and other persons working in the operation theatre.

Way back in 1656, Percival Wren and Daniel Major had explored the possibility of anaesthetising by injecting wine and ale intravenously to a dog. Despite many other experiments since with different drugs, introduction of thiopentone in 1936 started the trend of intravenous anaesthesia.

Regardless of the mode of administration and the agents used to provide anaesthesia, maintenance of the cardiovascular status within physiological limits has always been a problem. Newer drugs and modalities are always being explored to overcome this challenge. Presently, etomidate and propofol are two popular rapid acting intravenous drugs being used to provide general anaesthesia.

Etomidate was introduced in clinical practice in 1972. A carboxylate imidazole-containing compound, etomidate is

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characterised by haemodynamic stability, minimal respiratory depression and cerebral protective effects.[1] Its lack of effect on sympathetic nervous system, baroreceptor reflex regulatory system[1,2] and its effect of increased coronary perfusion even on patients with moderate cardiac dysfunction makes it an induction agent of choice. Use of etomidate declined due to reports of adrenocortical suppression and other minor side effects like pain on injection, myoclonus and postoperative nausea and vomiting.[3] Rediscovery of beneficial effect of etomidate and lack of new reports of adrenocortical suppression has led to renewal of interest for this agent.[4]

Propofol was introduced as an induction agent in 1977. Chemically, it is 2, 6 diisopropylphenol compound. Propofol decreases blood pressure, cardiac output and systemic vascular resistance[5,6] by inhibiting sympathetic vasoconstriction and impairing the baroreceptor reflex regulatory system.[1,7] In hypovolaemic and elderly patients with compromised left ventricular function due to coronary artery disease, this might get exaggerated. Propofol also causes dose-dependent depression of ventilation.

This study was an attempt to compare haemodynamic properties of both these drugs to help choose a safe induction agent. The parameters studied here were pulse rate and blood pressure variations and tissue oxygen saturation at regular intervals.

MATERIALS AND METHODS

After obtaining approval of the Ethics Committee of the hospital, 60 adult patients who satisfied the inclusion criteria of the study and gave their informed written consent were enrolled in this programme. The patients were divided into two equal groups of 30 each by use of random number tables as Group P (Propofol) and Group E (Etomidate).

The sample size was determined based on the reports of similar articles with similar sample size and using the select statistical server (https://select-statistics.co.uk/calculators) we calculated the minimal sample size to be 48 for a study population of 300 and 63 for study population of 400. Hence, we took our sample size to be 60.

The inclusion criteria comprised of patients between the ages 18 and 50 years belonging to American Society of Anaesthesiology grades I to III scheduled for elective surgery under general anaesthesia. The patients excluded from the study were- patients allergic to any drugs, history of seizure disorder, presence of primary and secondary steroid deficiency, history of steroid medication, presence of hypotension, patients with diabetes mellitus, hypertension, cardiovascular disorder, bronchial asthma and patients put up for emergency surgery.

After a thorough preoperative assessment, the patients were given Tab. Lorazepam (2 mg) and Tab. Ranitidine (150 mg) orally the night before surgery and advised fasting for at least 8 hrs.

On the day of surgery, the patients were attached to monitor for recordings of ECG, NIBP, pulse oximeter and $EtCO_2$. An intravenous line was secured with 18 g cannula in a big peripheral vein. All patients were premedicated with Inj. Glycopyrrolate (0.2 mg), Inj. Butorphanol (0.03 mg/kg) and Inj. Midazolam (0.03 mg/kg) IV. They were preoxygenated with 100% oxygen.

The Group P patients were induced with Inj. Propofol (2 mg/kg) and Group E patients were induced with Inj. Etomidate (0.3 mg/kg) slowly, intravenously, over 45 seconds.

Orotracheal intubation was done under direct laryngoscopy facilitated by Inj. Vecuronium (0.1 mg/kg) IV. Anaesthesia was maintained with N_2O-O_2 (60:40) and isoflurane (0.2%) and intermittent intravenous vecuronium with controlled ventilation. At the end of surgery, all anaesthetics were withdrawn and muscle paralysis was reversed with Inj. Neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (10 µgm/kg) IV. Trachea was extubated after the patient was fully awake and there was full recovery of muscle power.

All patients had continuous pulse oximeter, ECG, blood pressure and $ETCO_2$ monitoring. Their heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressures and SpO_2 were recorded in the following manner-

- Baseline value before securing the intravenous cannula.
- Two (2) minutes after premedication, just before induction of anaesthesia.
- Three (3) minutes after induction, just before laryngoscopy.
- Just after direct laryngoscopy and tracheal intubation.
- At every 3 minutes interval for next 15 minutes with reference to the time of administration of the induction agent.
- At 10 minutes interval, thereafter, till end of surgery and recovery from anaesthesia.

Statistical analysis of the data obtained was performed using the software GraphPad InStat. Unpaired Student's t-test was used for quantitative data and $p<0.05$ was considered significant.

RESULTS

There was no difference in the demographic data in both the group. They are listed in Table 1.

	Group E (Mean±SD)	Group P (Mean±SD)	p-Value
Age	36.8±9.46	33.1±10.28	0.302
Sex (M/F)	16/14	13/17	0.426

Table 1. Comparison of Demographic Data Between Two Groups

The preoperative parameters were comparable as shown in Table 2.

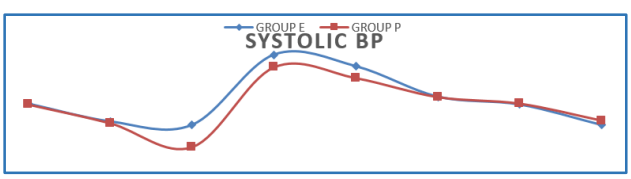
Preoperative	Group - E (Mean±SD)	Group - P (Mean±SD)	P-Value
Systolic BP (mmHg)	122.06±9.94	121.60±9.35	NS
Diastolic BP (mmHg)	74.53±5.51	75.33±4.40	NS
Heart rate (/min.)	72.3±3.69	70.93±3.5	NS
Saturation (SpO_2)	99.93±0.25	99.30±0.25	NS
Duration of surgery (min.)	46.7±3.22	49.2±3.15	NS

Table 2. Preoperative Observed Parameters and Duration of Surgery in Two Groups

In the following tables, baseline values are the values when the patient enters the operation theatre. The values at T=0 were the values just before induction, i.e. 2 minutes after premedication. T=3a denotes values that were 3 minutes after induction, but before intubation. T=3b denotes the values just after intubation. These observations were then repeated at 3 minutes interval up to 15 minutes.

SBP	Group E (Mean±SD)	Group P (Mean±SD)	P Value (Mean±SD)
Baseline	122.06±9.94	121.60±9.35	0.87
Before induction (T=0)	112.80±5.13	111.80±6.52	0.51
T=3a (min.)	111±5.41	99.3±5.85	0.0001
T=3b (min.)	147.7±8.43	141.1±8.03	0.002
T=6 (min.)	141.6±7.68	135.4±7.14	0.002
T=9 (min.)	125.7±11.9	125.5±7.32	0.93
T=12 (min.)	121.60±9.35	122.07±9.94	0.87
T=15 (min.)	110.90±4.5	113.23±5.32	0.07

Table 3. Changes in Systolic Blood Pressure

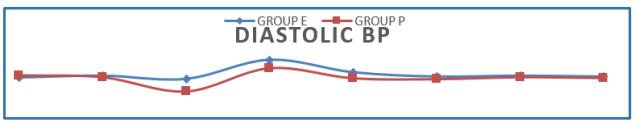


Graph 1. Systolic BP

As the values show there was a statistically significant fall in systolic blood pressure in Group P at 3a. After induction at T=3b, even though there was a rise in SBP, still the rise in Group P was significantly less than in Group E. SBP was significantly less in Group P at T=6 minutes as compared to Group E. At rest of time intervals both the groups were having statistically insignificant differences.

DBP	Group E (Mean±SD)	Group P (Mean±SD)	P Value
Baseline	74.53±5.50	75.33±4.40	0.53
Before Induction (T=0)	75.33±4.4	74.53±5.5	0.53
T=3a (min.)	73.93±4.16	68.4±3.74	<0.0001
T=3b (min.)	82.13±6.64	78.43±4.44	0.01
T=6 (min.)	76.77±6.22	74.06±4.14	0.04
T=9 (min.)	74.96±4.14	73.7±4.92	0.28
T=12 (min.)	75.33±4.40	74.53±5.50	0.53
T=15 (min.)	74.90±4.25	74.20±5.29	0.57

Table 4. Changes in Diastolic Blood Pressure

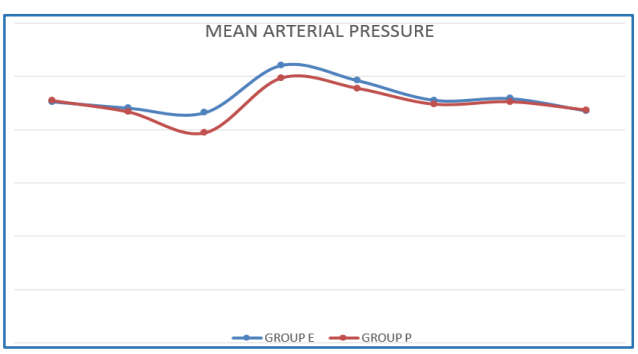


Graph 2. Diastolic BP

There was statistically significant fall in diastolic blood pressure in Group P at T=3a and 6 minutes after induction. At T=3b, even though there was a rise in DBP, the rise was significantly less in Group P than Group E. Rest all time intervals were comparable without any statistically significant difference between them.

	Group E (Mean±SD)	Group P (Mean±SD)	P Value
Baseline	90.37±6.06	90.77±4.69	0.77
T=0 (min.)	87.97±3.72	86.50±4.36	0.16
T=3a (min.)	86.29±3.86	78.68±3.4	<0.0001
T=3b (min.)	104.1±6.31	99.31±5.09	0.002
T=6 (min.)	98.33±5.91	95.38±4.51	0.03
T=9 (min.)	90.93±4.29	89.44±5.06	0.53
T=12 (min.)	91.57±6.49	90.37±6.06	0.46
T=15 (min.)	86.89±3.61	87.20±4.13	0.75

Table 5. Changes in Mean Arterial Pressure

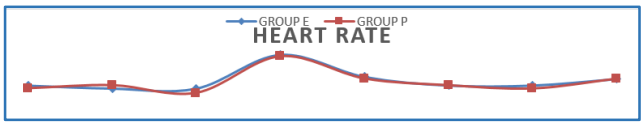


Graph 3. Mean Arterial Pressure

The fall in MAP in Group P was statistically significant at T=3a, T=6. The MAP rose at T=3b. Even though, there was rise in MAP, still it was significantly less in Group P than Group E. Rest of the values of MAP were comparable in both the groups.

HR	Group E (Mean±SD)	Group P (Mean±SD)	P Value
Baseline	72.30±3.69	70.93±3.50	0.14
Before Induction (T=0)	70.93±3.50	72.33±3.68	0.13
T=3a (min.)	70.93±3.50	68.81±3.22	0.85
T=3b (min.)	86.5±7.05	85.7±8.86	0.70
T=6 (min.)	76.30±5.83	75.4±5.27	0.86
T=9 (min.)	72.33±3.68	72.31±3.69	0.97
T=12 (min.)	72.33±3.68	70.80±3.49	0.10
T=15 (min.)	75.33±4.40	75.33±4.40	0.53

Table 6. Changes in Heart Rate



Graph 4. Heart Rate

There was no statistically significant difference noted in heart rates between the two groups.

	Group E (Mean±SD)	Group P (Mean±SD)	P Value
Baseline	99.93±0.25	99.30±0.25	0.99
Before Induction (T=0)	99.80±0.66	99.70±1.02	0.65
T=3a (min.)	99.40±1.00	99.53±1.22	0.64
T=3b (min.)	99.93±0.25	99.33±0.24	0.99
T=6 (min.)	99.70±1.02	99.93±0.25	0.23
T=9 (min.)	99.93±0.25	99.70±1.02	0.22
T=12 (min.)	99.80±0.66	99.53±1.22	0.30
T=15 (min.)	99.70±1.02	99.93±0.25	0.23

Table 7. Changes in Oxygen Saturation

There was no significant difference in oxygen saturation throughout the operations in both groups.

DISCUSSION

Propofol was discovered by Ronald and introduced into clinical practice by Brain and Rolly in the year 1977. Hypotension is known to occur with propofol administration due to its effect on sympathetic activity causing vasodilatation, its direct effect on intracellular calcium mobilisation and inhibition of prostaglandin synthesis in endothelial cells. But, sudden hypotension can have deleterious effects on maintaining circulation to vital organs in conditions like ischaemic heart disease, valvular heart disease, systemic hypertension and shock. Although, the decrease in systemic vascular pressure following propofol administration is due to vasodilation, the direct myocardial depressant effects of propofol are more controversial.[8]

Heart rate does not change significantly after induction with propofol. Propofol may either reset or inhibit the baroreflex reducing the tachycardic response to hypotension.[2] The most common side effect during induction of anaesthesia with propofol is hypotension, which is augmented by the concomitant administration of opioids and benzodiazepines.

The properties of etomidate include haemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetic properties that like propofol enables rapid recovery after a single dose as well as continuous infusion. The haemodynamic stability observed with etomidate is proposed to be related to its unique absence of effect on sympathetic nervous system and functions of the baroreceptor.[1,2] A large dose of etomidate (0.45 mg/kg) also produces minimal changes in cardiovascular parameters. Etomidate produces a 50% decrease in myocardial blood flow and oxygen consumption and a 20% to 30% increase in coronary sinus blood oxygen saturation. The myocardial oxygen supply-demand ratio is thus well maintained. It lacks analgesic effect and so may not totally ablate the sympathetic response to laryngoscopy and intubation.

Keeping these in mind, this study was carried out to compare the perioperative haemodynamic stability of these two drugs and in particular during laryngoscopy and endotracheal intubation.

A study by Shivaprakash Shivanna et al (2015) compared propofol (2 mg/kg) and etomidate (0.3 mg/kg) in coronary artery surgery. They found that propofol and etomidate groups showed significant reduction in arterial pressure (30%-22%), SVRI (31%-23%) and LVSWI (38%-32%) after anaesthesia induction. However, the heart rate (3%-10%) and cardiac index did not change significantly.[9]

In 2008, Jack and colleagues conducted a study on 10 patients to know cardiovascular changes after achieving constant effect-site concentration of propofol. Propofol TCI was started with a target of 8 µg/mL and then reduced to 4 µg/mL after 2 minutes. They observed a fall in heart rate by 21%, cardiac index by 14%, mean arterial pressure by 28% due to vasodilatation.[10]

In 1992, Ebert and colleagues conducted a study to know the sympathetic responses to induction of anaesthesia in humans with propofol (2.5 mg/kg plus 200 micrograms/kg/min.) or etomidate (0.3 mg/kg plus 15 micrograms/kg/min.). It showed that etomidate maintains haemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes, whereas propofol-induced hypotension by an inhibiting the sympathetic nervous system and impairment of the baroreflex regulatory mechanisms. Both cardiac and sympathetic baroslopes were maintained with etomidate, but were significantly reduced with propofol, especially in response to hypotension.

From our study, we also derived similar conclusion. Patients induced with propofol had significant decrease in systolic and diastolic blood pressures and mean arterial pressures at 2 to 3 minutes after induction when compared to those induced with etomidate. This characteristic indicates that etomidate maintained haemodynamic stability. Heart rate changes were not significant between the two groups in the present study.

CONCLUSION

Etomidate maintains haemodynamic stability unlike propofol, which causes significant decrease fall in both systolic and diastolic blood pressure.

Hence, etomidate should be a preferred choice of intravenous induction agent whenever haemodynamic stability in the peri-induction period is a major concern.

LIMITATIONS OF THIS STUDY

Adrenocortical suppression,[11,12] the major concern with use of etomidate has not been investigated as it was beyond the scope of the present study. Measurement of serum cortisol level would have better validated the results obtained with this study.

A bigger sample size would have perhaps helped in more statistical significance.

Further multicentric trials will vilify our findings.

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