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A COMPARISON OF PROPOFOL, ETOMIDATE AND KETOFOL AS INDUCTION AGENT: A RANDOMIZED CLINICAL STUDY

Anaesthesiology

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ABSTRACT

Introduction: Laryngoscopy and tracheal intubation is integral part of general anaesthesia but is frequently associated with haemodynamic disturbances. Propofol, ketamine and etomidate have their own limitations when they used alone for induction. Thus, this study was designed to compare haemodynamic changes during induction and intubation with propofol, etomidate and ketofol.

Materials And Methods: After taking Clinical Trial Registry of India (CTRI/2018/04/013409) registration, this prospective, randomized, comparative, double blind Study was conducted on 120 patients aged 18-60 yrs, ASA grade I or II, posted for elective surgery under general anaesthesia. The patients were randomly allocated into three groups. Group P- Inj Propofol (2.0 mg/kg), Group E -Inj Etomidate (0.3 mg/kg) and Group KP- Inj Propofol (1.5 mg/kg) plus Inj ketamine (0.5mg/kg) intravenously. Heart rate, systolic blood pressure , diastolic blood pressure and mean arterial blood pressure were recorded before induction, immediately after induction, 0,1,3,5 and 10 min after intubation.

Results: The data related analysed using Student t test, Pearson Chi-square test and ANOVA wherever applicable, $P<0.05$ was considered statistically significant. A statistically significant difference was noted between the groups regarding vital parameters at different time interval [$p<0.05$].

Conclusion: The combination of ketamine plus propofol has better haemodynamic stability without side effects than etomidate and propofol alone as an induction agent. Hence, combination (ketofol) may be better choice than either propofol or etomidate alone as induction agent with stable haemodynamics.

KEYWORDS

Etomidate, Haemodyanamic, Intubation, Ketofol, Propofol.

INTRODUCTION:

Laryngoscopy and tracheal intubation is commonly used for airway management during general anaesthesia. This procedure is frequently associated with haemodynamic disturbances including tachycardia, hypertension, arrhythmia or other undesirable haemodynamic changes. [1, 2] Propofol is an ultra-short-acting sedative-hypnotic agent, used for induction during general anaesthesia but it causes a dose-dependent hypotension and respiratory depression. [3] Etomidate is an intravenous anaesthetic induction agent, it has rapid onset and short duration of action, relative cardiovascular and respiratory stability as well as neuroprotective effects, making it as an attractive induction agent to facilitate intubation. [4,5] Ketamine is a short-acting general anaesthetic with distinct cardiovascular effect, characterized by increase in HR, BP and cardiac output. Ketofol is a combination of Ketamine and propofol in a single syringe and can be prepared in any desired concentration. [6] Ketamine-propofol mixture (ketofol) can be used as alternative induction agents, which overcome disadvantages of individual agents. [7, 8]

It theoretically seems that combined use of such drugs may balance the opposing haemodynamic effects. Lately, administration of simultaneous use of several anaesthetic agents (co-induction) to promote induction of anaesthesia has been better credited, particularly when its advantages over mono-therapy are established. [9]

However, there is scarcity of data which show comparable efficacy of etomidate and propofol as single drugs versus combination of ketamine-propofol as induction agents on haemodynamic stability during induction and intubation. This prompted us to undertake present study to evaluate effect of propofol, etomidate and ketofol as an induction agent, on haemodynamic responses following induction and intubation during general anaesthesia.

MATERIAL AND METHODS:

This prospective, randomized, comparative, double blind and clinical Study was carried out after taking institutional ethical committee clearance and CTRI registration (CTRI/2018/04/013409). 120 patients aged between 18 and 60 years of either sex, belonging to American Society of Anaesthesiology (ASA) physical status I and II scheduled for elective surgery under general anaesthesia were randomly allocated into three groups by computer generated sequence of random numbers. Patients having history of uncontrolled hypertension, hypotension, ischemic heart disease, chronic alcoholic, seizure disorder, steroid therapy, allergy to any study drug and adrenal insufficiency were excluded from the study. Primary objective of our study was to compare haemodynamic changes SBP and HR during induction and intubation in all the three groups. Secondary outcome was to evaluate any adverse effects.

Sample Size:

Sample size was calculated on the basis of studies by Masoudifar M et al [10] and Bajwa JM et al [11]. A minimum sample size of 36 patients is required in each group to study the minimum difference of 5 mmHg systolic blood pressure at power of 80% and confidence interval of 95%. 40 patients were taken in each group to compensate the dropouts, which resulted in total of 120 patients for the study.

Technique:

All the patients were subjected to detailed pre-anaesthetic evaluation to rule out any anatomical or systemic disorders. All patients were kept overnight fasting and received 2 ml/kg normal saline (NPO deficit) per each NPO hour before induction as a part of fluid therapy in addition to the crystalloids used for the maintenance throughout the operation. On arrival at operation theatre, after written informed consent and explanation of purpose and protocol of study, standard anaesthesia

monitoring including Electrocardiogram (ECG), Non-invasive blood pressure (NIBP), Pulse oximeter were attached and baseline vital parameters were recorded.

All patients received inj. midazolam (0.02 mg/kg) and inj. fentanyl (2µg/kg) intravenously. It was followed by an induction dose of either etomidate or propofol or ketofol given I.V. according to group allocations. Group E (etomidate group) received Inj. 0.3 mg/kg etomidate [Troymidate 10ml vial (2mg/ml) Troika Pharmaceutical Ltd.], Group P (propofol group) received Inj. 2 mg/kg propofol [Propofol 20ml vial(10mg/ml)vital healthcare pvt.ltd] and Group KP (ketofol group) received Inj.0.5mg/kg ketamine and 1.5 mg/kg propofol [ketamine 10ml vial (50mg/ml) vital healthcare pvt.ltd]. Patients in group E received etomidate (0.3mg\kg), group P received (2mg\kg) and group KP received ketamine (0.5mg\kg) plus propofol (1.5mg\kg) respectively. All medications were taken in 20ml syringe, provided at the same volume (15ml) and covered with masking tape to conceal any details of product.

Blinding:
The drug was prepared by the anaesthesiologist who was not involved in further study. Three anaesthesiologists were involved, one gave inducing agent, one did laryngoscopy and intubation and one who conducted study, recorded all data. All three anaesthesiologists were not aware of group allocation.

If patient could not be induced with the dose, extra dose was given and the case was excluded. Pain on injection and myoclonic movements were recorded, if occur at induction. Then intubating dose of vecuronium (0.1mg/kg) I.V was given and IPPV with 100% oxygen was started, the trachea was intubated after 3 minutes, with appropriate size of endotracheal tube. If laryngoscopy and intubation requires more than one attempt or more than 30 sec, the case was excluded. Endotracheal tube was secured after confirming correct position and positive pressure ventilation was initiated. Anaesthesia was maintained with oxygen, nitrous oxide (70:30), isoflurane (1-1.5%) along with intermittent boluses of vecuronium, as required throughout the surgery. At the end of surgery, the residual neuromuscular block was antagonized with Inj neostigmine (0.05 mg/kg) and Inj glycopyrrolate (0.01mg/kg) and extubated after complete recovery from neuromuscular blocked.

Systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP), heart rate(HR) were continuously monitored and recorded before induction, at induction and intubation followed by 1, 3, 5 and 10 minutes after intubation. If SBP decreased to less than 20% of the baseline, it was considered as hypotension and treated with fluid and if needed mephentermine was administered. Changes in MAP and HR +/- 20% of baseline was considered as hypertension or hypotension and tachycardia or bradycardia respectively. Pain on injection or myoclonus movements were recorded if any. Pain on injection was measured using 4 graded scale; 0 – no pain, 1 – verbal complaint of pain, 2 – withdrawal of arm, 3 – both verbal complaint and withdrawal of arm. The degree of myoclonic movements was also recorded as follows; 0 = no myoclonic movements, 1 = minor myoclonic movements, 2 = moderate myoclonic movements, 3 = major myoclonic movements. If any other side effects occur, was also be recorded.

Statistical Analysis:
Data were entered and analyzed using MS Excel & SPSS version 20. The data related to patient's distribution according to age, weight, indication of surgery, type of surgery were presented as number (proportion) and compared using Student t test, Pearson Chi-square test and ANOVA wherever applicable. All parameters like HR, SBP, DBP and MAP were expressed as Mean ± SD. P<0.05 was considered statistically significant.

RESULTS:
The demographic characteristics (age, gender and weight distribution) were comparable between all the three groups (Table 1). Baseline haemodyamic parameters (SBP, DBP, MAP, HR) were similar in all three groups (p>0.05).

Table 1: Demographic Distribution Of Patients

Mean ± SD	GROUP P (n=40)	GROUP E (n=40)	GROUP KP (n=40)	P value
Age (yrs)	37.85±11.94	39.10±14.17	38.90±11.95	0.89
Weight (kg)	52.13±7.87	53.23±8.41	51.43±5.33	0.54
Gender				
Male	13	19	21	0.17
Female	27	21	19	

On intergroup comparison between the three groups, heart rate showed statistically significant differences after induction and at 0, 1, 3 and 5 min after intubation. When groups P/E, P/KP and E/KP were compared, heart rate revealed significant differences after induction, at 0,1 and 3 min after intubation except Group E/KP(p=0.13) after induction. There were significant differences in Group P/KP at 5 min after intubation also (Table 2).

Table 2: Comparision Of Mean Heart Rate Between The Three Groups.

Time interval	Group P (Mean ±SD)	Group E (Mean ±SD)	Group KP (Mean ±SD)	p value			
				ANOVA test	P/E T -test	P/KP T -test	E/KP T –test
HR (BPM)							
Baseline	81.75±7.64	80.33±7.11	81.08±4.00	0.67	0.96	0.84	0.83
After induction	72.40±7.42	78.70±5.12	78.80±4.01	0.0000	<0.001	<0.001	<0.001
After Intubation	84.28±8.51	91.95±6.05	79.58±2.70	0.0000	<0.001	<0.001	<0.001
1 min	83.80±6.63	90.20±6.17	80.68±3.27	0.0000	<0.001	<0.001	<0.001
3 min	82.33±4.49	87.05±5.81	79.43±3.75	0.0000	<0.001	<0.001	<0.01
5 min	82.70±4.96	83.15±7.21	79.23±6.61	0.012	0.75	0.01	0.06
10 min	79.53±5.14	80.08±4.71	78.00±5.09	0.15	0.62	0.18	0.06

Table 3,4 showed statistically significant differences after induction and at 0, 1 and 3 min after intubation. On comparing group P/E and group P/K, SBP showed statistically significant differences after induction and at 0,1, 3 min after intubation. S. On comparing group E and KP, SBP showed statistically significant differences after induction and at 0 min after intubation only. When groups P/E, P/KP and E/KP were compared, DBP revealed significant differences after induction, 0,1 and 3 min after intubation.

Table 3: Comparision Of Mean SBP Between The Three Groups.

Time interval	Group P (Mean ±SD)	Group E (Mean ±SD)	Group KP (Mean ±SD)	p value			
				ANOVA test	P/E T -test	P/KP T -test	E/KP T –test
SBP (mmHg)							
Baseline	128.78±6.14	127.10±5.03	126.90±6.17	0.97	0.19	0.18	0.87
After induction	108.25±6.82	118.45±4.51	128.10±5.46	0.05	<0.001	<0.001	<0.001
Just after Intubation	118.65±5.61	128.80±5.02	126.45±5.32	<0.001	<0.001	<0.001	0.046
1 min	120.15±4.19	127.70±5.55	125.25±5.61	<0.001	<0.001	<0.001	0.053
3 min	128.10±4.35	125.75±5.02	123.43±6.09	<0.001	0.03	<0.001	0.067
5 min	125.00±3.14	125.00±4.25	123.50±3.71	0.12	1.00	0.30	0.051
10 min	123.50±4.85	123.50±4.18	121.15±6.40	0.07	1.00	0.068	0.055

Table 4: Comparision Of Mean DBP Between The Three Groups.

Time interval	Group P (Mean ±SD)	Group E (Mean ±SD)	Group KP (Mean ±SD)	p value			
				ANOVA test	P/E T -test	P/KP T -test	E/KP T –test
DBP (mmHg)							

Baseline	72.00± 4.68	71.50± 4.60	70.08± 5.65	0.96	0.63	0.10	0.22
After induction	60.20± 2.58	65.70± 2.03	68.18± 2.81	<0.001	<0.001	<0.001	<0.001
Just after Intubation	68.00± 2.52	73.80± 3.41	71.00± 3.12	<0.001	<0.001	<0.001	<0.001
1 min	68.10± 2.89	73.90± 2.45	72.28± 2.59	<0.001	<0.001	<0.001	0.005
3 min	69.50± 2.44	72.98± 1.93	71.90± 2.42	<0.001	<0.001	<0.001	0.03
5 min	71.10± 3.36	71.50± 2.88	70.93± 3.78	0.74	0.57	0.83	0.450
10 min	72.70± 3.57	71.60± 2.95	71.10± 3.86	0.11	0.14	0.06	0.517

On intergroup comparison between the three groups, MAP showed statistically significant differences after induction and at 0, 1 min after intubation. When groups P/E, P/KP and E/KP were compared, MAP revealed significant differences after induction, 0 and 1 min after intubation. (Table 5).

Table 5: Comparision Of Mean MAP Between The Three Groups.

Time interval	Group P (Mean ±SD)	Group E (Mean ±SD)	Group KP (Mean ±SD)	p value			
				ANOVA test	P/E T -test	P/KP T -test	E/KP T –test
MAP(mmHg)							
Baseline	90.90± 5.01	90.00± 3.36	89.05± 5.07	0.19	0.96	0.84	0.83
After induction	76.20± 4.59	83.15± 3.44	89.02± 5.82	<0.001	<0.001	<0.001	<0.001
Just after Intubation	84.95± 5.05	91.95± 3.46	88.15± 3.69	<0.001	<0.001	<0.001	<0.001
1 min	85.40± 4.71	91.80± 3.11	89.48± 3.85	<0.001	<0.001	<0.001	0.004
3 min	89.05± 3.75	90.68± 2.89	89.94± 3.60	0.108	0.10	0.282	0.314
5 min	89.15± 3.06	89.25± 1.84	89.08± 3.64	0.97	0.86	0.926	0.793
10 min	89.63± 3.36	89.20± 1.49	88.12± 4.76	0.14	0.46	0.105	0.175

In group P, 7.5% patients had incidence of pain on injection of grade I and in group E, 10% patients had myoclonus of grade II whereas group KP showed no side effects.

DISCUSSION:

Laryngoscopy and endotracheal intubation is the most important step during the administration of general anaesthesia but it is associated with variation in haemodynamic parameters. The attenuation of these changes is of paramount importance to prevent morbidity and mortality. [12] Numerous studies [1,5,7,9,10,13,14] have been performed to evaluate many induction agents such as etomidate, thiopental, propofol, ketamine, midazolam and fentanyl for attenuating haemodynamic responses to laryngoscopy. Rapid induction and haemodynamic stability in the absence of any serious side effects are important characteristics desired from an ideal induction agent. Unfortunately, none of the drug is an ideal induction agent due to its own side effects.

It theoretically seems that combined use of such drugs may balance the opposing haemodynamic effects. Lately, administration of simultaneous use of several anaesthetic agents (co-induction) to promote induction of anaesthesia has been better credited, particularly when its advantages over mono-therapy are established. This technique is applied to produce more appropriate desired outcomes with fewer adverse effects compared to single drug use.[9] The combinations of thiopentone-ketamine1,ketamine-propofol, etomidate-propofol have been evaluated as compared to single drugs in various studies.[13,14]

However, there is scarcity of data which show comparable efficacy of etomidate and propofol as single drugs versus combination of ketamine-propofol (ketofol) as induction agents on haemodynamic stability during induction and intubation. This prompted us to undertake present study to evaluate effect of propofol, etomidate and ketofol on haemodynamic response following induction and intubation during general anaesthesia.

In our study demographic data of all three groups were comparable in terms of gender, age and weight. Regarding haemodynamics, on intergroup comparison Propofol group has significantly lower HR, just after induction as compared to Etomidate group and Ketofol group but significantly higher just after intubation to 3 min when compare to ketofol group. In etomidate group HR increased significantly just after intubation to 3 min when compared with propofol and ketofol group.In ketofol group HR remained stable after induction to 10 min after intubation. It was may be due to opposing effects of ketamine and propofol.

Etomidate group SBP showed significantly lower after induction, DBP and MAP showed significantly lower after induction to 0 min after intubation as compared to ketofol group but haemodynamic variations were less with etomidate group as compare to propofol group.

Propofol group showed significantly lower MAP value after induction to 1 min after intubation. These results may be due to unique property of propofol for causing hypotension which may be explained due to reduction of sympathetic activity causing vasodilatation, direct effect on intracellular calcium mobilization, inhibition of prostaglandin synthesis in endothelial cells.

We found ketofol group better in respect of haemodynamic variations compared to propofol and etomidate alone. Reason of this may be due to opposing effects of propofol and ketamine on hemodynamic parameters. Ketamine is known to have sympathomimetic properties resulting in an increase in blood pressure and heart rate making it an appropriate choice for cases in which decrease in heart rate and blood pressure is feared as with propofol.

Study by Meena K et al [13] showed that there were significant differences in heart rate among all three groups (Etomidate, Propofol and Etomidate plus Propofol group) at time interval (after induction and 0,1,2,3 min after intubation) ($p<0.05$). Intergroup comparision of SBP, DBP, MAP revealed significant differences among various groups at different point of time except that among group etomidate and group ketofol was significant difference only at 1 min after intubation. This result were similar to our study.

Baradari A G et al [5] showed that HR changes overtime were not statistically significant ($p= 0.065$) and HR remain stable in ketofol group. Furthermore, after induction, the three study groups etomidate, thiopentone-ketamine and propofol –ketamine had significant different SBP, DBP, MAP changes over time($p <0.0005$).The results of this study showed that propofol-ketamine combination resulted in significantly better haemodynamic stability compared to these two induction regimes. These results were similar to our study. Lunia et al, [14]Masoudifer M et al[10] studies were in line with our study.

We found that in propofol group, 7.5% patients had incidence of pain on injection of grade I and in etomidate group 10% patients had myoclonus of grade II whereas group KP showed no side effects. The incidence of myoclonus and pain on injection in our study was lower than Lunia et al[14] and Aggarwal S et al[15] which may be due to fentanyl pretreatment in all patients before induction. No other complications were noted in all the three groups.

CONCLUSION:

We conclude that the combination of ketamine and propofol has better hemodynamic stability than etomidate and propofol alone. The combination proved to be significantly better than either propofol or etomidate alone as induction agent.

LIMITATIONS:

We have studied only ASA I and II grade patients so our findings cannot be extrapolated in compromised patients with respiratory diseases, ischemic heart disease, diabetes or difficult airway. No invasive methods of recording blood pressure were used, so beat to beat fluctuation of BP could not be measured. So further studies required to overcome these limitations.

Acknowledgment: None

Conflict Of Interest: Nil

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