Original Research Article

A comparative study of haemodynamic parameters using Etomidate and Ketofol as induction agents

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Abstract

Background: Etomidate is routinely used for intravenous induction where haemodynamic stability is essential. Ketofol, an ad-mixture of Propofol and Ketamine, which also has a stable haemodynamic profile, is recently being used as an induction agent. We compared the efficacy of Ketofol and Etomidate in terms of haemodynamic stability. **Methodology:** After ethical committee approval, this prospective randomized double blind study was conducted in seventy patients randomly divided into two groups. Group KP received Inj. ketofol [Inj.propofol 1mg/kg + Inj. Ketamine 0.75mg/kg] whereas Group E received Inj. Etomidate 0.3mg/kg. The vital parameters (HR, SBP, DBP, MAP) of the patient were noted after premedication (baseline), after induction, immediately after intubation (0 minute), from there onwards every 2 minutesutes for a period of 10 minutes and then at 15 minutes. Statistical significance in mean difference was calculated using student's t test. P value of < 0.05 was regarded as statistically significant and $p < 0.001$ was taken as highly significant. **Results:** Both the groups showed statistically significant rise in the heart rate when compared to the baseline immediately after intubation and at 2 minutesutes post intubation ($p < 0.05$) however there was no statistically significant difference between the two groups in the heart rate at any time interval. Group KP did not show any significant change in the SBP, DBP or MAP at any stage. In Group E, there was statistically significant rise in the SBP (9.5%, p=0.22) as well as DBP (7.6%, p=0.034) at 2 minutesutes post intubation, however no significant change in MAP at any time. The two groups showed statistically significant difference in SBP immediately after intubation (p=0.008) and at 2 minutes post-intubation (p=0.006) whereas there was a statistically significant difference in DBP and MAP between the two groups only at 2 minutes post intubation with Group E showing higher values (DBP - p=0.012) (MAP - p=0.035). **Conclusion:** Ketofol (propofol 1 mg/kg and ketamine 0.75 mg/kg) is an effective and safe alternative to etomidate as an induction agent with superior hemodynamic stability compared to etomidate in patients receiving general anaesthesia.

Key Word: Etomidate, Ketofol, Induction, Haemodynamic response

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INTRODUCTION

Commonly used intravenous agents for induction of general anaesthesia include propofol, Thiopentone sodium, etomidate, and ketamine. Etomidate is a carboxylated imidazole compound which results in almost no change in heart rate, MAP, mean pulmonary artery pressure, stroke volume, cardiac index, and pulmonary and systemic vascular resistance.[1] Propofol, a 2,6-diisopropylphenol decreases arterial blood pressure associated with a decrease in cardiac output/cardiac index, stroke volume index, and systemic vascular resistance (15–25%)[2]. Ketamine is a phencyclidine derivative which causes elevation of blood pressure and heart rate due to its sympathomimetic effects.[3] Ketofol is an ad-mixture of Propofol and Ketamine. The cardiovascular effects of each drug are opposing in action, thus theoretically balancing each other out when used together. Studies have shown that Ketofol induction had smaller reductions in stroke volume index and total peripheral resistance.[4] As both Etomidate and Ketofol have stable haemodynamic profile, we hypothesized that Etomidate and Ketofol are equally effective as induction agents in terms of haemodynamic stability which was our primary outcome. The secondary outcome of our study was the comparison of incidence of side effects during induction of anaesthesia.

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MATERIALS AND METHODS

After approval of ethical committee, this prospective randomized double blind study was conducted in department of Anaesthesia in MGM medical college and hospital, Aurangabad from December 2014 to August 2016. Before the study was carried out, a power analysis indicated that 31 patients per group would be required to detect a difference of 5 in hemodynamic parameters. The alpha error was set at 0.05 and beta error at 0.9. Thus a sample size of 35 patients per group was considered for our study. Patients in the age group of 18 – 65 years with American Society of Anaesthesiologists (ASA) physical status II and III who were to undergo elective general, urologic, orthopaedic, plastic or gynaecologic surgery were included in the study. Patients on chronic opiate therapy, psychotropic or sedative medications, patients with personality disorders, severe left ventricular systolic dysfunction (ejection fraction < 30%) and pregnant/lactating mothers were excluded from the study. Informed and written consent of the patients was taken. Weight of the patient was recorded. Patients were randomly divided using sealed envelope method into two groups. Group - KP received Inj. ketofol i.e. combination of Inj.propofol (Inj. Neorof by Neon pharmaceuticals) 1mg/kg and Inj. Ketamine (Inj. Aneket by Neon pharmaceuticals) 0.75mg/kg diluted up to 10ml using Normal Saline 0.9% in a single syringe Group – E received Inj. Etomidate (Inj. Troymidate by Troikaa pharmaceuticals) 0.3mg/kg diluted up to 10ml with Normal Saline 0.9% in a syringe. One anaesthesiologist prepared and injected the drugs while the second anaesthesiologist observed the parameters making the study double blind. On arrival in the operation theatre, an intravenous cannula of 20G was inserted into the arm. Patient was pre-loaded with 5 ml/kg of Ringer lactate (RL). All patients were monitored non-invasively for arterial blood pressure (BP), heart rate (HR), oxygen saturation (SpO_2) and ECG changes. The pre-operative parameters BP (Systolic, diastolic and mean), HR and SpO2 were recorded. Pre-medication in the form of Inj. Fentanyl 2µg/kg IV and Inj. Midazolam 0.03mg/kg IV was given. After a period of two min., vitals parameters (BP, HR, SpO_2) were noted and these values were considered as baseline parameters. The patients were induced with either Ketofol (Group-KP) or Etomidate (Group-E) given intravenously over a period of 30-45 seconds. Side-effects such as pain on injection and myoclonus were noted. Loss of eye lash reflex was the parameter used to confirm induction. Haemodynamic parameters were noted after induction. After giving Inj. Vecuronium in a dose of 0.1mg/kg, patients were ventilated with bag and mask using 100% O_2 for 3 minutes and trachea was intubated with appropriate sized cuffed endotracheal tube. Anaesthesia was maintained with Isoflurane 1% in nitrous oxide and oxygen (50:50). The vital parameters (SBP, DBP, MAP, HR and SpO_2) of the patient were noted immediately after intubation (0 minute), from there onwards every 2 minutesutes for a period of 10 minutes and then at 15 minutes. During this period, hypertensive episodes (increase in MAP by 20% from baseline) were treated by adjusting the dial concentration of inhalational agents. Hypotensive episodes (decrease in MAP by 20% from baseline) were corrected using Inj. Mephentermine 5mg IV. To treat tachycardia (HR >110 bpm) Inj.Esmolol 0.5mg/kg IV was given and for bradycardia (HR < 50 bpm) Inj. Atropine 0.06mg/kg IV was given.

Statistical analysis

All data was presented as Mean ± Standard Deviation (SD). Demographic data was analyzed using Chi-square test and statistical significance in mean difference was done using student's t test. All statistical analysis was made using Minitab 15. *P* value of < 0.05 was regarded as statistically significant and $p < 0.001$ was taken as highly significant.

RESULTS

The demographic data (age, sex, weight) were comparable in both groups ($p < 0.05$) (Table 1) Both the groups showed statistically significant rise in the heart rate when compared to the baseline immediately after intubation and at 2 minutes post intubation ($p < 0.05$) however there was no statistically significant difference between the two groups in the heart rate at any time interval. (Table 2, Fig. 1) Group KP did not show any significant change in the SBP, DBP or MAP at any stage. In Group E, there was statistically significant rise in the SBP (9.5%, p=0.22) as well as DBP (7.6%, p=0.034) at 2 minutes post intubation, however no significant change in MAP at any time. (Table 3, 4, 5) The two groups showed statistically significant difference in SBP immediately after intubation (p=0.008) and at 2 minutes post-intubation (p=0.006). (Fig. 2) whereas there was a statistically significant difference in DBP and MAP between the two groups only at 2 minutes post intubation with Group E showing higher values (DBP - p=0.012). (Fig. 3) (MAP - p=0.035) (Fig. 4) None of the patient in any group had pain on injection or myoclonus following administration of the study drugs.

Table 1: Demographic data. Results are given as mean ± SD

Parameters		Group KP (n = 35)	Group E (n = 35)	*P* value
Age (in years)		54.14±7.87	56.46 ±9.86	*P*=0.282 NS
Weight (in Kilograms)		55.43 ±8.08	57.29±7.70	*P*=0.328 NS
Gender distribution (given as percentage)	Male	45.71%	48.57%	*P*=0.6324 NS
	Female	54.29%	57.43%	

NS = Not significant

Table 2: Intra Group Comparisons of Pulse Rate in minutes at different time intervals compared to the baseline value

Pulse Rate (at different time intervals compared to baseline)	Group KP		Group E	
	Mean % Change	P - Value	Mean % Change	P - Value
Post induction	- 3.39	0.051 NS	- 1.41	0.228 NS
Post intubation (0 min)	- 5.58	0.020 **S**	- 4. 96	0.030 S
2 minutes	- 6.64	0.027 **S**	- 9.40	0.001 HS
4 min	- 4.12	0.110 NS	- 2.22	0.426NS
6 min	- 2.11	0.423 NS	1.72	0.589 NS
8 min	- 1.54	0.599 NS	5.67	0.085 NS
10 min	1.86	0.528 NS	7.77	0.020 **S**
15 min	5.72	0.065 NS	10.71	0.001HS

NS = Not significant S = Significant HS = Highly significant

Table 3: Intra Group Comparisons of Systolic BP in mm of Hg at different time intervals compared to the baseline value

Systolic BP (at different time intervals compared to baseline)	Group KP		Group E	
	Mean % Change	P - Value	Mean % Change	P - Value
Post induction	2.24	0.544 NS	0.57	0.758 NS
Post intubation (0 min)	2.36	0.594 NS	- 5.00	0.143 NS
2 minutes	- 0,58	0.914 NS	- 9.50	0.022 S
4 min	2.59	0.533 NS	2.55	0.510 NS
6 min	3.13	0.425 NS	5.49	0.143 NS
8 min	- 1.19	0.769 NS	6.00	0.113 NS
10 min	2.45	0.538 NS	7.55	0.052 NS
15 min	6.83	0.085 NS	10.14	0.11 NS

NS = Not significant S = Significant

Table 4: Intra Group Comparisons of Diastolic BP in mm of Hg at different time intervals compared to the baseline value

Diastolic BP (at different time intervals compared to baseline)	Group KP		Group E	
	Mean % Change	P - Value	Mean % Change	P - Value
Post induction	- 0.87	0.716 NS	2.38	0.314 NS
Post intubation (0 min)	0.74	0.835 NS	- 3.22	0.311 NS
2 minutes	- 0.15	0.968 NS	- 7.64	0.034 S
4 min	2.84	0.447 NS	0.00	1.000 NS
6 min	0.87	0.750 NS	3.74	0.295 NS
8 min	- 2.60	0.436 NS	4.99	0.220 NS
10 min	1.89	0.580 NS	3.63	0.394 NS
15 min	7.04	0.021 S	4.64	0.241 NS

NS = Not significant S = Significant

Table 5: Intra Group Comparisons of Mean BP in mm of Hg at different time intervals compared to the baseline value

Mean BP (at different time intervals compared to baseline)	Group KP		Group E	
	Mean % Change	P - Value	Mean % Change	P - Value
Post induction	0.84	0.700 NS	2.39	0.179 NS
Post intubation (0 min)	1.29	0.752 NS	- 1.13	0.690 NS
2 minutes	0.40	0.929 NS	- 5.81	0.090 NS
4 min	2.40	0.495 NS	- 0.49	0.892 NS
6 min	2.40	0.339 NS	5.25	0.132 NS
8 min	- 0.47	0.862 NS	6.25	0.098 NS
10 min	2.49	0.388 NS	5.09	0.195 NS
15 min	7.16	0.009 S	6.32	0.091 NS

NS = Not significant S = Significant

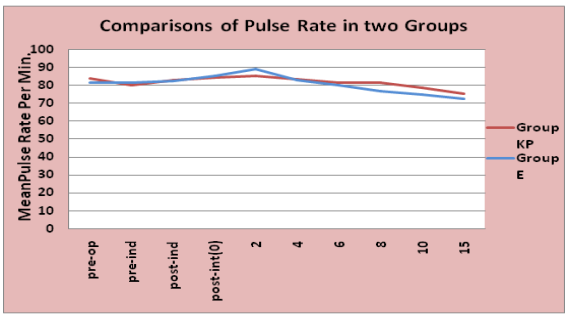

Figure 1

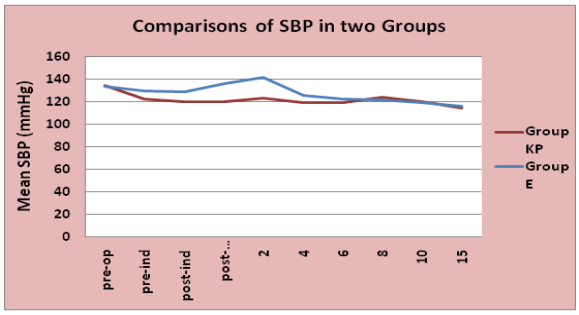

Figure 2

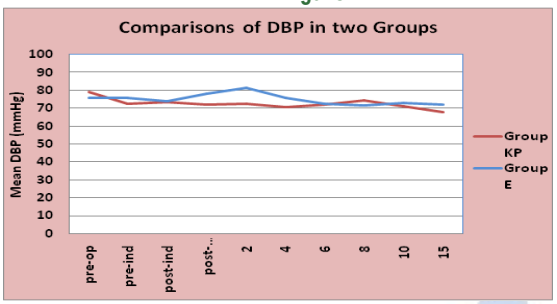

Figure 3

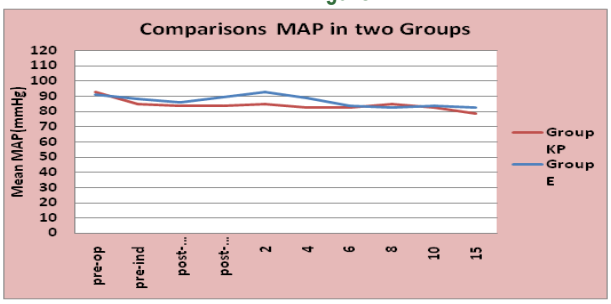

Figure 4

Legend

Figure 1: Comparisons of Pulse rate at different time intervals in the two Groups; **Figure 2:** Comparisons of Systolic BP (SBP) at different time intervals in the two Groups; **Figure 3:** Comparisons of Diastolic BP (DBP) at different time intervals in the two Groups; **Figure 4:** Comparisons of Mean Arterial Pressure (MAP) at different time intervals in the two Groups

DISCUSSION

In this study we compared the effectiveness of Ketofol (Ketamine- 0.75mg and Propofol-1.5mg) and Etomidate (0.3mg) as induction agents in terms of haemodynamic changes in patients undergoing elective surgeries. Etomidate is an induction agent of choice in patients with cardiovascular disease for maintaining haemodynamic stability. Ketofol (an ad-mixture of Propofol and Ketamine) is a relatively new induction agent. The additive effects of both the drugs help in decreasing the dose of each drug, taking benefit from the advantages regarding amnesia, analgesia, hypnosis and hemodynamic stability and on the other hand lessening the disadvantages attributed to either drug. The visual compatibility and composition stability of propofol-ketamine mixture was evaluated by Calimaran *et al*[5] and they concluded that both drugs were stable in the ketamine and propofol mixture. The standard induction dose of etomidate is 0.2-0.4 mg/kg. Based on the available literature a dose of 0.3mg/kg was used in our study. Same dose was used in the studies conducted by Harris *et al*[6], Aggarwal *et al*[7], Abbasivash *et al*[8] and Baradari *et al*[9]. The standard induction dose of propofol is 2-2.5mg/kg and that of ketamine is 0.5-2 mg/kg. The ED95 as calculated by Hui *et al*[10] based on a dose response curve at end points of anaesthesia was 1.56-3.82 for propofol and 0.52-1.27 for ketamine in an ad-mixture of ketofol. A dose of 1.5mg/0.75mg of propofol/ketamine in ketofol was used in our study which coincides with the dosage used in the study by Smischney *et al*[11]. In our study demographic parameters and baseline vital parameters (HR, SBP, DBP, MAP) were comparable with no statistically significant differences ($p > 0.05$) seen between the two groups. We observed that there was no statistically significant difference between the two groups in the heart rate at any time interval. However individually both the groups showed statistically significant rise in the heart rate when compared to the baseline immediately after intubation and at 2 minutes post intubation ($p<0.001$). Aboeldahab *et al*.[12] compared propofol -2mg/kg, ketamine -2mg/kg and ketofol (propofol: ketamine 1:1mg/kg) as induction agents. Their study showed a statistically significant rise in the HR at intubation (7.8%) in the ketofol group whereas our study at intubation showed a rise of only 5.6%. More increase in HR in their study may be because of the higher dose of ketamine (1mg/kg) used. Hosseinzadeh *et al*[13] compared the hemodynamic effects of ketofol (ketamine-0.75 mg/kg and propofol-1 mg/kg) to those of etofol (combination of etomidate-0.2mg/kg and propofol-1 mg/kg) at induction in elderly patients. They reported a significant increase followed by a decrease in HR at one and six min respectively after intubation in the ketofol group. They have used a lower dose of propofol(1mg/kg)in the ketofol admixture as opposed to our study. This may be the reason for the difference in the

HR at different time intervals between the two studies. In our study, the two groups showed statistically significant difference in SBP immediately after intubation (p=0.008) and at 2 minutes post-intubation (p=0.006) whereas there was statistically significant difference in DBP and MAP between the two groups only at 2 minutes post intubation with Group E showing higher values ($p < 0.05$). Group KP did not show any significant change in the SBP, DBP or MAP at any stage. In Group E, there was statistically significant rise in the SBP (9.5%, p=0.22) as well as DBP (7.6%, p=0.034) at 2 minutes post intubation, however no significant change in MAP at any time. Baradari *et al*[9] in a study comparing etomidate (0.3 mg/kg) and ketofol (propofol 1.5 mg/kg and ketamine 0.5 mg/kg) found a statistically significant difference in the SBP, DBP as well as MAP between the two groups at 1 min and 3 min post-intubation with Etomidate group showing higher values. Their observation correlates with our study. Hayakawa-Fujii *et al*[14] compared the haemodynamic stability between combinations of propofol-fentanyl (2/3 mg/kg), ketofol (propofol/ketamine -2/0.1 mg/kg) and ketofol-fentanyl(2/0.1mg/kg + 3 µg/kg) at induction and intubation. The study drugs were taken in different syringes and were administered one after the other. Their study showed a 4% rise in the SBP as well as DBP immediately post intubation in the ketofol group which did not receive fentanyl premedication unlike our study. This may be the reason of rise in BP after intubation in their study in spite of using lower dose of ketamine. The ketofol- fentanyl group showed a 22.5% fall in the SBP and 25.9% fall in the DBP post-intubation when compared to the baseline. A lower dose of ketamine (0.1mg/kg) was used in the ketofol admixture and was administered in a different syringe one after the other unlike in our study where the two drugs were prepared in the same syringe. This may be the reason for the fall in the SBP in their study when we did not observe any rise or fall in SBP or DBP in ketofol group at any time interval. In our study there was statistically significant difference seen between the two groups at 2 minutes with Etomidate group showing higher values(group KP- 84.8 ±17.9 mmHg and group E- 93.0 ± 12.8 mmHg, p=0.035). We did not observe any statistically significant rise or fall in MAP when compared to the baseline at any time interval following administration of the study drugs in both the groups. This co-relates with the findings of Aboeldahab *et al* who studied haemodynamic effects of Ketofol.[12] Saleem *et al*[15] compared the haemodynamic effects of induction doses of propofol thiopentone (1.25/0.5 mg/kg) and ketofol(propofol ketamine- 2/0.5 mg/kg). Similar to our study, they also did not observe any statistically significant fall or rise in MAP from the baseline at any time intervals following the administration of ketofol. In our study, even though there was statistically significant rise in the haemodynamic parameters in the two study groups at different time intervals after intubation, when compared to the baseline, the overall difference was way below 30% which was not significant enough to warrant any pharmacological interventions. In our study there were no cases of pain on injection noted following administration of the study drugs. Aggarwal *et al*[7] compared propofol and etomidate as induction agents. Their study also showed only 4% cases having mild pain on injection following administration of etomidate. We did not observe myoclonus in any patient following injection of the study drugs. Aggarwal *et al*[7] and Baradari *et al*.[9] reported statistically significant number of cases in the etomidate group with respect to ketofol group having myoclonic movements. The reason for this difference in myoclonus may be due to use of higher dose of midazolam (0.03 mg/kg) in our study compared to both these studies (0.02 mg/kg).

Limitation of study

Due to the time constraints and availability of limited number of patients, our sample size was just adequate for the statistical purpose. A study involving bigger sample size would give more authenticity to the results.

CONCLUSION

Ketofol (propofol 1 mg/kg and ketamine 0.75 mg/kg) is an effective and safe alternative to etomidate as an induction agent with superior hemodynamic stability when compared to etomidate in patients receiving general anaesthesia.

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