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HEMODYNAMIC EFFECTS OF KETAMINE WITH PROPOFOL (KETOFOL) AND PROPOFOL ON INDUCTION OF ANAESTHESIA IN ELECTIVE SURGERIES UNDER GENERAL ANAESTHESIA: A CLINICAL COMPARATIVE STUDY

Anaesthesiology

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ABSTRACT

Background: The induction of anaesthesia is the most crucial process with an intravenous agent. Hypotension, arrhythmia, cardiovascular collapse due to propofol injection may be life threatening in hemodynamically unstable and cardio vascular diseased patients. It is advantageous to use a safe agent with less adverse effect for induction of anaesthesia. The aim of the study was to determine the effects of Ketofol and Propofol for induction of anaesthesia and post intubation hemodynamic changes.[1].

Material and Methods: The study was conducted in 30 patients who were candidate for elective surgeries under general anaesthesia and divided into two random groups of ketofol and propofol (15 each). The hemodynamic changes were observed at induction, for 5 and 10 minutes after intubation[1].

Results: There was significant variability of heart rate in propofol group in comparison to ketofol group (p value =0.0001). Significant differences of systolic (p value=0.0053), diastolic (p value=0.0017) and mean arterial blood pressure (p value=0.0092) were seen in propofol group in comparison to ketofol group.

Conclusion: We surmised that for proper stability of heart rate and blood pressure, ketofol is a better substitute to propofol in patient put for elective surgeries under general anaesthesia.

KEYWORDS

Hemodynamic, Induction, Ketofol.

INTRODUCTION:

Hemodynamic stability is the major concern for an anaesthesiologist which may vary during induction of anaesthesia and intubation. It may also vary during surgical incision and stress, in hypovolemic state, administration of anaesthetic drugs and volatile anesthetics. Heart rate and blood pressure increases due to surgical incision and pain[1].

Administration of anaesthesia in patients with cardiovascular disease is more challenging for an anaesthesiologist[1,2,3]. Some induction agent used for induction of anaesthesia decrease blood pressure profoundly[1]. The induction agent propofol decreases blood pressure by several mechanism but ketamine increases blood pressure which has beneficial effect for hemodynamic stabilization[1]. In our study, the aim is to evaluate hemodynamic changes during induction of anaesthesia with ketamine and propofol combination and propofol to find out proper drugs establishing more stable hemodynamic[3].

Propofol decreases arterial blood pressure due to inhibition of sympathetic vasoconstrictor activity that lead to drop in systemic vascular resistance. Propofol also decreases preload and cardiac contractility. It impede the normal arterial baroreflex response to hypotension and plunging of preload causes vagally mediated reflex bradycardia. Propofol is used at a dose of 1-2.5 mg/kg for induction of anaesthesia[1].

Ketamine is an antagonist of NMDA receptors which could ameliorate systolic and diastolic blood pressure, heart rate and cardiac output by stimulation of sympathetic system[1]. It also has hypnotic and analgesic effects. The intravenous induction dose of ketamine is 1-2 mg/kg, onset of effect is 15-30 seconds after injection and the duration of action is 5-10 minutes. The intramuscular induction dose of ketamine is 4-6 mg/kg, onset of effect is 3-4 minutes and the duration of action is 12-25 minutes after injection.

Ketofol is a newly coined word referring the combination of ketamine and propofol in a single syringe[4]. Pharmacologically the two drugs are compatible with each other and it is in used since 1990 for surgical anaesthesia[4,5]. There is growing interest of ketamine with propofol combination for short procedural sedation and analgesia in adults and children. The absolute dose ratio of ketamine with propofol combination is not established, however, most appropriate ratio of racemic propofol to ketamine of 1:3 for short procedures (10-20 minutes) has been suggested[4,5,6]. Ketamine and propofol could also be mixed in equal amounts (1:1) as an induction agent for induction of anaesthesia in adult patients[1]. There are different studies in recent times where beneficial effect of combination of ketamine and propofol were demonstrated[7]; which also providing cardiovascular stability[8] and therefore can be compared with etomidate[1]. The adverse effects of etomidate associated adrenal insufficiency in critically ill and septic patients were not steer with ketofol mixture[1,9]. However, recent studies does not admonished use of ketofol as an induction agent, our aim of the study was to evaluate hemodynamic changes during induction of anaesthesia with ketofol and propofol.

Material and methods :

This study was conducted under the Department of Anaesthesiology and Critical Care, Diphu Medical College & Hospital, Diphu, Karbianglong, Assam, India after obtaining informed written consent from the patient. The study was carried out in 30 hemodynamically stable patients put for elective surgeries from 14th November, 2019 to 15th May, 2020. Patients of both sexes between the age group of 20 to 50 years and weight 50 to 70 Kg put for elective surgeries were included in our study and the patients were randomly allocated into two groups of 15 each. Patients who were addicted to drugs, pregnant women, received sedatives and anti psychotic drugs in the last month and patient who have personality disorder, obese patient and contraindicated to ketamine and propofol administration were excluded from our study population. The aim of the study was to determine the effects of Ketofol and Propofol for induction of anaesthesia and to look for hemodynamic changes during induction of anaesthesia and, at 5 minutes and at 10 minutes after intubation[1].

Physical examination was done after obtaining detailed history of the patient and on arrival at operation theatre, patients heart rate, systolic, diastolic, mean arterial pressure and SpO_2 were recorded and ECG done.

Randomly allocated patients in Group A, the ketofol Group, prehydration were done with 350 ml of normal saine and premedication were done with inj. Glycopyrrolate 0.2 mg, inj. Midazolam 0.2 mg/kg and inj. Fentanyl 3µg/kg intravenously. Induction of anaesthesia were done after preoxygenation for 3 minutes where in ketofol Group, ketofol 1.5mg/kg were administered and in propofol group 1.5mg/kg of propofol were administered. Ketofol was

prepared in a single syringe at 1:1 ratio of ketamine and propofol. For proper muscle relaxation, inj. Atracurium 0.5mg/kg were administered and after 3 minutes of face-mask ventilation, intubation done with endotracheal tube and positive pressure ventilation were initiated after confirming the correct position of the endotracheal tube. Capnography was connected after intubation was done. Anaesthesia was maintained with oxygen and nitrous oxide at a ratio of 33%:67% and isoflurane along with intermittent doses of inj. Atracurium was given as required throughout the surgery.

Heart rate, non invasive blood pressure and oxygen saturation by pulse oxymetry were recorded at induction, 5 minutes and 10 minutes after intubation.

RESULTS AND OBSERVATIONS:

Our study was done on 30 patients randomly assigned to one group (15 each) of the study. Induction of anaesthesia were done with Ketofol in Group K and Propofol in Group P.

Table 1. Division of the study population in two groups.

Group K	Ketamine+Propofol	N=15
Group P	Propofol	N=15

Statistical analysis was done with GraphPad statistical software. Chi-square test or Fisher Exact test was used for qualitative data and Student Unpaired t-test was used to analysis the quantitative data. P value was determined as P>0.05 is insignificant, P<0.05 is significant and P<0.001is highly significant.

The following observations were made in our study population-

Table 2. Demographic characteristics of the patients between the two groups: Data are expressed as mean±standard deviation for age and weight; absolute number for gender of the two groups.

Category	Group I	Group S	P=Value
Age (in years) Mean± SD	38.60±6.56	38.40±5.70	0.9296 (NS)
Sex Male Female	9 (60%) 6 (40%)	8 (53.33%) 7 (46.66%)	1.0000(NS)
Weight (kg) Mean±SD	61.47±5.25	62.20±5.40	0.7089 (NS)

Abbreviation: SD = Standard deviation, NS = Not significant

Unpaired student t test was used to calculate the p value of age and weight of the study population. Fisher Exact test was used to calculate the p value of sex distribution among the groups.

On statistical analysis of age by Unpaired student t test among the groups, the mean group K minus group P equals 0.20 and the 95% confidence interval of this difference is from -4.40 to 4.80. The standard error of this difference is 2.244.

Statistical analysis of the sex distribution among the groups were done using Fisher Exact test and absolute number was used for percentage distribution of gender.

The statistical analysis of weight of patients were done by Unpaired student t test between the groups where the mean group K minus group P equals to 0.73 and 95% confidence interval of this difference is from -4.72 to 3.25. Standard error of difference is 1.945.

On statistical analysis, the p value of age, sex and weight were found to be >0.05; by conventional criteria this difference is considered to be statistically not significant.

Table 3. Distribution of type of surgeries between the groups.

Surgeries performed	Group K	% percentage	Group P	% percentage	P value
Cholecystectomy	8 (8/15)	53.33%	6 (6/15)	40%	0.7152 Not significant
Appendicectomy	7 (7/15)	46.66%	9 (9/15)	60%	

The distribution of surgeries among the groups were 53.33% (8/15) patients put for elective cholecystectomy and 46.66% (7/15) patients put for appendicectomy in group K. Surgeries were performed in 40% (6/15) patients put for elective cholecystectomy and 60% (9/15) patients put for elective appendicectomy in group P study population. The surgeries performed were comparable between the two groups but statistically (Fisher Exact test) insignificant (P value =0.7152).

Table 4. Preinduction heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation of patients among the groups.

Vital parameters	Group K		Group P		P value	Results
	Mean	SD	Mean	SD		
Heart rate	82.93	8.40	81.20	8.49	0.5786	Not significant
Systolic BP	126.47	11.90	126.67	9.15	0.9592	Not significant
Diastolic BP	67.87	5.46	66.13	5.63	0.3994	Not significant
MAP	73.60	6.86	75.00	6.83	0.5801	Not significant
SpO_2	97.40	1.64	96.00	2.17	0.0561	Not significant

Preinduction heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were calculated with Unpaired student t test and the p values were >0.05, hence comparable between the two groups but by conventional criteria this difference is statistically quite insignificant.

Table 5. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation of patients among the groups at induction.

Vital parameters	Group K		Group P		P value	Results
	Mean	SD	Mean	SD		
Heart rate	75.47	1.88	67.93	4.01	0.0001	Extremely significant
Systolic BP	124.40	2.16	119.33	6.11	0.0053	Very significant
Diastolic BP	73.00	1.51	69.60	3.48	0.0017	Very significant
MAP	93.07	2.02	88.13	6.52	0.0092	Very significant
SpO2	97.53	1.55	97.73	1.58	0.7291	Not significant

The heart rate of the study population were compared between the two groups at induction and found to be extremely significant (p value =0.0001). The systolic blood pressure, diastolic blood pressure and mean arterial pressure were compared among the groups and found to be very significant (p value <0.001).

Table 5. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation of patients among the groups at 5 minutes after intubation.

Vital parameters	Group K		Group P		P value	Results
	Mean	SD	Mean	SD		
Heart rate	75.07	1.22	72.80	3.49	0.0247	Significant
Systolic BP	115.27	1.94	113.13	2.47	0.0139	Significant
Diastolic BP	63.93	1.98	65.53	1.92	0.0329	Significant
MAP	88.73	2.58	86.13	1.88	0.0038	Very significant
SpO2	97.07	1.67	97.27	1.62	0.7418	Not significant

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation of the study population were measured at 5 minutes after intubation. The heart rate of patients between the two groups were compared and found to be significant (p value =0.0247). The systolic blood pressure and diastolic blood pressure were compared which found to be statistically significant (p value =<0.05). On comparison of mean arterial pressure, they were statistically very significant (p value =0.0038).

Table 5. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation of patients among the groups at 10 minutes after intubation.

Vital parameters	Group K		Group P		P value	Results
	Mean	SD	Mean	SD		
Heart rate	75.47	2.00	73.53	1.55	0.0062	Very significant
Systolic BP	118.13	2.33	114.07	2.52	0.0001	Extremely significant
Diastolic BP	72.80	1.74	68.33	0.90	0.0001	Extremely significant
MAP	89.13	1.30	86.07	1.53	0.0001	Extremely significant
SpO2	97.80	1.15	98.07	1.28	0.5526	Not significant

The heart rate was recorded at 10 minutes after intubation and on statistical analysis with Unpaired student t test, by conventional criteria the difference was found to be very significant (p value =0.0062). The systolic blood pressure, diastolic blood pressure and mean arterial pressure were noted at 10 minutes after intubation which were by conventional criteria the difference was extremely significant (p value =0.0001).

In our study, the heart rate was compared between the two groups and was significantly high in ketofol group than propofol group at induction (p=0.0001) and at 5 minutes (p=0.0247), and at 10 minutes (p=0.0062) after intubation.

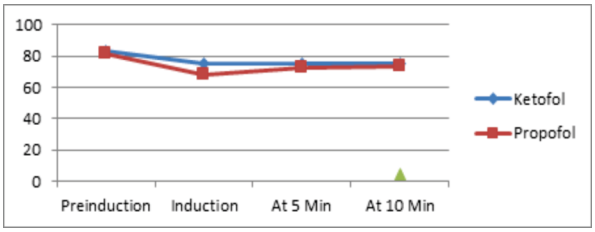

Figure 1. Heart rate in Ketofol compared with propofol group.

Systolic blood pressure was compared between the two groups and found to be significantly high in ketofol group compared to propofol group at induction (p=0.0053) and at 5 minutes (p=0.0139), and at 10 minutes (p=0.0001) after intubation.

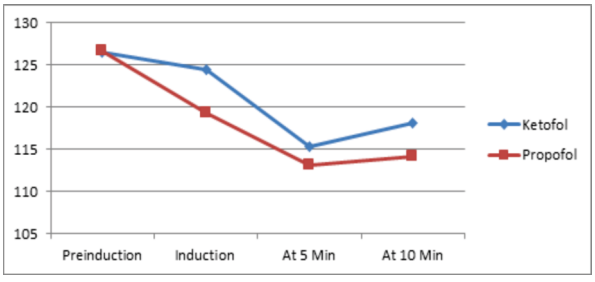

Figure 2. Systolic blood pressure in Ketofol compared with Propofol group.

Diastolic blood pressure was compared between the two groups of our study population where diastolic blood pressure was lower in propofol group compared to ketofol group at induction. Diastolic blood pressure was significantly higher in ketofol group compared to propofol group at induction (p=0.0017) and at 5 minutes (p=0.0329), and at 10 minutes (0.0001) after intubation.

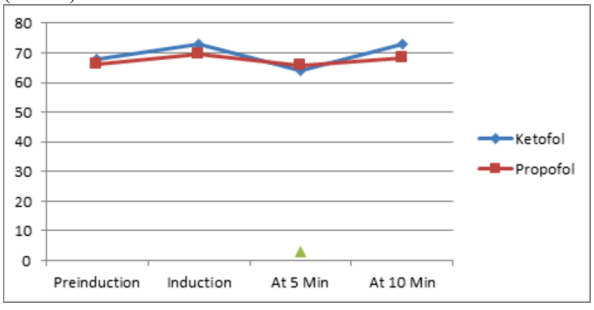

Figure 3. Diastolic blood pressure in Ketofol compared with Propofol group.

Mean arterial pressure was an important vital parameters for hemodynamic stabilization and was compared between the two groups. At induction the mean arterial pressure was significantly higher in ketofol group (p=0.0092). It was also significantly higher in ketofol group compared to propofol group at 5 minutes (p=0.0038) and at 10 minutes (p=0.0001) after intubation.

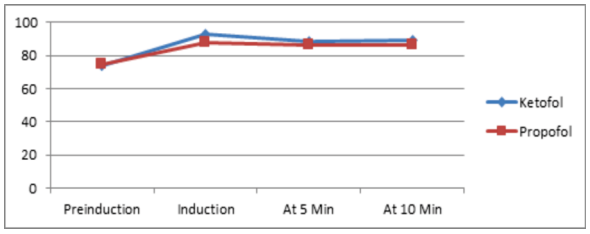

Figure 4. Mean arterial pressure in Ketofol compared with Propofol group.

The oxygen saturation of patients underwent elective surgeries in this study was within normal range throughout the surgery.

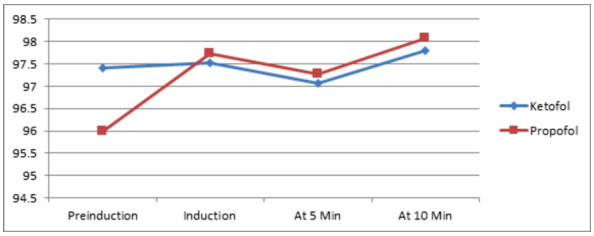

Figure 5. Oxygen saturation in Ketofol compared with Propofol group.

DISCUSSION:

In our study, we compare the hemodynamic consequences of ketofol and propofol on patient go through the elective surgeries during induction and post intubation schedule. The results of our study render that the ketofol stabilize hemodynamic sequel during induction and post intubation schedule and it is ketofol not propofol that brace the hemodynamics in elective surgeries. Significant effects were seen throughout the study with ketofol that gravitate in heart rate, systolic, diastolic and mean arterial blood pressure.

The crucial challenges of an anaesthesiologist is to maintain normal vital parameters within normal range during induction, post intubation and at the time of application of noxious stimuli.

Hamzeh et al[3] in a study of hemodynamic stability during Induction of Anaesthesia in Elderly Patients with Propofol+Ketamine and Propofol+Etomidate found that both maintain hemodynamic stability during induction, intubation and post intubation time. They also proffer that no significant difference between propofol+ketamine versus propofol+etomidate in mean arterial pressure (MAP) and heart rate during induction of anaesthesia in elderly patients.

Kayalha et al[1] studied the effect of ketofol instead of propofol on hemodynamic stabilization for induction of anaesthesia in laparotomy and conclude that ketofol conserved cardiovascular stability.
In a study by Yousef et al[10] surmised that ketofol is safe and effective induction agent for insertion of laryngeal mask airway and supplement cardiovascular stability in children.

Ketamine impede afferent pain and sensory inputs. It also abate spinothalamic transmission thereby diminishing sympathetic stimulation of pain, heart rate and blood pressure. Metabolism of ketamine eventuate in liver and its elimination half life is 2-3 hours. Ketamine expeditiously disseminate and captivate in the brain.

Nociceptive stimulation eventuate during skin incision is in between the electrical noxious stimuli and, laryngoscopy and intubation[1,11]. Clinical feedback of noxious stimuli is predominantly significant feedback to depth of anaesthesia. In this study, we used Bispectral index monitor to observed the depth of anaesthesia and kept it at the level of BIS: 40-60 which has low probability of explicit recall and unresponsive to verbal and noxious stimuli[11]. Intubation may requires supplemental opioid and hypnotic to quash the refractory response to hypertension and tachycardia. The quelling effect of ketofol to refractory pain sensation and hemodynamic feedback is better than propofol[1]. This effect of ketofol prospectively reduce the need of surge of opioid dosage.

The principal effect of ketofol is its trend on blood pressure (both systolic and diastolic) and heart rate. It follows a steady state throughout the schedule of induction, intubation and post intubation. The corresponding effect of stability presumably due to reduction of sympathetic stimulation by somatic pain stimulatory input. Therefore, it is suggested that the primary hurdle for hemodynamic stability is over activity of sympathetic nervous system[1].

CONCLUSION:

We conclude that our results indicates induction with ketofol is significantly effective in maintaining hemodynamic stability and impede hemodynamic changes due to administration of propofol. Hence, ketofol is a better substitute to propofol in elective surgeries to stabilize heart rate and blood pressure.

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