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COMPARISON OF HEMODYNAMIC RESPONSE OF SMALL DOSE KETAMINE VERSUS MIDAZOLAM AS CO- INDUCTION AGENT TO PROPOFOL: A RANDOMIZED DOUBLE BLIND INTERVENTIONAL STUDY

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ABSTRACT
The Anaesthesiology Department at Sawai Man Singh Medical College carried out this study. For this, 60 ASA grade I and II patients undergoing planned general surgery were randomly assigned into two groups of 30 each, with Group KP (n=30) receiving injections of ketamine at 0.3 mg/kg and Group MP receiving injections of midozolam at 0.03 mg/kg and Propofol I.V. The main goal of the study was to find the best induction by analysing changes in hemodynamic indicators from baseline to various time points after induction. On the basis of the necessary induction dose and hemodynamic characteristics, the groups were contrasted. The strategy used was to present the categorical data as percentages and compare them between groups using the Chi square test. The mean and standard deviation of the quantitative data were displayed, and students' t-tests were used to compare them. According to the study described above, group MP saw a greater fluctuation in heart rate than did group KP, whose heart rate remained more constant during the anaesthetic time. Group MP's blood pressure dropped more quickly after induction compared to group KP. The ketamine group's blood pressure remained the most stable out of all the groups. Apnea, pain upon injection, and uncontrollable movements were absent in the KP group. Of all the groups, the ketamine-propofol group required the least induction dose. As a result, we came to the conclusion that pretreatment with ketamine at a dose of 0.3 mg/kg results in better hemodynamic stability and requires less propofol for induction than midazolam does. The ketamine-propofol group is therefore the best of the two groups, making it the optimum induction agent.

INTRODUCTION

Modern anaesthesia is not complete without intravenous anaesthetic. Intravenous induction agents are more popular now that there are new intravenous anaesthetics available, patients absorb them better, and there is more worry about anaesthetic gas pollution in operating rooms. However, no one intravenous

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substance currently exists that satisfies all the criteria for a perfect anaesthetic. Co-induction anaesthesia was introduced as a result. This method's primary goal is to lessen the side effects and dosage of induction drugs like propofol. Midazolam has been the most often used co-induction drug with propofol thus far. Ketamine as co-induction drug include better hemodynamic stability. This comparative study is planned to compare the hemodynamic changes and dose reduction of Propofol when small dose of Ketamine versus Midazolam as co- induction to Propofol [1,2]. The aim of study the study is comparison of hemodynamic response of small dose ketamine versus midazolam as co- induction agent to propofol. The primary objective of the study is to determine the changes in hemodynamic variables from baseline to different time intervals post induction and the secondary objective is to compare the dose requirement of propofol for induction and to note any significant side effects of the drugs used [3].

MATERIAL AND METHODS

Study Location: This study was conducted in general surgery OT in the Department of Anaesthesiology, SMS Medical College and attached group of hospitals, Jaipur by taking ethical committee permission with reference no 167-(28) MC/EC/2020 dated 22/5/2020

Study Design: Hospital based, randomized, double blind, interventional study.

Study Period: After approval from research review board till desired sample size is achieved.

Sample Size: A sample of 30 cases in each group is needed at 95% confidence & 80% power to verify the expected difference of 9.84 (+7.96) in variation of HR from baseline to 1 minute post induction in both groups.

Randomization: was by sealed envelope method

Double Blinding: This trial is so planned that neither the anesthesiologist nor the patients will be aware of the groups and the drugs used. Both drugs are clear colourless solution. Anaesthesiologists who would prepare and administer the drugs would be different from anesthiologist who would observe study variables.

STUDY GROUPS: Total 60 patients randomized in two groups

Group A (n=30): Patients will receive 0.3 mg/kg ketamine i.v. as co induction agent dilute in normal saline up to 5 ml.

Group B (n=30): Patients will receive 0.03 mg / kg midazolam i.v. as co induction agent dilute in normal saline up to 5 ml.

ELIGIBILITY CRITERIA

A) Inclusion Criteria

- Patients willing to give written informed consent.
- ASA Grade I & II and Age Groups-25-55 years
- Planned for elective general surgery patient under general anesthesia.

B) Exclusion Criteria

- Patients with history of hypertension, asthma, diabetes mellitus, drug or alcohol abuse.
- Patients on concurrent drug therapy with beta blockers, beta agonists, alpha blockers, digitalis and antiarrhythmic drugs.
- Patients with history of allergic reaction to any of the drug used in the study

DATA ANALYSIS

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by students t-test. Probability was considered to be significant if less than 0.05.

RESULTS AND DISCUSSION

There was statistically no significant difference in the demographic data between the groups. The preoperative history, examination, biochemical value, ASA grading in two groups were comparable.

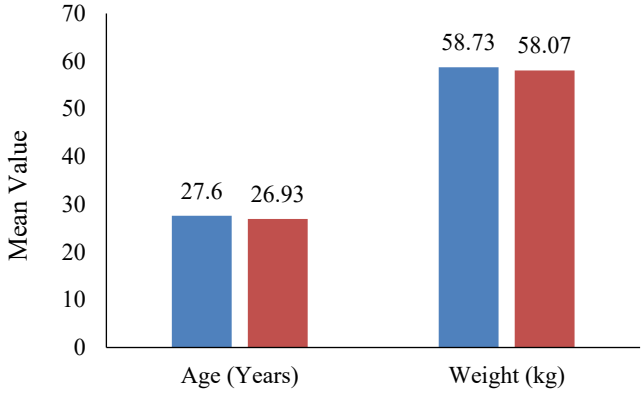

Fig 1: Age and weight wise distribution

Table 2: Induction dose and prop up in number of patients

	Induction dose (mg/kg)	Prop up in no. of patients	Total dose of propofol (mg)
Group A (KP)	1.21± 0.04	0	71.67±6.48
Group B (MP)	1.46± 0.04	6	81.67±7.91
P value	p<0.001(S)		p<0.001(S)

The table shows number of patients, induction dose, prop up in number of patients and total dose of propofol. Induction dose and total dose of propofol was least in group KP and prop up dose is also not required in group KP. The P value for induction dose, prop up in number of patients and total dose of propofol is <0.001 that is highly significant.

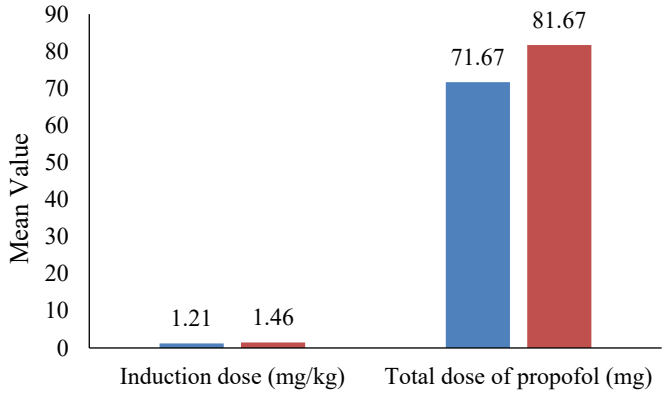

Fig 2: Induction dose and prop up in number of patients

The graph shows eyelash reflex, face mask tolerance, involuntary movements and other side effects like apnea and pain on injection in two groups. Eyelash reflex was absent in all the patients in group KP & MP. Face mask tolerance was present in all the patients in group KP & MP. Involuntary movements were present 5 patients in group MP but involuntary movements were absent all the patients of group KP. Apnea was not seen in group KP & MP. Pain on injection was present in 2 patients in group MP but pain on injection was not present in any patients in group KP.

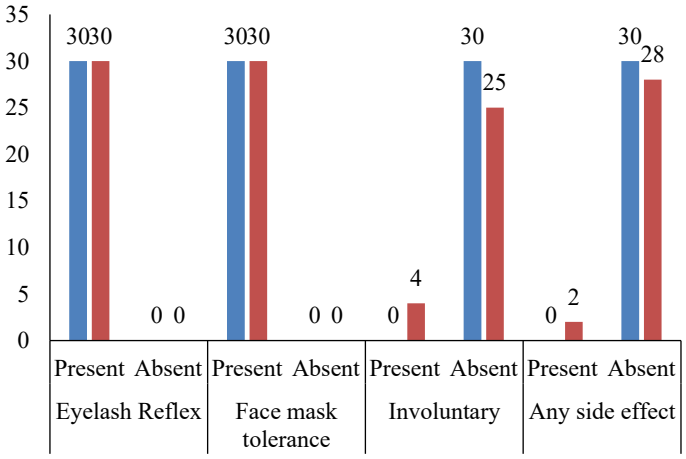

Fig 3: Eyelash reflex, face mask tolerance and side effects

The table show total dose of propofol in group KP & MP. Total dose of propofol less required in group KP compared to group MP.

Table 4: Total Dose of Propofol

	Group A (KP)		Group B (MP)	
	Mean	**SD**	**Mean**	**SD**
Mean Total dose of propofol	71.67	6.48	81.67	7.91
Min.-Max.	60-80		70-100	
Result (p value)	p<0.001 (S)			

S=significant; NS = Non significant

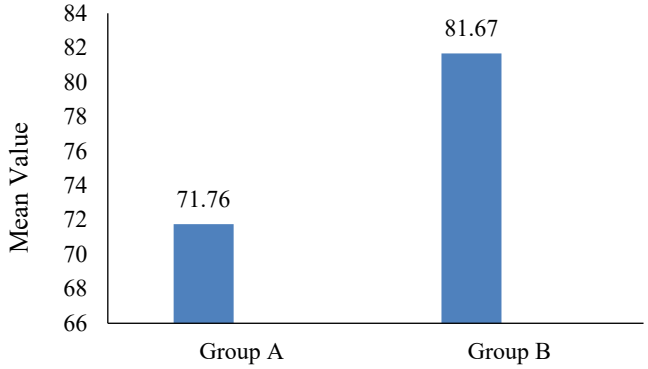

Fig 4: Total Dose of Propofol

Table 5: Heart Rate at Different Time Intervals (Mean±SD)

	Group A (KP)		Group B (MP)		p value
	Mean	**SD**	**Mean**	**SD**	
Pre Operative	86.27	8.48	90.20	9.56	0.097(NS)
After Premedication	89.07	8.49	92.93	9.71	0.106(NS)
1 min after co-induction	95.20	8.26	86.77	9.68	0.0006(S)
1 min after induction	78.70	7.81	72.30	9.20	0.0005(S)
5 min after induction	91.20	7.87	83.23	9.35	0.0007(S)
10 min after induction	80.07	7.67	78.37	9.23	0.440(NS)
15 min after induction	83.27	8.48	75.70	9.53	0.001(S)
20 min after induction	83.27	8.48	74.20	9.56	0.0002(S)

S=significant; NS = Non significant

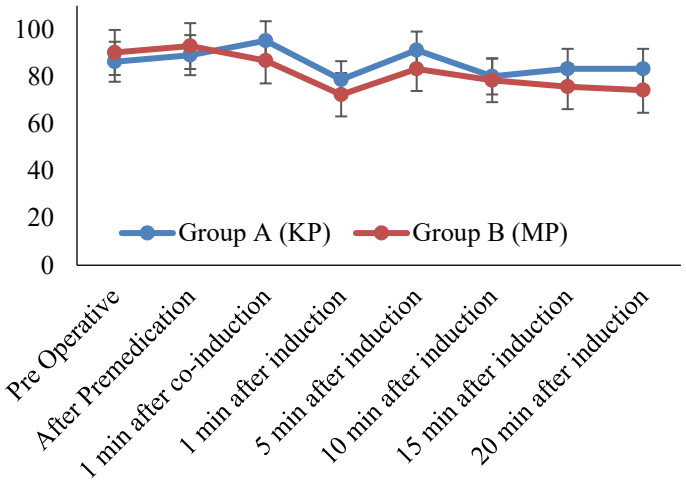

Fig 5: Heart Rate at Different Time Intervals (Mean±SD)

The table show mean heart rate with standard deviation at different time intervals in group KP & MP. There was initially rise in heart rate after premedication. After induction heart rate decreased in all the group and was statistically significant. Change in heart rate was least in group KP among all the groups

The table show mean systolic blood pressure with standard deviation at different time intervals in group KP & MP. After induction systolic blood pressure decreased in all the groups that was statistically highly significant. Change in systolic blood pressure was least in group KP Among all the group

Table 6: Systolic blood pressure at different time intervals

	Group A (KP)		Group B (MP)		p value
	Mean	SD	Mean	SD	
Pre Operative	124.20	7.90	119.93	5.16	0.016(S)
After Premedication	124.47	7.46	120.40	4.85	0.015(S)
1 min after co-induction	126.87	8.33	117.87	5.51	0.001(S)
1 min after induction	114.07	7.92	99.40	6.67	0.001(S)
5 min after induction	120.20	7.90	102.67	6.71	0.001(S)
10 min after induction	119.93	7.64	102.96	5.29	0.001(S)
15 min after induction	118.87	7.06	101.53	6.27	0.001(S)
20 min after induction	120.20	7.90	99.80	6.86	0.001(S)

S=significant; NS = Non significant

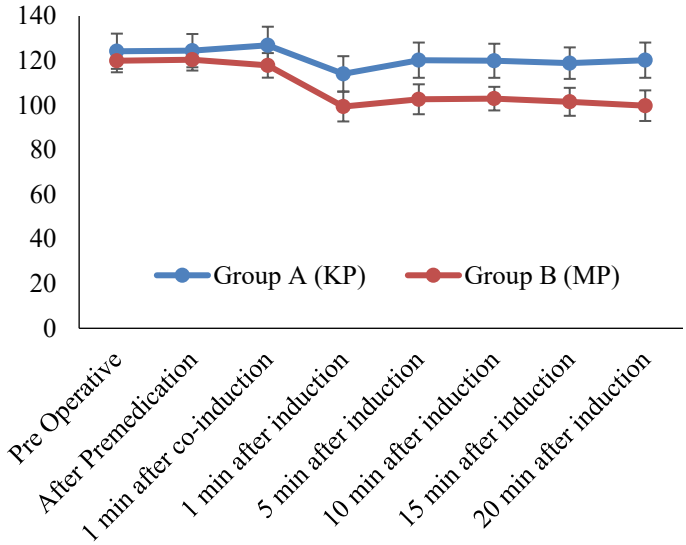

Fig 6: Systolic Blood Pressure at Different Time Intervals

The table shows mean diastolic blood pressure with standard deviation at different time intervals in group KP & MP. After induction diastolic blood pressure decreased in all the groups that was statistically highly significant. Change in diastolic blood pressure was least in group KP among all the groups

Table 7: Diastolic blood pressure at different time intervals

	Group A (KP)		Group B (MP)		p value
	Mean	SD	Mean	SD	
Pre Operative	80.20	4.91	78.73	5.16	0.263(NS)
After Premedication	80.47	4.35	78.73	4.94	0.154(NS)
1 min after co-induction	83.13	4.86	76.00	5.30	0.001(S)
1 min after induction	73.47	4.30	67.00	4.29	0.001(S)
5 min after induction	77.73	4.66	69.87	4.45	0.001(S)
10 min after induction	76.73	4.18	69.20	4.48	0.001(S)
15 min after induction	76.47	4.35	69.67	4.40	0.001(S)
20 min after induction	77.80	5.13	68.20	4.59	0.001(S)

S=significant; NS = Non significant

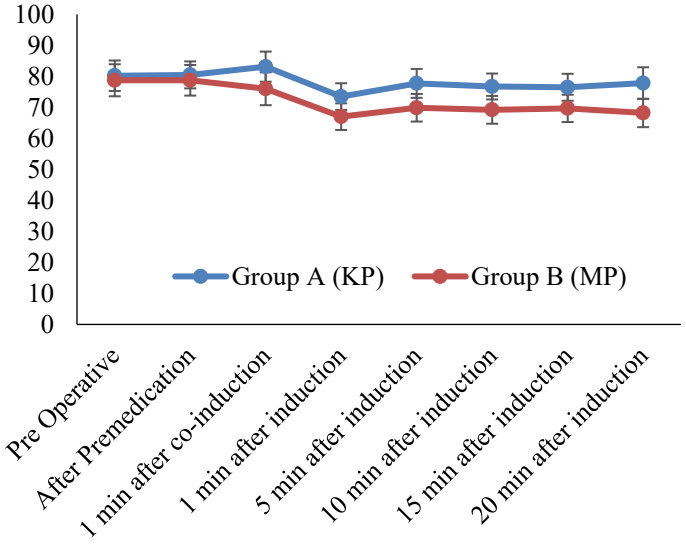

Fig 7: Diastolic Blood Pressure at Different Time Intervals

Table 8: Mean Arterial Pressure at different time intervals

	Group A (KP)		Group B (MP)		p value
	Mean	SD	Mean	SD	
Pre Operative	94.87	5.53	92.47	3.82	0.055(NS)
After Premedication	95.13	5.03	92.62	3.59	0.030 (S)
1 min after co-induction	97.71	5.65	89.96	3.91	0.001(S)
1 min after induction	86.99	5.07	77.84	2.98	0.001(S)
5 min after induction	90.99	6.64	80.81	3.02	0.001(S)
10 min after induction	91.13	4.99	80.34	3.20	0.001(S)
15 min after induction	90.60	4.92	80.29	2.84	0.001(S)
20 min after induction	91.93	5.63	78.73	2.95	0.001(S)

S=significant; NS = Non significant

The table shows mean arterial pressure with standard deviation at different time intervals in group KP & MP. After induction mean arterial pressure decreased in al the groups that was statistically highly significant. Change in mean arterial pressure was least in group KP among the groups.

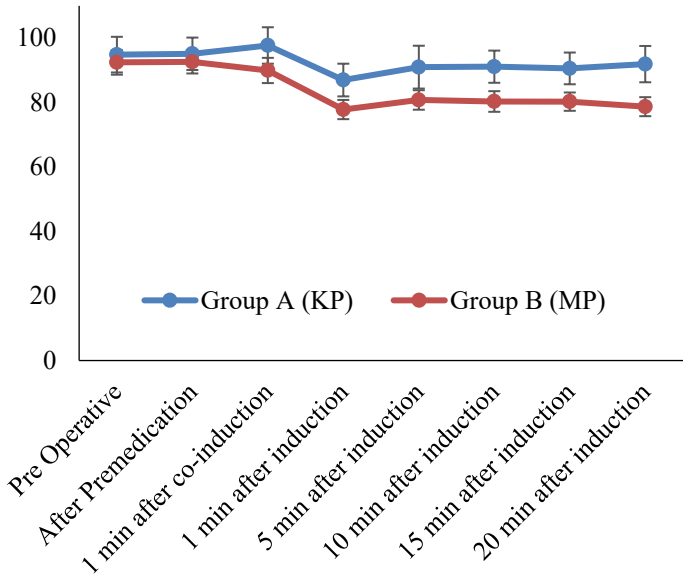

Fig 8: Mean Arterial Pressure at different time intervals

The table 9 shows percentage oxygen saturation (**SpO_2**) with standard deviation at different time intervals in group KP & MP

Table 9: Mean Arterial Pressure at different time intervals

	Group (KP)		AGroup (MP)		Bp value
	Mean	**SD**	**Mean**	**SD**	
Pre Operative	99.80	0.55	99.77	0.63	0.827(NS)
After Premedication	99.83	0.53	99.83	0.53	--
1 min after co-induction	99.83	0.53	99.83	0.53	
1 min after induction	99.83	0.53	99.83	0.53	
5 min after induction	99.83	0.53	99.83	0.53	
10 min after induction	99.83	0.53	99.83	0.53	
15 min after induction	99.83	0.53	99.83	0.53	
20 min after induction	99.83	0.53	99.83	0.53	

S=significant; NS = Non significant

The table 10 show percent reduction of induction dose from group B (MP). Reduction in induction dose was maximum in Group KP comparison to group MP. % reduction in induction dose in group A (KP) is 17.12%. Comparison to group B (MP)

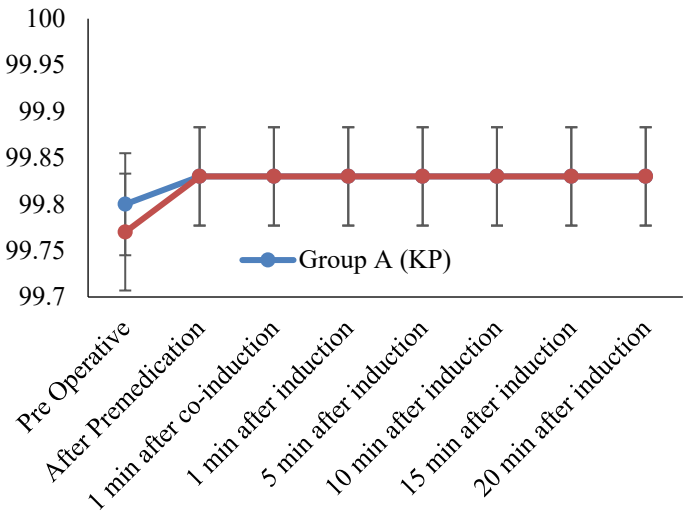

Fig 9: SpO_2(%) Oxygen saturation at different time intervals

Table 10: Percent reduction of induction dose in group A (KP) from group B (MP)

	% reduction of induction dose	
Group A (KP)	1.21	17.12%
Group B (MP)	1.46	

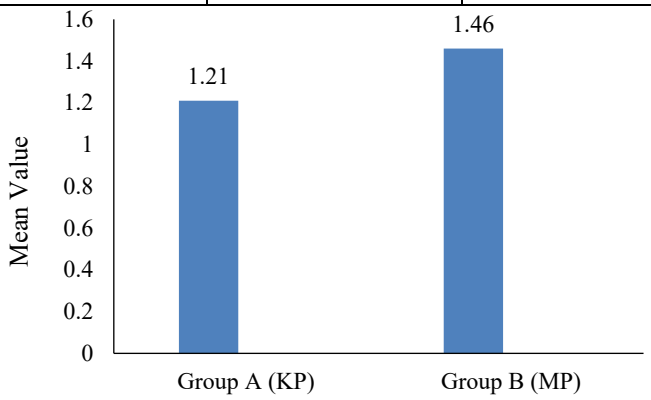

Fig 10: Reduction of induction dose in group A (KP) from group B (MP)

The table 11 show percent fall of heart rate from baseline values that was least in group KP (ketamine-propofol) indicating haemodynamic stability.

Table 11: Percent fall of Heart rate from baseline value

	%fall of HR
Group A (KP)	0.52%
Group B (MP)	10.75%

The table 12 show percent reduction of mean arterial pressure from baseline that was least in group KP (Ketamine-propofol) indicating haemodynamic stability

Table 12: Percent reduction of Mean Arterial Pressure (MAP) from baseline

	% reduction of MAP
Group A (KP)	4.57%
Group B (MP)	11.76%

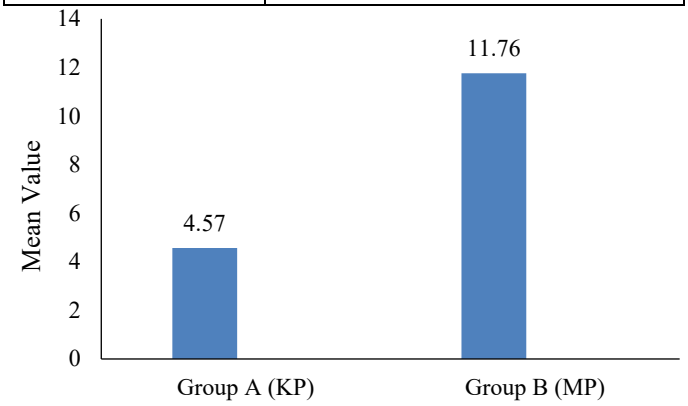

Fig 12: Percent reduction of Mean Arterial Pressure (MAP) from baseline

DISCUSSION

In search of better co-induction agent, the study was conducted in 60 ASA grade-1 & II patients undergoing planned General Surgery. They were divided in two groups of 30 each according to the combination used. In all two groups, induction was done with propofol after co-induction with ketamine 0.3 mg/kg in group KP (ketamine-propofol) and midazolam 0.03 mg/kg in group MP (midazolam-propofol) [4]. All patients were demographically similar. There were no statistically significant intergroup variations regarding age and weight.

Induction dose and prop up doses of propofol

Mean indication dose of propofol in Group KP (ketamine-propofol) was 1.21± 0.04 and in group MP (Midazolam-propofol) was 1.46 ± 0.04. Thus, above finding in our study may substantiate the fact that sub-anaesthetic doses of ketamine reduce effectively the induction dose of propofol in comparison to other groups [5]. In our study five patients in midazoiam-propofol group prop up doses required but prop up dose was not required in ketamine propofol group. Mean induction dose of propofol was least in ketamine propofol group.

Total Induction Dose of Propofol

The total induction dose was reduced by 17.12% (Group KP) compare to group MP. Our results are consistent with studies of Srivastava et al. (2006) [5]. They reported that total induction dose was reduced in group KP compared to group MP. Maximum reduction in induction dose of propofol was in group-KR ketamine- propofol. While Djaini et al. (1999) [1] reported reduction in total induction dose of propofol is more in group KP compare to group MP.

Heart Rate

The preoperative heart rate was almost equal in all the two groups. After premedication there was little rise in heart rate. In group KP (ketamine-propofol) after co-induction with ketamine there is increase in the heart rate which is due to a reflex cardiac stimulant action of ketamine.

In group MP after co-induction with midazolam and propofol respectively there is decrease in heart rate due to cardio depressant action. After induction with propofol heart rate decreased in all the two groups and was statistically significant. Percent fall in heart rate from baseline was 0.52% in ketamine-propofol group, 10.75% in midazolam-propofol group. Our results are similar with Srivastava et al study [5]. Change in heart rate was least in group KP indicated hemodynamic stability.

Our results are also comparable to Tomatir. et al. (2004) [6]. They studied effects of low dose ketamine before induction on propofol anaesthesia for pediatric MRI. They reported that heart rate decreased less in the propofol-ketamine group as compared to propofol-propofol group.

The lowering of heart rate might be because of resetting of baroreceptor reflex by propofol which allowed slower heart rate inspite of a decreased blood pressure. Our results were similar to Anderson et al. (1998) [3].

Blood Pressure

The baseline values of mean arterial pressure in all the groups were almost equal. After co-induction mean arterial pressure in group KP increased and in group MP it decreased that was statistically highly significant. After induction mean arterial pressure decreased in all the groups that was statistically highly significant. In group KP change in mean arterial pressure was least in comparison to rest all the groups. The fall in mean arterial pressure just after induction in all the groups may be explained by an inhibition of sympathetic vasoconstrictor tone by propofol which leads to relaxation of vascular smooth muscles and decrease in systemic vascular resistance. The

negative ionotropic effect of propofol may also be associated with a fall in mean arterial pressure. In group KP ketamine may have counter balanced the hemodynamic effects of propofol that's why the fall of mean arterial pressure in group KP just after induction, was not as much as in other groups. Ketamine is known to produce as effect that resembles central sympathetic stimulation, which produces a dose related increase in the rate-pressure product, leading to a rise in heart rate and mean arterial pressure. Rise of mean arterial pressure at 5 minutes after induction may be explained by laryngoscopy & intubation. Hui et al (1995) [7] also reported a fall in mean arterial pressure in patients induced with propofol + ketamine but the magnitude of the fall was significantly less than propofol alone. They observed that the combination of propofol-ketamine ensured a stable hemodynamic status. Short et al (1991) [8] studied interactions between i.v propofol and midazolam for induction of anaesthesia. They reported that the reduction in arterial pressure at induction was the same for the combination as for the individual agents. Wilder et al. (2001) [9] studied midazolam premedication with propofol. They reported that midazolam premedication 20 minutes prior to induction of anaesthesia reduces the propofol doses necessary to attain the multiple anaesthetic end points without affecting haemodynamics in this otherwise healthy population. Propofol in the recommended dose of 2 - 2.5 mg/kg almost always causes fall in blood pressure. The extent of fall depends upon the dose and adjuvant drugs used. The fall in mean arterial pressure in ketamine group (KP) and midazolam group (MP) was 4.57% and 11.76% respectively. So, the fall in mean arterial pressure was least in group KP. The minimum change observed in arterial pressure in group KP may be dose related and also because sympathomimetic actions of ketamine were effective in counteracting the hemodynamic depression of propofol. Our results coincide with Srivastava et al. (2006). Our results are similar with Djaiani et al (1999) [1] who reported 14.9% reduction in mean arterial pressure in midazolam propofol group.

Involuntary Movements

Involuntary movements were not present in any patient in ketamine-propofol group. Our results correlated with Tan et al. (1998) [10] study. Tan et al. [10] studied "The effect of ketamine pretreatment on propofol injection pain in 100 women". They observed that incidence of excitatory effects such as twitching, Writhing and jerking was 6% in the ketamine group and 26% in the control group. While in group MP 5 patients involuntary movements were present.

OTHER SIDE EFFECTS

Pain on injection

Pain on injection was not present in any patient in ketamine-I propofol group. This can be explained by local anaesthetic action of ketamine when administered intravenously for regional anaesthesia which attenuated the afferent pain pathway as well as central analgesic effect. As a non-competitive NMDA receptor antagonist, ketamine may activate NMDA receptors either in the vascular endothelium or in the central nervous system; this is another possible mechanism Tan et al. (1998) [10]. While pain on injection was present in 2 patients in group MP.

Apnea

In our study ketamine-propofol and midozolam-propofol group apnea was not there in any patient. Hui et al (1995) [7] reported superior analgesia with less respiratory depression when propofol-ketamine combination was compared to the propofol-fentanyl combination. We concluded that the ketamine-propofol combination is suitable for induction of anaesthesia as compared to midazolam-propofol. In Ketamine-propofol combination induction dose of propofol required was least compared to any other group with better haemodynamic stability, no respiratory depression and with minimal side effects. The combination of propofol with 0.3 mg/kg ketamine can be considered as near ideal regimen for induction of anaesthesia.

CONCLUSION

The study was conducted in 60 ASA grade I & II patients undergoing planned general surgery. They were randomly divided in 2 groups of 30 each, according to the combination used. Group KP (n=30): Inj. ketamine 0.3 mg/kg + Inj. propofol I.V. Group MP (n=30) : Inj. midozolam 0.03 mg/kg + Inj. propofol I.V. The groups were compared on the line of induction dose required and hemodynamic variables. The following conclusions were made in the above study:

1. There was greater change in heart rate in group MP as compared to group KP in which the heart rate remained more stable throughout the period of anaesthesia.
2. The fall in blood pressure just after induction was more in group MP as compared to group KP. The blood pressure in ketamine group remained more stable among all the groups

3. Pain on injection, apnea and involuntary movements were not present in KP group
4. Requirement of induction dose was least in ketamine-propofol group among all the groups.
5. Thus, we concluded that pretreatment with ketamine in dose of 0.3 mg/kg provides better haemodynamic stability and less induction dose of propofol as compared to midazolam. Thus ketamine-propofol group is best among all the two groups.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Nitish Chaudhary contributed in conceptualizing, data curating and formal analysis. He also contributed in writing original draft. Sunil Chauhan contributed in investigation and supervision of whole study. Sandeep Kothari contributed in writing, reviewing and editing the manuscript. Kiwi Mantan contributed in accessing resources and reviewing and editing the manuscript. All authors read and approved the manuscript.

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