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A STUDY OF KETOFOL VERSUS PROPOFOL AS ANAESTHETIC INDUCTION AGENT IN LAPAROSCOPIC CHOLECYSTECTOMY

Anaesthesiology

Dr. Sekhar Jyoti Sharma* DA, DNB, Consultant Anesthesiologist, Cardiothoracic and Neurosciences centre, Gauhati medical College and hospital *Corresponding Author

Dr. Jayashree Sood MD, Director, Department of Anesthesiology, Pain & perioperative medicine, Sir Gangaram Hospital, New Delhi

ABSTRACT

Introduction: Propofol is one of the most preferred intravenous agents for induction of anaesthesia. It causes rapid and smooth induction, and a smooth recovery from anaesthesia. But, it leads to hypotension and respiratory depression which limits its use in haemodynamically unstable patients. Ketamine, on the other hand, is not very commonly used for induction of anaesthesia because of a number of adverse effects. But, it has its own advantages. It leads to cardiovascular stimulation and helps in maintaining spontaneous respiration. It also has good analgesic properties. Combining propofol and ketamine has been found to have more favorable patient outcomes. This novel combination has gained popularity for use in procedural sedation and analgesia, and is commonly being referred to as "ketofol". Aims & Objectives: This study undertook comparative evaluation of propofol and ketofol (ketamine + propofol) as anaesthetic induction agents in terms of haemodynamic stability, in patients undergoing laparoscopic cholecystectomy under GA. Material & methods:The study was conducted in the Department of Anaesthesiology, of a tertiary care hospital. After obtaining institutional ethics committee approval and written informed consent of the patients, 100 ASA-I/II adults were randomly assigned into two groups of 50 participants each, to receive propofol 2mg/kg or ketofol (ketamine 0.5mg/kg + propofol 1.5mg/kg) for induction of anaesthesia. SBP, DBP, MAP and HR were recorded at 0, 2, 5, 10, 15, 30, 60 mins, end of surgery and then hourly upto 4 hours post-operatively. Data obtained from the study was analysed by the statistical package of Windows, the SPSS version 17.0. Results: Patients who received ketofol had a lesser fall in SBP, DBP, MAP while the HR remained unchanged.Discussion: Propofol is an excellent induction agent but causes hypotension. Combining both these drugs leads to stable haemodynamics. Conclusions:Ketofol used as induction agent provides greater haemodynamic stability as compared to propofol alone, without any significant adverse effects

KEYWORDS

Ketofol, Propofol, cholecystectomy,induction

INTRODUCTION

Propofol is presently the most widely used intravenous agent for induction of anaesthesia. Structurally, it is 2,6-di-isopropylphenol[1]. It provides general anaesthesia by facilitation of inhibitory neurotransmission mediated by $GABA_2$. It is preferred over other induction agents because of its rapid and smooth onset and recovery profile. At a dose of 1.5-2.5 mg/kg body weight, it requires only one arm-brain circulation time (about 30 secs.) for induction of anaesthesia[3]. In addition, it also has anti-emetic property. The major disadvantages of propofol include dose-dependent hypotension, respiratory depression and pain on injection[4,5]. Besides, it lacks any analgesic property and hence requires the addition of other analgesic(s) for painful procedures.

Ketamine is a phencyclidine derivative and is known to cause 'dissociative anaesthesia'[6]. Its major advantage is that it causes cardiovascular stimulation via the sympathetic system. It does not suppress the protective airway reflexes and helps in maintaining spontaneous respiration. Besides, it has excellent analgesic properties[7,8]. Hence, it is used in many short-duration painful procedures like burn dressings and closed reduction of bone fractures. But it has a number of adverse effects which have limited its use. These include nausea & vomiting, emergence hallucinations and increased intracranial tension[9,10].

It was postulated that combining propofol and ketamine will result in a mixture (ketofol) that has additive effects during induction of anaesthesia, which implies a reduction in the requirement of either drug[11,12]. In addition, ketamine and propofol may counter the effects of each other resulting in a greater haemodynamic stability, while decreasing the adverse effects. Besides, the analgesic properties of ketamine can also be exploited. Moreover, the pain due to injection of propofol can be blunted by prior administration of ketamine[13,14]. Ketamine has also been reported to decrease post-operative shivering[15,16].

Hence, our study is aimed at evaluating whether the adverse effects of ketamine and propofol balance each other on combining the two and provide a better patient outcome. Therefore, our study compares the haemodynamic changes after induction of anaesthesia when ketofol and propofol are used as anaesthetic induction agents.

AIMS AND OBJECTIVES

To compare propofol and ketofol (propofol + ketamine) asanaesthetic induction agents in patients undergoing elective laparoscopic cholecystectomy.

The Two Drugs Were Compared To Evaluate :-

i/ the haemodynamic changes after induction of anaesthesia

MATERIAL AND METHODS

Studysite : The study was conducted in the Department of Anaesthesiology, Pain & Peri-operative medicine, Sir Ganga Ram Hospital, New Delhi.

Duration Of Study : 1 year

Sample Size Calculation *:*

For the sample size calculation, we defined a relevant difference of 25% in the fall in mean arterial pressure in the control and study groups. Using a two tailed alpha value (0.05) and a beta value (0.1), 45 observations per group were found to be sufficient to detect a significant difference(>20% from baseline). To make up for any data loss due to drop outs we included 50 patients in each group.

Study Design :

Prospective, controlled, randomized and double-blind.

Group Allocation—

100 adult patients belonging to ASA I or II scheduled to undergo elective laparoscopic cholecystectomy under GA were recruited for the study. They were randomized by a computer generated program into two groups of 50 patients each.

Group 1 received a combination of ketamine 0.5 mg/kg + propofol 1.5 mg/kg body weight for induction.

Group 2 received propofol 2 mg/kg body weight for induction.

Inclusion Criteria

I) ASA physical status I and II
II) Age group 18-60 years
III) Elective laparoscopic cholecystectomy

Exclusion Criteria

I) Not consenting for participation in the study.

II) Known allergy to either of the drugs under study or to egg-albumin.
III) Pregnant females
IV) Known personality disorder
V) Chronic opioid or alcohol intake
VI) Any known contraindication to propofol (shock) or ketamine (cardiac disease, raised intracranial tension) use.
VII) Known seizure disorder.

Pre-anaesthetic Evaluation—
A thorough evaluation of the patients was done, which included a detailed clinical history, physical examination and airway assessment
The following **investigations** were done in all patients:
- Complete blood count
- Blood sugar
- Urine routine and microscopic examination

In Addition, Investigations As Dictated By Patient Condition:-
- ECG (age more than 40 years, diabetes and hypertension.)
- Chest X-ray (age more than 40 years)
- BUN and serum creatinine (age more than 40 years)

Patient Preparation—
The anaesthetic procedure was explained to the patients and an informed consent was obtained from the patients and their relatives.

All patients were advised to take light diet on the night beforesurgery and nothing by mouth for 8 hours before surgery.

The following **premedication** was ordered:
- Tab. alprazolam 0.25 mg night before and the morning of surgery.
- Tab. ranitidine hydrochloride 150 mg night before and the morning of surgery.

Anaesthesia Technique—
In the operative room, a 20 G intravenous cannula was secured on the non-dominant hand of the patient and an intravenous drip started. Standard anaesthesia monitors were attached and the baseline blood-pressure, heart rate and peripheral oxygen saturation were recorded. Inj. glycopyrrolate 0.2mg i.v.and Inj.fentanyl citrate 2 µg/kg body weight i.v. were given 5 minutes before induction.

The patient was then pre-oxygenated with 100% oxygen for 3 minutes. Induction of anaesthesia was done with either of the two drugs under study as per randomization. The two drugs were prepared by an independent anaesthesiologist and the one recording the data was not aware of the drug being given.

Vecuronium bromide 0.1mg/kg body weight was used to facilitate endotracheal intubation and the trachea was intubated with an appropriate size endotracheal tube when the train of four(TOF) count was < 2. Bilateral air entry was checked and intermittent positive pressure ventilation(IPPV) started with volume-control mode and tidal volume(TV) of 6-8ml/kg maintaining $EtCO_2$ between 30-40 mm of Hg.

Anaesthesia was maintained with oxygen, nitrous-oxide and sevoflurane with a MAC between 0.9-1.2. Top-up doses of the relaxant were administered as and when required, on the basis of neuromuscular monitoring.

At the end of the surgery, neuromuscular blockade was reversed with Inj. neostigmine (0.05mg/kg) + Inj. glycopyrrolate(0.01mg/kg) after adequate respiratory efforts had returned and the trachea extubated when T4/T1 ratio reached 90% or higher. Post-extubation blood pressure, heart rate and SpO_2 values were recorded. Then the patient was shifted to the post-anaesthetic care unit(PACU).

Postoperative analgesic requirement was assessedby Visual Analog Scale (VAS).Fentanyl 0.5 µg/kg was administered as rescue analgesic when VAS was more than 3. Depending on the pain severity, Inj. diclofenac sodium 75 mg as i.v. infusion or paracetamol 1 g infusion was administered additionally, if needed. Any postoperative adverse effect, like nausea, vomiting, any abnormal movement or abnormal behaviour wasrecorded .Patients experiencing nausea or vomiting received Inj. ondansetron 4 mg i.v. as a rescue anti-emetic.

Intraoperative Monitoring
Intraoperatively, 5-lead ECG, SpO_2, NIBP and $EtCO_2$ monitoring was done as standard. Additionally, neuromuscular monitoring was done to monitor muscle relaxation status.

Statistical Analysis
The data generated after the assessment of the subjects in the two groups were tabulated and analysed statistically using the statistical package for the social science system version SPSS 17.0. Continuous variables are expressed as mean ± SD(standard deviation), and categorical variables are presented as absolute numbers and percentages. The comparison of normally distributed continuous variables between the groups was performed using student's T test. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

Ethical Issues:
1. A fully informed and freely volunteered written consent was taken from all the participants and their relatives prior to collection of data.
2. The information gathered during the study was kept confidential and was shared with the treating team only when thought to be of benefit to the patient.
3. The participation or non-participation did not alter the services offered to the patients in the hospital.
4. No incentives of any kind were offered to the participants in the study.

RESULTS AND OBSERVATIONS:
The mean age of patients in group 1 was 40.28 ± 10.14 years and 42.6 ± 11.657 years in group 2. The p value of 0.291 shows no statistically significant difference in the mean age in between the two study groups. In both the groups 66% of the patients were females and only 34% were males. Hence, both the groups were comparable.

Table 1 shows the mean heart rate of the patients in the two groups. The heart rates were comparable in both the groups at all time-intervals.

Heart rate (beats per minute)	Group 1 (n=50)		Group 2 (n=50)		P Value
	Mean ± SD	Range	Mean ± SD	Range	
Baseline	82.98 ± 16.779	54 – 108	80.64 ± 11.754	56 – 98	0.421
2 mins	87.76 ± 20.906	54 – 130	84.66 ± 9.510	60 – 92	0.342
After intubation	94.12 ± 16.758	66 – 128	97.70 ± 11.285	62 – 105	0.213
5 mins	88.38 ± 16.484	68 – 130	87.86 ± 14.060	56 - 96	0.866
10 mins	79.78 ± 18.835	54 – 116	80.20 ± 10.474	52 – 85	0.891
15 mins	77.72 ± 17.964	54 – 114	76.24 ± 9.968	50 – 87	0.612
30 mins	77.70 ± 16.737	51 – 100	76.14 ± 7.791	52 – 84	0.552
60 mins	78.90 ± 14.241	60 – 108	76.44 ± 9.128	52 – 82	0.315
end of surgery	79.94 ± 16.303	52 – 116	77.94 ± 10.334	50 – 84	0.466
after reversal	94.18 ± 13.018	67 – 118	96.76 ± 10.599	75 – 112	0.280
1sthr post-op	75.48 ± 9.671	52 – 88	78.40 ± 7.489	60 – 89	0.095
2ndhr post-op	73.86 ± 6.138	58 – 84	74.26 ± 5.394	64 – 85	0.730
4thhr post-op	73.16 ± 7.611	60 – 84	71.80 ± 6.289	60 – 83	0.332

Table 2 shows the comparison between the systolic blood pressure between the patients in the two groups.

SBP (mm of Hg)	Group 1 (n=50)		Group 2 (n=50)		P Value
	Mean ± SD	Range	Mean ± SD	Range	
Baseline	127.34 ± 17.462	95 - 166	133.40 ± 15.480	110-61	0.069
2 mins	100.88 ± 14.488	76 - 137	93.68 ± 9.584	77-114	0.004
After intubation	129.82 ± 31.289	78 - 205	120.20 ± 27.544	82-175	0.106
5 mins	120.14 ± 24.346	84 - 173	105.40 ± 17.989	80-144	0.001
10 mins	100.98 ± 15.755	71 - 146	96.68 ± 13.036	77-122	0.14
15 mins	98.60 ± 11.792	73 - 121	99.74 ± 16.471	75-139	0.692
30 mins	122.94 ± 24.790	87 - 177	120.90 ± 24.868	85-164	0.682
60 mins	121.48 ± 20.422	79 - 160	121.02 ± 14.682	97-146	0.898
End of surgery	123.28 ± 17.971	99 - 166	120.68 ± 12.021	102 - 142	0.398

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After extubation	137.72 ± 16.130	102 - 170	147.26 ± 15.110	125 - 183	0.003
1sthr post-op	125.24 ± 11.563	104 - 144	131.48 ± 13.902	106 - 158	0.016
2ndhr post-op	120.06 ± 10.215	107 - 143	125.68 ± 10.643	109 - 147	0.008
4thhr post-op	121.00 ± 9.129	108 - 141	124.20 ± 9.495	108 - 140	0.089

The baseline SBP was comparable in the two groups under study. Group 1 had a mean SBP value of 127.34 ± 17.462 mm of Hg, while group 2 had a mean value of 133.40 ± 15.480 mm of Hg. The p-value of 0.069 indicates that there was no statistically significant difference between the two groups.

2 mins after induction, there was a fall in SBP in both the groups. In group 1 the mean SBP came down to 100.88 ± 14.488, while in group 2 it came down to 93.68 ± 9.584. The p-value of 0.004 shows that the fall in SBP after 2 mins was statistically significant in group 2.

There was a transient rise in SBP after intubation in both the groups. In group 1 the SBP was 129.82 ± 31.289 while in group 2 it increased to 120.20 ± 27.544. The difference in both the groups was not statistically significant (p=0.106).

After 5 mins, the SBP in group 1 was again decreased to 120.14 ± 24.346 and to 105.40 ± 17.989 in group 2. The p- value of 0.001 shows that the difference in the two groups is statistically significant.

At 10, 15, 30 and 60 mins, till the end of surgery there was no statistically significant difference in the two groups.

After extubation, the SBP in group 1 was 137.72 ± 16.130 and in group 2 was 147.26 ± 15.110, which shows a statistically significant increase in the latter.

After the 1st and 2nd post-operative hours, group 2 shows a significant increase in the SBP compared to group 1, while after 4 hours the SBP in both groups was comparable.

Table 3 shows the comparison between the diastolic blood pressure between the patients in the two groups.

DBP (mm of Hg)	Group 1(n=50)		Group 2 (n=50)		P Value
	Mean ± SD	Range	Mean ± SD	Range	
Baseline	78.30 ± 9.455	61 – 96	79.98 ± 11.089	60 - 97	0.417
2 mins	62.70 ± 14.009	45 – 97	55.20 ± 5.364	46 - 68	0.001
After intubation	80.72 ± 16.135	52 - 106	74.46 ± 20.454	44-102	0.092
5 mins	74.68 ± 14.242	49 - 105	66.60 ± 15.370	46 - 94	0.008
10 mins	63.04 ± 11.858	45 – 99	59.26 ± 8.015	46 - 73	0.065
15 mins	65.06 ± 9.470	49 – 85	64.68 ± 14.892	48 - 96	0.879
30 mins	80.38 ± 17.064	48 - 107	75.98 ± 18.674	48-115	0.222
60 mins	80.60 ± 14.969	53 - 108	73.48 ± 11.891	55 - 97	0.010
End of surgery	76.84 ± 13.244	48 - 101	74.36 ± 8.241	60 - 91	0.264
After extubation	87.84 ± 12.856	65 - 107	88.76 ± 10.733	67-106	0.699
1sthr post-op	78.46 ± 9.662	62 – 97	80.22 ± 9.006	67 - 92	0.348
2ndhr post-op	75.48 ± 7.996	66 – 93	79.10 ± 8.392	68 - 96	0.03
4thhr post-op	72.64 ± 6.262	63 – 84	78.50 ± 7.141	68 - 88	<0.001

The baseline DBP was comparable in the two groups under study. Group 1 had a mean DBP value of 78.30 ± 9.455 mm of Hg, while group 2 had a mean value of 79.98 ± 11.089 mm of Hg. The p-value of 0.417 indicates that there was no statistically significant difference between the two groups.

2 mins after induction, there was a fall in DBP in both the groups. In group 1 the mean DBP came down to 62.70 ± 14.009, while in group 2 it came down to 55.20 ± 5.364. The p-value of 0.001 shows that the fall in DBP after 2 mins was statistically significant in group 2.

There was a transient rise in DBP after intubation in both the groups. In group 1 the DBP was 80.72 ± 16.135 while in group 2 it increased to 74.46 ± 20.454. The difference in both the groups was not statistically significant (p=0.106).

After 5 mins, the DBP in group 1 was again decreased to 74.68 ± 14.242 and to 66.60 ± 15.370 in group 2. The p- value of 0.008 shows that the difference in the two groups is statistically significant.

At 10, 15 and 30 mins, there was no statistically significant difference in the two groups.

At 60 mins, the DBP in group 2 again shows a significant difference.

After extubation and in the 1st post-operative hour both the groups were comparable.

After the 2nd and 4th post-operative hours, group 1 shows a significant decrease in the DBP compared to group 2.

Table 4 shows the comparison between the mean arterial blood pressure between the patients in the two groups.

MAP (mm of Hg)	Group 1 (n=50)		Group 2 (n=50)		P Value
	Mean ± SD	Range	Mean ± SD	Range	
Baseline	94.74 ± 11.087	74 – 119	99.12 ± 10.783	81- 121	0.048
2 mins	75.16 ± 14.514	53 – 108	66.58 ± 5.241	57 - 79	<0.001
After intubation	98.06 ± 21.781	60 – 140	90.26 ± 25.436	57 - 136	0.103
5 mins	91.48 ± 17.536	61 – 133	79.68 ± 15.691	59- 106	0.001
10 mins	76.92 ± 13.440	54 – 114	71.52 ± 9.558	55 - 89	0.023
15 mins	77.16 ± 9.984	56 – 97	78.18 ± 18.693	55- 131	0.734
30 mins	95.80 ± 18.821	65 – 125	91.20 ± 20.232	60- 126	0.243
60 mins	94.88 ± 16.263	64 – 128	90.12 ± 13.170	68- 112	0.111
End of surgery	92.24 ± 14.691	66 – 123	90.38 ± 9.916	77- 116	0.460
After extubation	105.66 ± 12.961	78 – 126	110.18 ± 11.126	93 - 132	0.064
1sthr post-op	94.58 ± 9.691	78 – 113	98.30 ± 12.271	81 - 125	0.096
2ndhr post-op	90.26 ± 8.302	81 – 109	95.22 ± 9.137	83 - 114	0.005
4thhr post-op	88.64 ± 6.445	80 – 100	94.14 ± 7.698	82 - 106	<0.001

The baseline MAP was comparable in the two groups under study. Group 1 had a mean MAP value of mm of Hg, while group 2 had a mean value of mm of Hg. The p-value of indicates that there was no statistically significant difference between the two groups.

2 mins after induction, there was a fall in MAP in both the groups. In group 1 the mean MAP came down to 75.16 ± 14.514, while in group 2 it came down to 66.58 ± 5.241. The p-value of < 0.001 shows that the fall in MAP after 2 mins was statistically significant in group 2.

There was a transient rise in MAP after intubation in both the groups. In group 1 the MAP was 98.06 ± 21.781 while in group 2 it increased to 90.26 ± 25.436. The difference in both the groups was not statistically significant (p=0.103).

After 5 mins, the MAP in group 1 was again decreased to 91.48 ± 17.536 and to 79.68 ± 15.691 in group 2. The p- value of 0.001 shows that the difference in the two groups is statistically significant.

Similarly, at 10 mins, the MAP in group 1 decreased to 76.92 ± 13.440, while in group 2 it decreased to 71.52 ± 9.558 which was statistically significant (p=0.023).

At 15, 30 and 60 mins,till the end of surgery, there was no statistically significant difference in the two groups.

After extubation and in the 1st post-operative hour both the groups were comparable.

After the 2nd and 4th post-operatie hours, group 1 shows a significant decrease in the MAP compared to group 2.

DISCUSSION

Propofol is the most preferred drug for intravenous induction of anaesthesia for elective surgical procedures. Its rapid onset of action

and smooth emergence makes it the induction agent of choice for short duration surgical procedures. Its main disadvantage is that it causes hypotension, which has limited its use in patients with haemodynamic instability and cardiac insufficiency. The addition of ketamine to propofol has been found in many studies to provide stable haemodynamics and a decreased incidence of adverse effects attributed to the two drugs when used individually.

This study was conducted among 100 adult patients schedued forelective laparoscopic cholecystectomy. It was done to compare propofol and ketofol used as anaesthetic induction agent with respect to haemodynamic stability after induction. The study reveals that patients who received ketofol as induction agent had greater haemodynamic stability compared to the control group.

Our study shows that the fall in systolic BP, diastolic BP and mean BP was lesser in the ketofol group after induction. The heart-rate was comparable in both the groups. In a study by Smischney et al to assess the haemodynamic effects of ketofolin a fixed dose combination versus propofol during induction of general anaesthesia, they observed that ketofol was associated with a lesser fall in SBP during the first 10 mins after induction when compared to propofol. This corroborates with our study which shows that the fall in systolic, diastolic and mean BP was lesser in the ketofol group in the first 5 mins after induction. Similar findings were also found in the study by Goh et al who compared ketamine-propofol, fentanyl-propofol and propofol for induction of anaesthesia. They included 90 adult patients planned for surgery under general anaesthesia and studied the haemodynamic profile and the LMA insertion conditions associated with the 3 drug combinations. They concluded that the addition of ketamine to propofol during induction of anaesthesia improves haemodynamics when compared to fentanyl-propofol or propofol alone.

To conclude, this study shows that there is a definite advantage of ketofol over propofol when used as an anaesthetic induction agent. Use of ketofol results in greater haemodynamic stability. It can replace propofol as an induction agent in short-duration surgical procedures, especially in patients with haemodynamic instability and in critically ill patients.

Limitations Of The Study:

The present study had certain limitations--

1. A small sample size limits its generalisation.
2. The pre-operative fasting duration could not be meticulously standardized. Though we ordered a preoperative fasting of 8 hours in all the patients, but due to non-uniformity in the OT schedule the period of fasting in some patients even exceeded 12 hours. This might have a bearing on the haemodynamic parameters in this study.

CONCLUSIONS

From the study we concluded that the 2 groups under study were comparable with respect to age, sex, height and weight and the ketofol group showed greater haemodynamic stability after induction of anaesthesiacompared to the propofol group.

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