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EVALUATION OF COMBINATIONS OF I/V PROPOFOL-KETAMINE AND I/V PROPOFOL-FENTANYL IN RELATION TO HEMODYNAMIC VARIABLES AND RECOVERY CHARACTERISTICS IN PATIENTS UNDERGOING GENERAL ANAESTHESIA (A MULTI INSTITUTIONAL OBSERVATIONAL STUDY)

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ABSTRACT:

Background : Of all other milestones and achievements of anesthesia, invention and practice of co-induction of anaesthesia has proved to have a better outcome in all phases of anesthesia including induction , maintenance and recovery. Co-induction refers to the administration of a small dose of sedative or other anesthetic agent to reduce the dose of induction agent and to achieve more specific responses while minimizing side effects. **OBJECTIVES**: The study aims to look for an ideal combination of co –induction agents to achieve the best hemodynamic variables with ideal recovery characteristics . **STUDY DESIGN**:A multi institutional prospective observational study**. PARTICIPANTS**:100 patients undergoing elective laparoscopic cholecystectomy under general anesthesia. **METHODS:** A total of 100 patients of both sexes in the age group of 20–50 years, belonging to ASA I and II undergoing elective laparoscopic cholecystectomy surgery under general anesthesia, were divided into two groups : Group A (n=50) – who received combination of Inj. ketamine 0.5 mg/kg I/V slowly over 2 minutes followed by Inj. Propofol-2 mg/kg I/V using separate syringes and Group B (n=50) – who received combination of Injection propofol-2 mg/kg I/V + Injection fentanyl 1 mcg/kg I/V where fentanyl was given slowly over 3 minutes prior to propofol to achieve optimum effect and subsequent reduction in the total dose of propofol. In both the groups I/V injection propofol was injected slowly till loss of verbal commands. **RESULTS**: Propofol combined with ketamine group showed hemodynamic stability significantly better than propofol –fentanyl group whereas post-operative recovery characteristic of the two groups were comparable .**CONCLUSION**: It was concluded that propofol combined with ketamine is a

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better co induction agent than propofol –fentanyl group in terms of hemodynamic stability howere the recovery post anesthesia was comparable in the two groups.

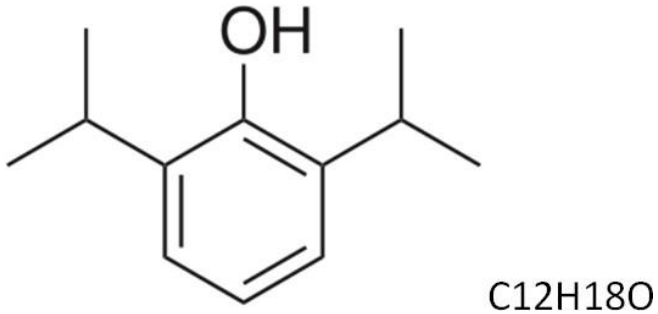
Keywords: **propofol-ketamine, propofol-fentanyl, anesthesia**

Introduction

General anaesthesia should provide a quick and pleasant induction, predictable loss of consciousness with stable operating condition, minimal adverse effects followed by rapid recovery of protective reflexes and psychomotor function. Ever since anesthesia was introduced to clinical practice, it has undergone vast number of improvements and modifications for minimizing post anaesthetic side effects, hemodynamic[1] stability along with early recovery.
In recent years general Anesthesia has become more popular and practical which is possible due to pharmacodynamic and pharmacokinetic properties of modern drugs like Propofol which make them very suitable for administration by continuous infusion. Co-induction of anaesthesia,the rationale[2]behind it being the combination therapy using two or more different drugs with the intention of reaching the same therapeutic goal was heavily criticized for a long time. However, it is widely accepted today, especially when advantages over monotherapy can be shown. Over the years various intravenous drugs have been used for induction of anaesthesia. These include thiopentone , opioids, benzodiazepines, ketamine and propofol. Propofol is the most commonly used induction agent nowadays. The technique of co-induction with propofol would prove to be very useful to improve the ratio of desired versus adverse effects and to reduce the cost of induction[3].So far, the commonest co-induction agent to propofol has been midazolam[2].Ketamine can also be used as a co-induction agent with propofol with the added advantage of more hemodynamic stability. Co-induction refers to the administration of a small dose of sedative or other anaesthetic agent prior to induction of anaesthesia to reduce the dose of induction agent, and to achieve more specific responses while minimizing side effects[4].

PHARMACOLOGY OF DRUGS

PROPOFOL is an alkylphenol compound and is virtually insoluble in aqueous solution**.** IUPAC Name of propofol is (2,6-bis(1-methylethyl)- 2,6-Diisoprophylphenol)



.Its uses include the induction and maintenance of general anaesthesia, sedation for mechanically ventilated adults and procedural sedation. Chemically propofol is unrelated to barbiturates.
Recovery from propofol is more rapid and clear. Propofol is not considered as analgesic, so opioids such as fentanyl may be combined with propofol to alleviate pain[5].

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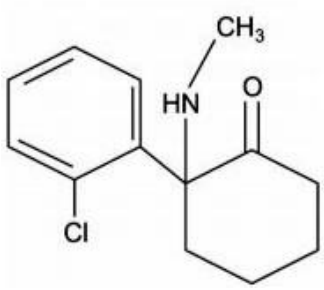
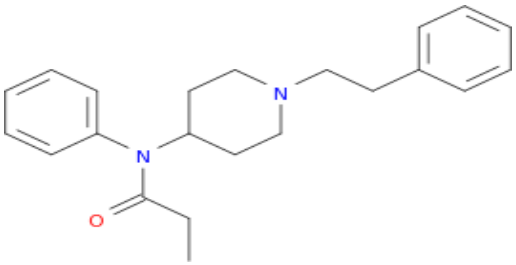
KETAMINE

Ketamine[6] is a drug classified as an NMDA receptor antagonist. Ketamine is a noncompetitive NMDA receptor antagonist. At high fully anaesthetic level concentrations, ketamine has also been found to bind to opioid mu2 receptor in cultured human neuroblastoma cells.



FENTANYL[7]

Fentanyl citrate is a white powder, sparingly soluble in water, is chemically designated N-(1-phenethl-4-piperidyl) propionilidecitrate(1:1).The molecular formula is C22H28N2O.C6H807 and the molecular weight is 528.60.



Material &Methods

The present prospective observational study was conducted at government Medical College Srinagar and its associated Hospitals, from 2018-2021 in association with SKIMS Soura postgraduate resident in Anesthesiology. The study was undertaken after obtaining the ethical clearance from the Institutional Ethical Committee in the Department of Anaesthesiology and Department of General Surgery, Government Medical College, Srinagar and associated hospitals.

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The current study inculded patients who were scheduled to undergo elective laparoscopic cholecystectomy under general anaesthesia. Patient classified as American Society of Anaesthesiologist (ASA) I and II going for elective surgery between ages of 20-50 years were included.

Study design: Multi institutional prospective observational study

Inclusion criteria:

Patients aged between 20 - 50 years old
Physical status ASA I and II
Patients undergoing laparoscopic cholecystectomy surgery.
Patients giving valid informed consent.

Exclusion criteria:

Refusal of procedure or participation in the study
Physical status: ASA III or above
Allergies to drugs used in study
Difficult airway.

Method:

A total of 100 patients of both sexes in the age group of 20–50 years, belonging to ASA I and II undergoing elective laparoscopic cholecystectomy surgery under general anesthesia, were divided into two groups : Group A (n=50) – who received combination of Injection ketamine 0.5 mg/kg I/V slowly over 2 minutes followed by Injection Propofol-2 mg/kg I/V using separate syringes and Group B (n=50) – who received combination of Injection propofol-2 mg/kg I/V + Injection fentanyl 1 mcg/kg I/V where fentanyl was given slowly over 3 minutes prior to

propofol to achieve optimum effect and subsequent reduction in the total dose of propofol. In both the groups I/V injection propofol was injected slowly till loss of verbal commands. Separate syringes were used to inject each drug. All patients received premedication with Injection Pantoprazole 40mg and Injection Metoclopramide 10 mg I/V 5 minutes prior to induction.
Additional analgesia and muscle relaxant was provided by I/V injection Paracetamol @15mg/kg body weight over 15 minutes and Injection Atracurium 0.5mg/kg body weight I/V for muscle relaxation followed by 0.1mg/kg I/V top ups every 15 minutes as per institute protocol.
Technique of anesthesia was standardized for all the patients in the study. Maintenance of anesthesia was done by Inhalational isoflorane ≤1MAC, Oxygen 33% and N^2O 66%. Heart rate (HR), blood pressure (systolic, diastolic, and mean arterial pressure), and oxygen saturation were recorded at baseline, before induction and at 5,10, and 15 minutes after induction.
Recovery characteristics in the form of stewards scoring system (ventilation, movements and wakefulness) and return of protective reflexes like gaging, coughing and response to verbal commands was noted where a total score of 6 denotes a fully recovered patient and a score 0 would be assigned to an unresponsive, immobile patient whose airway system requires maintenance.

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The Post-Anaesthetic Steward Scoring System (Total Score-6)	
Consciousness Awake Responding to stimuli Not responding	**2** **1** **0**
Airway Coughing on command or crying Maintaining good airway Airway requires maintenance	**2** **1** **0**
Movement	
Moving limbs purposefully	**2**
Non-purposeful movements Not moving	**1** **0**

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Statistical Methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables will be expressed as Mean±SD and categorical variables will be summarized as frequencies and percentages. Graphically the data will be presented by bar and pie diagrams. A p value of < 0.05 will be considered as statistically significant.

Observations and Results

A total of 100 patients were included in this observational study for statistical purpose. Patients were divided into two groups. Group A 50 patients and Group B 50 patients. The groups were comparable with respect to age, gender, weight and ASA status [Table 1 & 2]. There was a statistically significant difference between the two groups with regards to the average induction dose of propofol (mg) . The average dose being higher in group A (1.75 Mg/ kg) in comparison to group B (1.08 mg/ kg) .Comparing the mean values of heart rate at baseline, before induction,5min,10min and 15min after induction between group A and group B, we found statistically significant increase in heart rate in group A. Similarly comparing systolic blood pressure, diastolic blood pressure and mean arterial pressure at baseline, before induction,5min, 10 min and 15min after induction between two groups, there was statistically significant decrease in systolic blood pressure, diastolic blood pressure and mean arterial pressure from 5min after induction and then there was a rise after 10minute of induction. There was statistically significant increase in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure from the baseline in group A . Recovery characteristic was recorded according to steward scoring system where total scoring is 6 and responses were recorded at 5-minute post-operative, 15-minute post-operative and 30 min post-operative. Mean recovery score of Group A at 5-minute post-operative was 5.74, at 15 minute 5.90 and at 30 min 5.94. Mean recovery score of Group B at 5-minute post-operative was 5.76, 15 minute 5.98 and at 30 minute 6 according to steward scoring system. The difference of mean recovery scoring between two groups were statistically insignificant with a p-value of 0.07.

Comparison of baseline parameters between the two groups [table 1]

parameter	Group A (mean ±SD)	Group B mean ±SD)	P value
Age (years)	39.68±10.10	42.72±11.57	0.73
Weight (kg)	66.78±6.45	68.98±7.90	0.67

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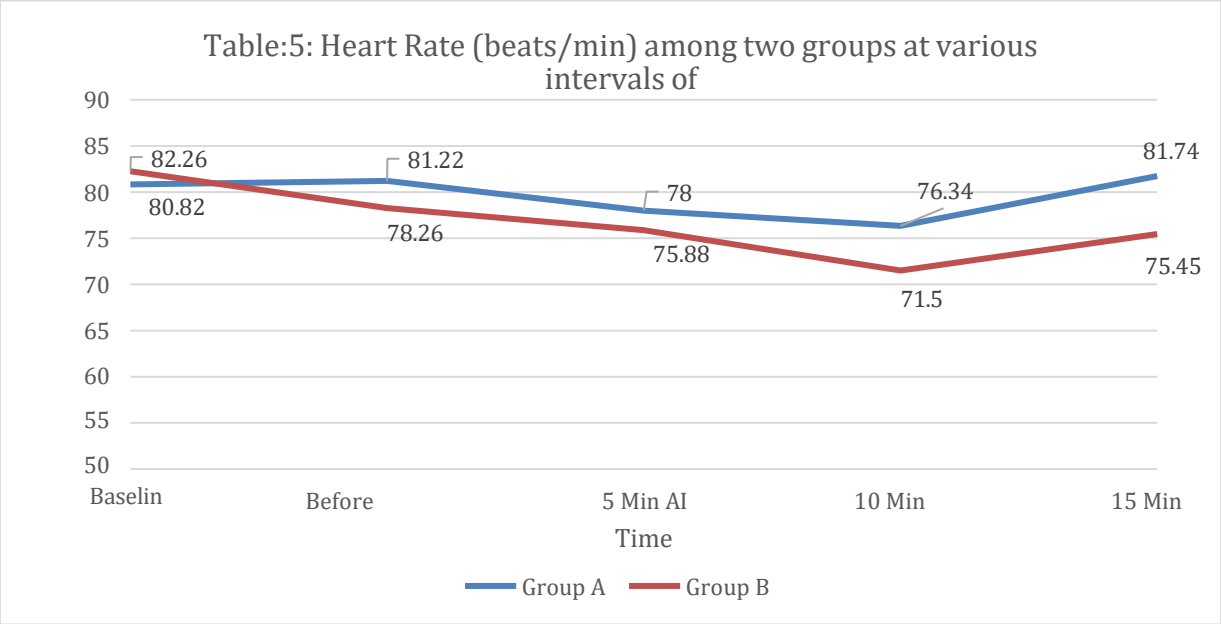
Comparison of baseline parameters between the two groups. [table 2]

Parameter	**Group A (percentage)**	Group B (percentage)	
MALES	**30%**	26%	
FEMALES	**70%**	**74%**	**0.45**
ASA II	**70%**	**66%**	
ASA II	**30%**	**34%**	**0.95**



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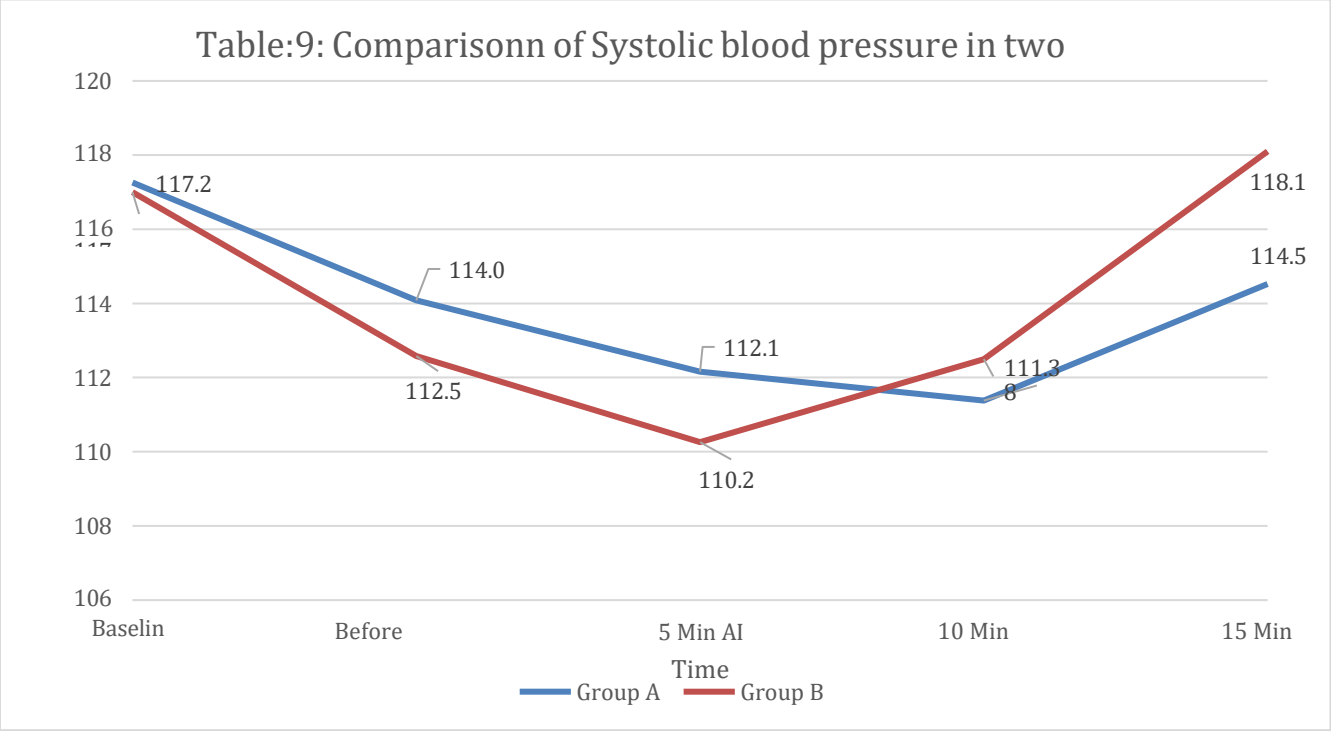

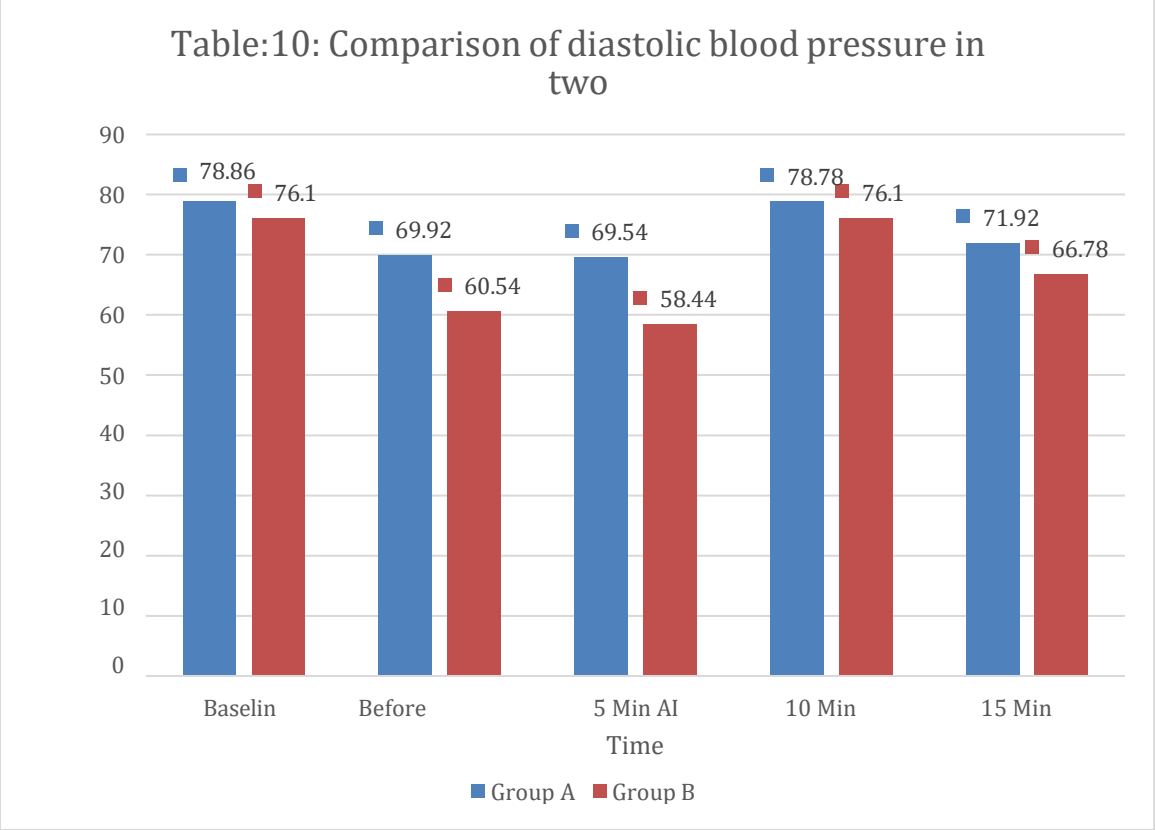

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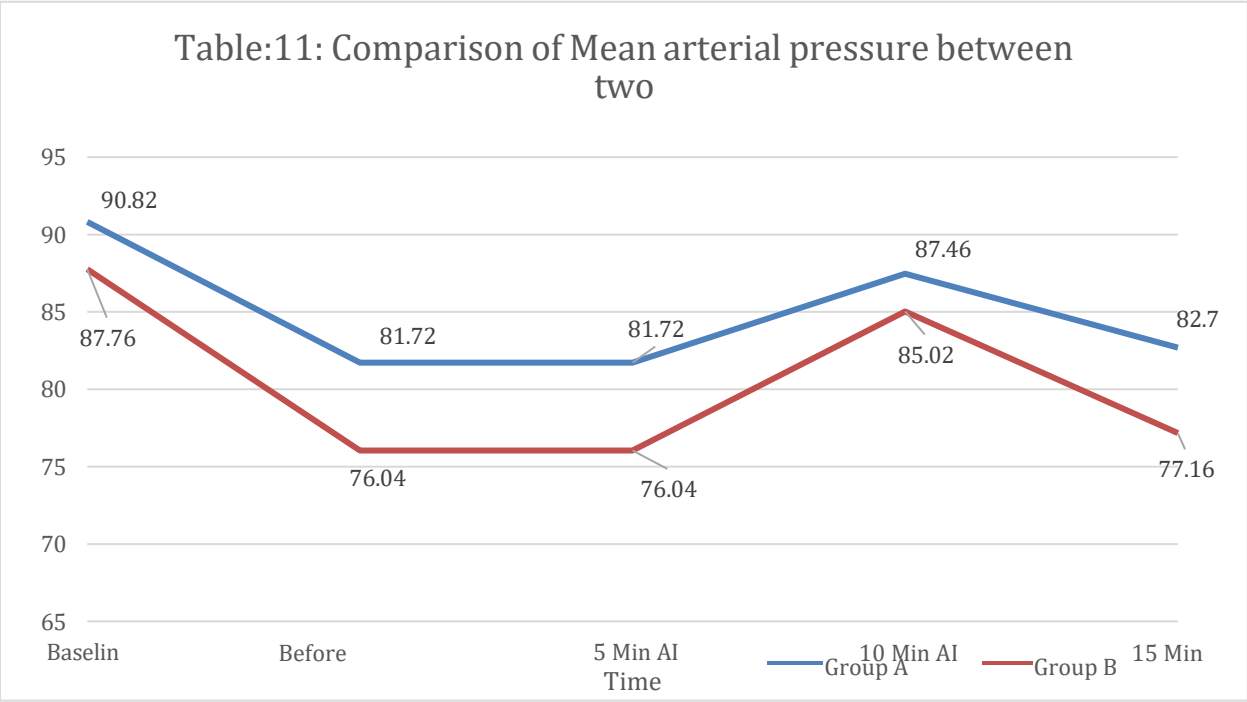

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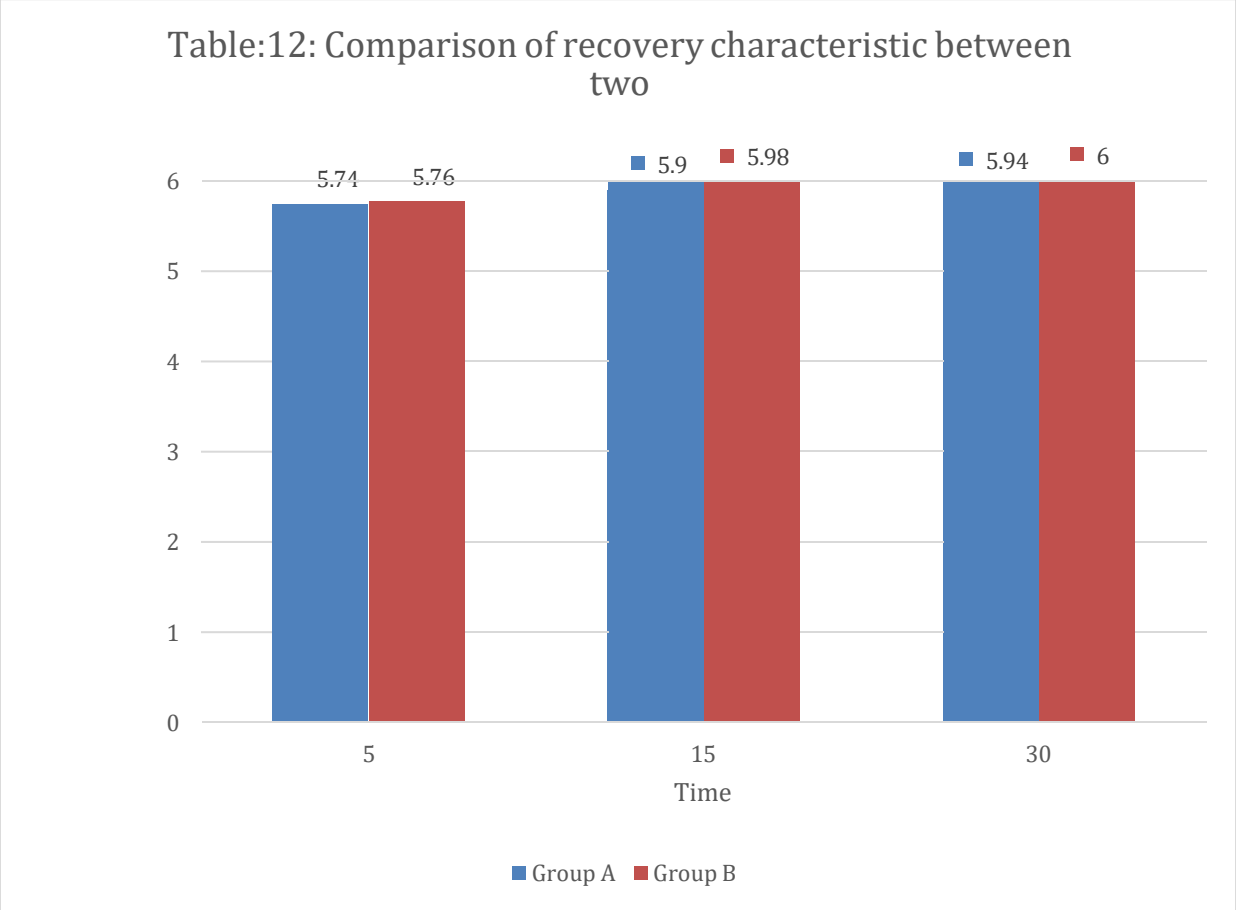

Discussion

The present prospective observational study was conducted at government Medical College Srinagar and its associated Hospitals, from 2018-2021 in association with SKIMS soura postgraduate resident in Anesthesiology. We observed patients of American Society of Anaesthesiology (ASA) physical status I – II of both genders aged between 20 and 60 years, undergoing elective laparoscopic cholecystectomy surgery under general anaesthesia, after approval from Institutional Ethical Committee and written informed consent.

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Demographic profile of the patients:

The physical characteristics including age, gender and weight in both groups in our study were comparable. The mean age of patients was 39.68 and 42.72 in group A and B respectively with a p-value of 0.73(statistically insignificant). Similarly gender distribution in both groups were comparable with male and female percentage of 30% & 70% in Group A and male 26% & female 74% in Group B respectively with p-value of 0.45 which was statistically insignificant. Likewise, the mean weight of patients of group A and B were 66.78kg and 68.98kg respectively. Difference between mean weight distribution between two groups was statistically insignificantly with p-value of 0.67.

ASA Status: All patients of group A and B were comparable regarding the ASA status of the patients. Majority of patients in the study belonged to ASA I in both groups which was 70% in group A and 66% in group B . ASA- II patients in group A and B were 30% and 34% respectively. Difference in ASA distribution between two groups was statistically insignificant with p-value of 0.95.

Average induction dose of propofol (mg) of both groups:

Average induction dose of group A and group B were 115.1 mg and 73.44 mg respectively. The difference between two groups were statistically significant when compared with a p value of 0.02. In our study fentanyl is most effective in reducing the induction dose of propofol when compared to ketamine. The results of our study were comparable to study done by **Bansal, S., Ramesh, V. J., & Umamaheswara Rao, G. S. (2012).** A total of 80 patients were selected randomly to receive propofol alone or propofol preceded by fentanyl for induction of anesthesia. Their study found that Propofol dose for induction of anesthesia was significantly reduced when administered after fentanyl in patients with supratentorial tumors.

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Hemodynamic parameters at baseline, before induction, 5min, 10min and 15min after induction:

Comparing the mean values of **heart rate** at baseline, before induction, 5min,10min and 15min after induction between group A and group B, there was statistically significant increase in heart rate in group A.

Similarly comparing **systolic blood pressure**, **diastolic blood pressure** and **mean arterial pressure** at baseline, before induction, 5min, 10 min and 15min after induction between two groups, there was statistically significant decrease in systolic blood pressure, diastolic blood pressure and mean arterial pressure from 5min after induction and then there was a rise after 10 minute of induction. There was statistically significant increase in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure from the baseline in group A with a p-value<0.05. Thus only in Group A (ketamine group) the HR and MAP was increased significantly compared with baseline values. The rise in HR and MAP in ketamine group may be attributed to the sympathetic stimulation produced by ketamine and could be beneficial in patients with pre-existing hypotension. There may be a possibility that laryngoscopy and tracheal intubation counteracting the cardiovascular depression caused by propofol and other co-inducing agents like fentanyl in our study. Ketamine co-induction to propofol preserves better hemodynamic stability. Our results regarding hemodynamic parameters were similar to **Furuya A et al (2001)** who investigated efficacy of ketamine before induction with propofol .They found that the administration of ketamine before induction with propofol preserved hemodynamic stability compared with induction with propofol alone.

Recovery characteristic was recorded according to steward scoring system where total scoring is 6 and responses were recorded at 5- minute,15 minute and 30 minute post-operative. The difference of mean recovery scoring system between two group was statistically insignificant with p- value of 0.07.

Conclusion

The average dose of propofol for induction of anaesthesia was found to be significantly reduced in both groups where co-induction agent ketamine & fentanyl were used respectively. Although fentanyl showed more reduction of average induction dose of propofol than ketamine.Propofol combined with ketamine group showed hemodynamic stability significantly better than propofol-fentanyl group. Whereas post-operative recovery characteristic of both the groups were comparable.

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