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ORIGINAL ARTICLE

CO-INDUCTION: A COMPARATIVE STUDY OF MIDAZOLAM KETAMINE AND PROPOFOL AS COINDUCING AGENTS TO PROPOFOL

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ABSTRACT: INTRODUCTION: "Co-induction" refers to the administration of a small dose of a sedative or anaesthetic agent prior to the induction of anesthesia, with the aim of achieving more specific 'target' responses, while minimizing side effects. Although Propofol is a very popular IV induction agent, it causes various adverse effects like hypotension and apnoea and it is expensive. So the present study was designed to find whether the concept of co-induction can be used to overcome the above mentioned short comings of Propofol induction. **AIM:** To compare the effectiveness and evaluate the use of midazolam, ketamine and propofol as co-inducing agents to propofol for general anesthesia. **DESIGN**: A Prospective Randomized Double blind study was planned. **METHODS:** 100 adult patients of ASA grade 1 and 2 aged between 18–50 yrs. undergoing elective general, orthopedic or gynecological surgeries under general anesthesia were randomly allocated into four groups of 25 each: Group SP: received normal saline 3 ml IV as co-induction agent. Group MP: received inj. Midazolam 0.03mg\kg IV Group KP: received inj. Ketamine 0.3mg\kg IV. Group PP: received inj. Propofol 0.4mg\kg IV (auto-co-induction). All patients received inj. Pentazocine 0.3 mg\kg IV followed by blinded pretreatment with either saline 3ml IV, (group SP-control), inj.Midazolam.0.03mg\kg IV (group M), Inj. Ketamine 0.3mg\kg IV (group KP) or inj. Propofol 0.4mg\kg IV (group PP). Two min later induction was done with inj Propofol until loss of verbal contact or resistance to placement of facemask. Total induction dose of Propofol, associated haemodynamic parameters (HR, MAP) at 1min interval for five min after induction and occurrence of significant apnoea (>20 sec or Spo2 < 90%) were recorded. The obtained data was analyzed using Chi-square test and Students "t" test. **RESULTS & CONCLUSION**: The mean induction dose of propofol was 1.31mg\kg, 1.39mg\kg,1.59mg\kg in groups MP, KP, PP respectively as compared to 1.96mg\kg in control group (group SP). Midazolam was most effective in reducing the induction dose of propofol (33.16% compared to control).Total induction cost reduced by 22.2% &14% in groups MP&KP respectively compared to control. The Propofol-Propofol Group PP (auto-co-induction) appeared to be the most expensive combination (1.65% increase in cost compared to control).Midazolam–Propofol appeared to be the most economical combination. When compared to control group – none of the three groups- viz Midazolam-Propofol, Ketamine-Propofol and Propofol-Propofol provided more haemodynamic stability during induction. In group Ketamine-Propofol, the HR and MAP were increased significantly ($p<0.05$ for HR and $p<0.01$ for MAP) compared with baseline values. Midazolam co-induction was associated with least incidence of Apnea during induction with Propofol compared to other groups.

KEYWORDS: Midazolam, Ketamine, Propofol, Co-induction, Auto-co-induction.

INTRODUCTION: In the world of anesthesia, "induction" is a very familiar word and one of those important events with which every anesthesiologist and surgeon is well versed with. 'Co'-enzyme, 'Co'-efficient, 'Co'-author Co'-induction-in these words the prefix **'Co'** means "support, going together, and

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equal". 'Co-induction' means using two or more agents to induce anaesthesia.[1] it involves the administering of a small dose of sedative or anaesthetic agent to reduce the dose of induction agent.[2]

The induction of general anesthesia can be either inhalational or intravenous. The intravenous route is more popular in adults. This popularity is because of two reasons:

1. The patient likes the pleasantness and speed of induction when compared to the application of face mask and the inhalation of gases with unpleasant odor.
2. The method is simple and minimum complicated equipment is required to administer the anaesthesia.[3] the induction of general anesthesia is an event wherein the anaesthetic agent used has variable effects on respiratory and circulatory systems. The hypo or hypertensive effect of the induction agents or pressor response to laryngoscopy and intubation may be deleterious in many patients with pre-existing cardiovascular diseases. Sensitivity to IV induction agent may occur in many pathological conditions, most commonly shock, severe anemia and uremia. In obstetrics, the dose of IV induction agent should be kept to a minimum since the agent can cross the placenta and have depressant effect on fetus.[3]

Over the years various drugs have been used the intravenous induction. These include Thiopentone, opioids, benzodiazepines, Ketamine and Propofol. Propofol is a very popular IV anaesthetic agent. It has a good safety record but when used as a sole induction agent it causes various adverse effects like reduction of systemic arterial pressure, apnoea, and pain on injection. Also, it is very costly. Here the technique of co-induction to propofol would prove to be very useful to improve the ratio of desired vs adverse effects and to reduce the cost of induction.[4] So far, the commonest co-induction agent to propofol has been midazolam.[5] Ketamine can also be used as a co-induction agent to propofol with the added advantage of more haemodynamic stability. Propofol-propofol "auto co-induction" would appear to reduce the overall propofol requirements and improve discharge time from hospital.[4]

Keeping all this in mind, the present study was designed to compare the effectiveness and evaluate small doses of midazolam, ketamine and propofol as co-induction agents to propofol.

AIMS AND OBJECTIVES:

1. To find the average induction dose of Propofol with:
   i. Midazolam as co-induction drug.
   ii. Ketamine as co-induction drug.
   iii. Propofol as co-induction drug (Auto co-induction).
   iv. Saline (control) as co-induction drug.
2. To find whether each of the drugs- Midazolam, Ketamine and Propofol is effective in reducing the induction dose of Propofol.
3. To compare the induction dose of Propofol between the four groups [midazolam, ketamine, propofol and saline (control) as co-inducing drugs] and thereby to compare the efficacy of Midazolam, Ketamine, Propofol in reducing the induction dose of Propofol.
4. To compare the haemodynamic effects of midazolam when used as a co-induction agent to propofol with those each of ketamine and propofol when used as co-induction agents to propofol and thereby to find out which of these combinations-Midazolam-Propofol, Ketamine –Propofol, Propofol-Propofol provides more haemodynamic stability.

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5. To determine which drug combination Midazolam-Propofol, Ketamine-Propofol or Propofol-Propofol proves to be more cost effective for induction.
6. To determine which of the three co-induction agents when used in conjunction with induction agent propofol is associated with the least incidence of apnoea.

MATERIALS AND METHODS: This clinical study was conducted on 100 adult patients of physical status ASA I & II aged between 18 – 55 yrs. scheduled to undergo elective general surgical procedures, orthopedic or gynecological surgery under general anesthesia at VIMS Hospital, Bellary. After approval from the hospital ethics committee, a prospective randomized double blind placebo controlled study was carried out on 100 adult patients.

Inclusion Criteria:

1. ASA grade I and II patients.
2. Age group of 18–55 yrs.
3. Patients giving valid informed consent.
4. Patients scheduled to undergo elective general, orthopedic or Gynecological surgery under general anaesthesia with propofol as intravenous induction agent.

Exclusion Criteria:

1. Patients with significant cardivovascular, renal, hepatic or respiratory disorders.
2. Patients taking Benzodiazepines, clonidine, beta – blockers or thyroxine.
3. Patients with history of known allergy to study drugs.
4. Patients with psychiatric illness.
5. Patients with history of preoperative pain having received analgesics ornarcotics in preceeding.
6. Who refused to give a valid consent.

Methods of Collection of Data: A prospective randomized double blind study was planned. 100 adult patients of ASA Grade I & II aged between 18 to 55 years undergoing elective general surgical procedures, orthopedic or gynecological surgeries, under general anesthesia were randomly allocated into four groups. Group SP: n=25; received 3ml normal saline as IV co-induction agent. Group MP: n=25; received 3 ml of Midazolam (0.03 mg/kg) as IV co-induction agent. Group KP: n=25; received 3 ml of Ketamine (0.3mg/kg) as IV co-induction agent. Group PP: n=25; received 3ml of Propofol (0.4mg/kg) as IV co-induction agent.

Study Design:

- All patients who matched the inclusion criteria were assessed by a pre-anaesthesia examination.
- Premedication was not given.
- Baseline measurements of blood pressure, pulse rate, arterial oxygen saturation were taken.
- IV cannula was placed
- During pre-oxygenation all the patients received intravenous Fentanyl (1mcg/kg)

One minute later, 3 ml of co-induction agent was injected intravenously. This was either saline (control groups) 0.03mg/kg midazolam (group MP), 0.3mg/kg, Ketamine (Group KP), or 0.4mg/kg Propofol (Group PP).

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The co-induction agent was prepared in a 5ml syringe by a separate anesthesiologist or trainee anesthesiologist who did not take part in the study. The total amount was made to 3ml and was disguised by a paper wrap. Two minutes after the injection of co-induction agent, each patient received IV lignocaine 20mg followed by propofol 30mg IV every 10 seconds. Patients were encouraged to keep talking during induction and when the patients stopped talking, they were asked to open the eyes. If there was no response, the propofol injection was stopped at this point and the face mask was applied firmly. If there was any response to placement of mask, an additional bolus dose of Propofol was given. All this was observed by the trainee anesthesiologist conducting the study. Both he and the patient were blind to the drug combination used.1min after Propofol induction, succinylcholine 1.5mg\kg IV was given and the endotracheal intubation was done. Standard uniform conditions for endotracheal intubation were maintained in all the patients (ASA1 & 2, normal airway, experienced anesthesiologist, and 15 sec for intubation). The study was taken complete at this point and further anesthesia technique did not influence the study.

PARAMETERS OBSERVED:

1. BP and heart rate measurement were recorded before commencement of IV line. Also they were recorded at 1 min intervals using automated oscillometric arterial pressure recorder for 5 min post induction.
2. SpO_2 and ECG were monitored according to standard practice. Apnoea:
   Defined as loss of respiratory effort for more than 20 sec or fall of SpO_2 below 95% were watched for.

Statistical Analysis: Statistical analysis of data was done using;

- Student t test for parametric data.
- Chi-square test for non-parametric data.
- $P<0.05$ was considered as statistically significant.
- Continuous variables expressed as mean (SD).

RESULTS:

Variable	Group SP (n=25)	Group MP (n=25)	Group KP (n=25)	Group PP (n=25)
Age (yrs) Mean (SD)	 32.4 (11.36)	 34.72 (7.57)	 34.08 (11.76)	 33.44 (10.76)
Sex(M/F)	15/10	15/10	13/12	14/11
Weight(kg) Mean (SD)	 53.24 (7.86)	 56.08 (8.43)	 55.28 (11.76)	 51.92 (7.92)
Pentazocine (mg)	16	17	16	16

Table: 1 Demographic Data

n- Number of patients; values are expressed as mean (SD)

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The above table reveals the patients demographic data. All groups were similar in respect of age, sex, weight, ASA physical status. There were no significant differences in the demographic data between the four groups (p>0.05), on applying student't' test.

Groups	Age (Yrs) (mean ± SD)
Group SP (n = 25)	32.4±11.36
Group MP (n = 25)	34.72±7.57
Group KP (n = 25)	34.08±11.76
Group PP (n = 25)	33.44±10.76

Table 2: Mean age distribution (Yrs)

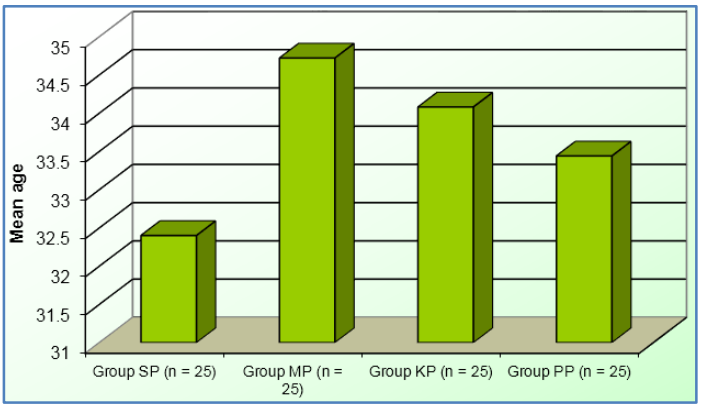

Figure 1: Mean Age Distribution (Yrs)

Groups	Weight (kg) (mean ± SD)
Group SP (n = 25)	53.24±7.86
Group MP (n = 25)	56.08±8.43
Group KP (n = 25)	55.28±11.76
Group PP (n = 25)	51.92±7.92

Table 3: Weight distribution

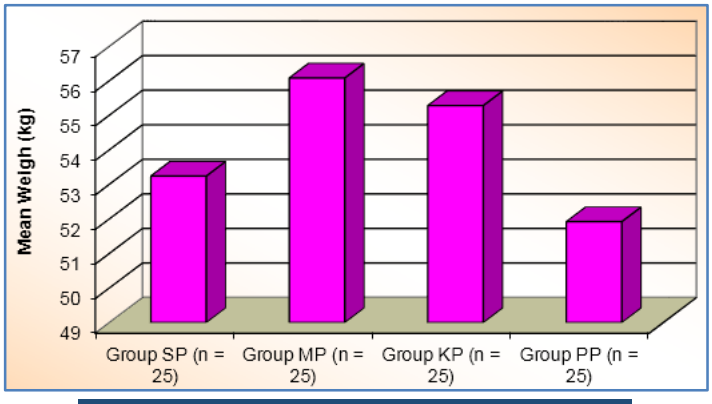

Figure 2: Weight Distribution (Kg)

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Groups	Male	Female
Group SP (n = 25)	15	10
Group MP (n = 25)	15	10
Group KP (n = 25)	13	12
Group PP (n = 25)	14	11

Table 4: Sex distribution

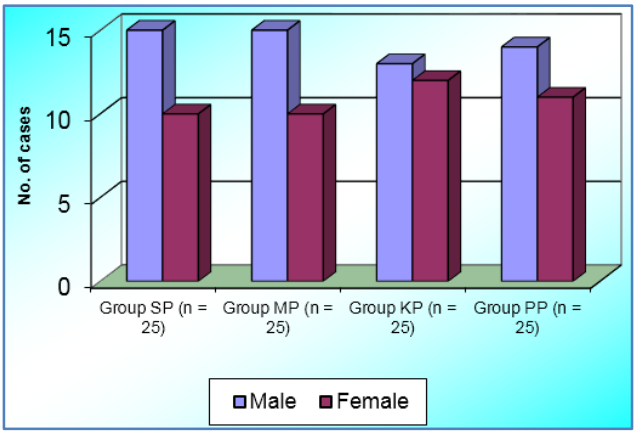

Figure 3: Sex Distribution

Groups	Induction dose(mgs) Mean ± SD
Group SP	104.4±15.02
Group MP	73.64±18.71
Group KP	77.02±23.36
Group PP	83.04±16.41

Table 5: Comparison Of Induction Dose Of Propofol (mg)

The table shows that the mean induction dose of Propofol was 104.4mg, 73.64mg, 77.2mg and 83.04mg in groups SP, MP, KP and KP respectively. There was a highly significant reduction ($p<0.001$) in induction dose of Propofol in the study groups MP, KP and PP compared to control group (group SP), on applying student't' test.

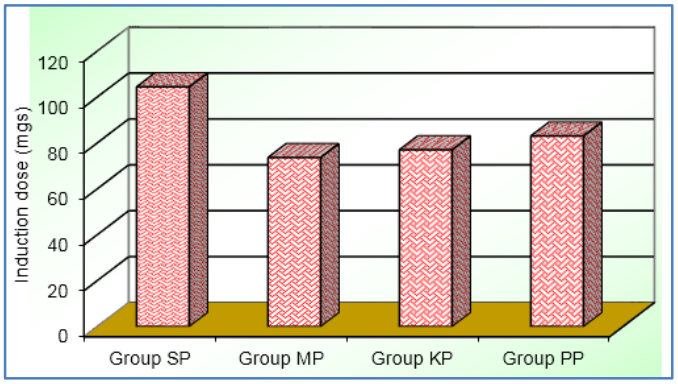

Figure 4: Comparison of Induction Dose of Propofol (mg)

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Groups	Induction dose(mg\kg)Mean ± SD
Group SP	1.96±1.91
Group MP	1.31±2.21
Group KP	1.39±1.98
Group PP	1.59±2.07

Table 6: Induction Dose Of Propofol in mg\kg Body Weight

This table shows the induction dose of propofol in mg\kg body weight. There was a significant ($p<0.001$) reduction in induction dose of propofol in study groups (group MP, KP and PP) compared to control group (groupSP), on applying student't' test.

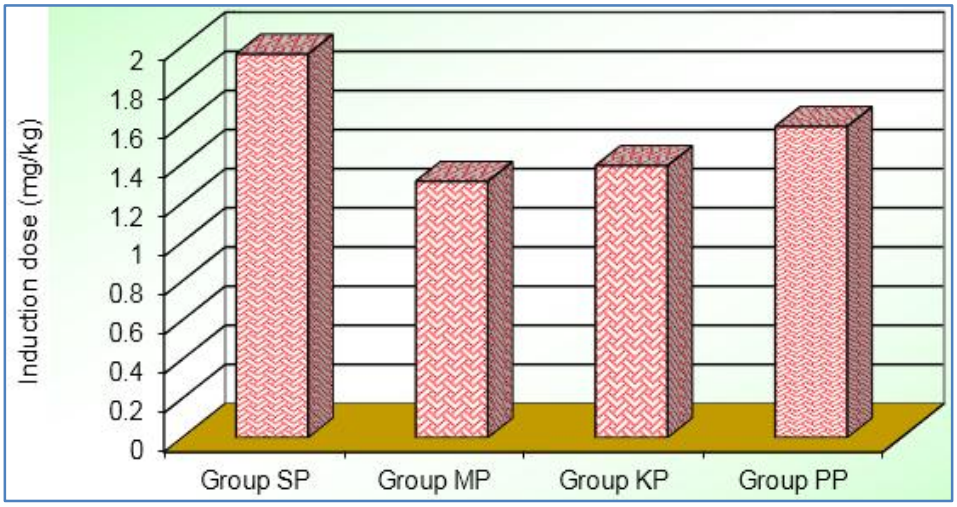

Figure 5: Induction Dose of Propofol in mg\kg Body

Time		Gr. SP	Gr. MP	Gr. KP	Gr. PP
Base line		81.60 ± 7.00	85.12±9.64	86.96±13.52	85.56±8.89
Minutes after induction	1st min	81.52 ±7.00	80.24±10.96	100.1±26.98	84.16±8.74
	2nd min	81.60±7.56	86.20±11.36	102.9±19.22	90.32±12.52
	3rd min	71.70±7.62	87.80±9.61	103.00±19	95.4±12.4
	4th min	90.12±6.77	84.60±9.19	103.2±17.04	93.04±13.01
	5th min	87.12±4.79	83.84±10.21	101.2±20.31	91.2±10.97

Table 7: Mean Heart Rate (beats\min)

Values are expressed as mean±SD

This table shows that basal mean heart rate was 81.6, 85.12, 86.96 and 85.56 beats per minute in groups SP, MP, KP and PP respectively. There was no statistically difference between the four groups ($P>0.05$), on applying student't' test.

After induction, mean heart rate did not show any significant difference in groups SP,MP and PP compared to baseline heart rate but group KP showed a significant increase ($P<0.01$) i.e.17.3% increase in heart rate compared to baseline, on applying student 't' test.

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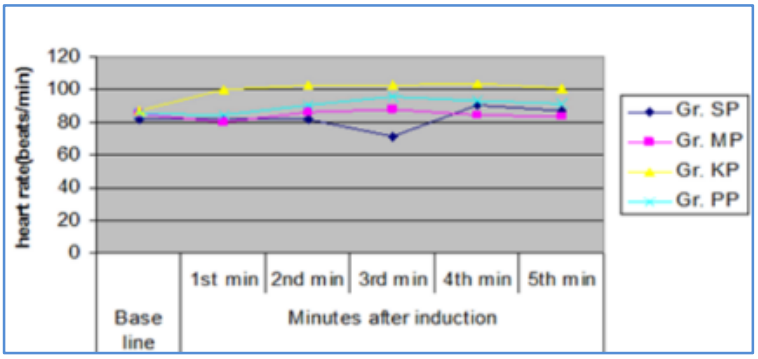

Figure 6: Mean Heart Rate (Beats/min)

Time		Gr. SP	Gr. MP	Gr. KP	Gr. PP
Base line		92.23±3.86	94.69±6.8	91.8±10.6	93.8±8.58
Minutes after induction	1st min	89.76±4.7	89.01±8.47	93.9±14.5	84.16±8.9
	2nd min	88.8±4.8	97.79±16.17	102.2±19.25	87.78±9.23
	3rd min	81.62±5.4	99.08±13.73	104.5±13.27	96.44±12.43
	4th min	106.2±9.8	94.13±13.67	100.3±13.6	93.48±10.29
	5th min	99.27±6.44	94.96±15.92	99.6±13.1	90.18±8.45

Table 8: Mean Arterial pressure (mm Hg)

Values are expressed as mean±SD.

This table shows that baseline MAP was 92.23, 94.69, 91.8 and 93.8 mm Hg in groups SP, MP, KP and PP respectively. There was no statistically significant difference between the four groups ($p>0.05$) on applying student 't' test.

After induction, MAP did not show any significant difference in groups SP, MP, PP but group KP showed significant increase in MAP i.e9.1% ($p<0.01$), on applying student t test.

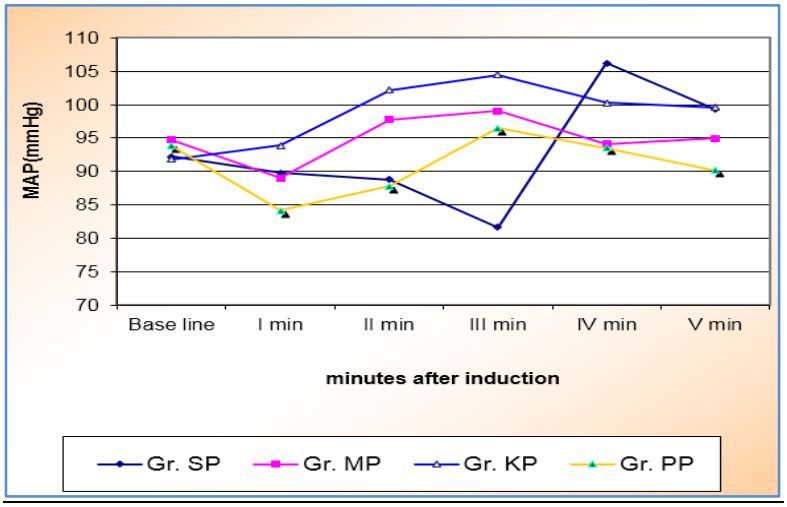

Figure 7: Mean Arterial Pressure

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(Including only cost of induction agent- Propofol and Co-induction agent).
(Propofol, Midazolam and Ketamine from Neon Labs).

	Gp SP	Gp MP	Gp KP	Gp PP
Total induction cost for a 50 kg adult (Rs)	114.5	89	98.5	116.4
% reduction / increase in induction cost compared to control		22.2% ↓	14% ↓	1.65% ↑

Table 9: Cost Effectiveness

It also reveals that there was 22.2% and 14% decrease in induction cost in group MP and KP respectively compared to control group (SP) ($p<0.01$) which was statistically significant. Group PP showed 1.65% increase in induction cost compared to control group ($p>0.05$).

	Gr. SP		Gr. MP		Gr. KP		Gr. PP	
Apnoea	4/25	16%	2/25	8%	3/25	12%	3/25	12%

Table 10: Incidence of apnoea

The above table shows that the incidence of Apnoea during induction with Propofol was 16%, 8%, 12% and 12% in groups SP, MP, KP and PP respectively. Midazolam co-induction was associated with least incidence of Apnoea compared to others groups.However this difference was not statistically significant ($p>0.05$) by Chi-square test.

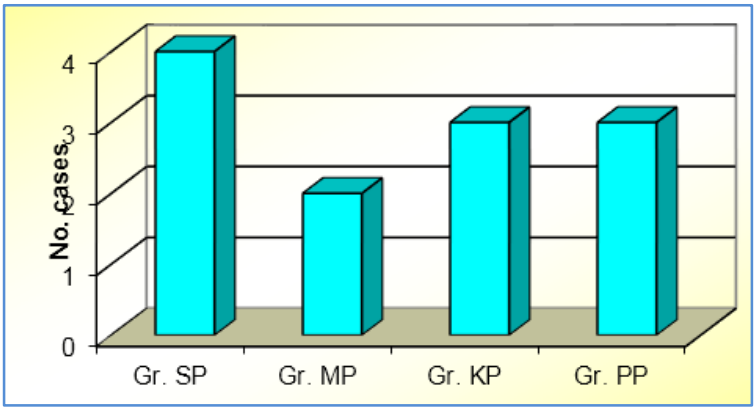

Figure 8: Incidence of Apnoea

DISCUSSION: 'Co-induction', the concurrent administration of two or more drugs that facilitate the induction of anaesthesia with the intention of reaching the same therapeutic goal was heavily criticized for a long time. However it is accepted today, especially when advantages over monotherapy can be shown.[1]

"Co-induction" refers to the administration of a small dose of a sedative or anaesthetic agent prior to the induction of anesthesia, with the aim of achieving more specific "target" responses, while minimizing side effects.[2]

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Planned co-induction of anaesthesia makes use of synergistic drug interactions between drugs like midazolam, fentanyl, sufentanil, alfentanyl, ketamine and propofol in order to produce an improvement in induction, maintenance and recovery characteristics of anaesthesia.[3]

A randomized, double blind, placebo controlled study was undertaken to evaluate the efficacy of Midazolam, Ketamine and Propofol as co-induction agents to propofol on 100 ASA 1 & 2 patients aged between 18–50 years who were scheduled to undergo elective general, orthopedic or gynecological surgery under general anesthesia. Uma Srivastava et al.,[4] Anderson et al[5] and many other investigators have used the same end points as used in the present study. However Mcclune et al.[6] have used the following as end points in their study- loss of response to command (patients were asked to open their eyes), loss of eyelash reflex and failure to move when a facemask delivering 1% Isoflurane in 66% Nitrous oxide in Oxygen applied for atleast 30 sec. Jones N. A et al.[7] have used loss of verbal contact and insertion of oropharyngeal airway as two end points.

In the present study the HR, BP, SPO2 were recorded every min for the first five min after induction and the average induction dose of Propofol was recorded. Direct laryngoscopy and endotracheal intubation was done during the third min post induction. Endotracheal intubation after co-induction has been done in the studies of Ni Ni Win et al and Anil K et al.[8] Both these investigators have studied the haemodynamic changes during induction and endotracheal intubation.

However, in the studies of Uma Srivastava et al, Jones N.A.et al, Djaiani G.[9] and many others the haemodynamic changes were studied only during induction. Nevertheless, Ni NiWin in 2007 has stated that co-induction with Midazolam and Propofol has been studied in relation to the synergistic.

Hypnotic actions of the drugs and haemodynamic changes during induction of anesthesia, but there are no reports to date of the haemodynamic changes occurring during endotracheal intubation.

The average age of the patients in the present study was 32.4, 34.72, 34.08 and 33.44 yrs. in Groups SP, MP, KP and PP respectively. However, many studies have been done for studying co-induction with Midazolam for Propofol induction in different age groups viz- Olms et al.,[10] Cressy D.M.,[11] and Jones N. A.et al have stated that age can affect the requirement of Propofol for induction of anesthesia.

In our study the mean induction dose requirement of Propofol was 104.4mg (1.96mg\kg), 73.64mg (1.31mg\kg), 77.2mg (1.39mg\kg) and 83.02mg (1.59mg\kg) in groups SP, MP, KP and PP respectively. The reduction in induction dose of Propofol in the study groups was highly significant ($P<0.001$) when compared to Control group (gr.SP). However there was no statistically significant difference between the study groups.

Among our study groups Midazolam was most effective in reducing the induction dose of Propofol (33.16% reduction compared to Control group). However Adams et al (2000.[12] found a 50% reduction in induction dose with Midazolam co-induction.

Propofol co-induction caused 18.87% reduction in induction dose compared to Control Group in our study. Anil K et al in their study observed a reduction of 27.48% in the induction dose of Propofol during Propofol co-induction (20% of calculated predicted induction dose). Maroofet al.[13]and Pallavi.S.et al.[14] found a reduction of 21.4% and 35% respectively in the induction dose of Propofol during co-induction with Propofol.

Anderson et al in 1998 observed that the dose of Propofol required to induced anesthesia was significantly smaller in patients given Propofol (1.87mg\kg) or Midazolam (1.71mg\kg) when compared to Control group (2.38mg\kg). In 1999 Djaiani et al also observed similar results and

concluded that dose reduction achieved by both Propofol and Midazolam co-induction was similar to control group.

In the present study Ketamine co-induction also resulted in a significant reduction (29.08% reduction) in the induction dose of Propofol compared to control group. This matches with the results of Kaushik Saha et al.[15] in 2001 where in they found that Ketamine – Propofol combination reduced the induction dose of Propofol and also the subsequent number of top up doses of Propofol for maintenance of anaesthesia. However, our findings do not confirm with those of Ong E.L.[16]- who state that low dose IV Ketamine (0.3 mg\kg) does not decrease the induction dose of Propofol.

Uma Srivastava et alin 2000 found that Midazolam, Ketamine and Propofol as co-inducing agents decrease the induction dose of Propofol, maximum reduction being in Ketamine co-induction. This has been attributed by them to synergism between Propofol and Midazolam but not so between Propofol and Ketamine. Our findings confirm with these findings except that the maximum reduction in induction dose of Propofol in our study was with Midazolam co-induction. This can be linked to synergism between the two drugs - Midazolam and Propofol. Short T G, Chui P T.[17] in 1991 have also shown that the combination of Propofol-Midazolam is synergistic when used in the commonly accepted dose range.

Synergy: Occurs when the combination of two drugs with similar properties produce supra-additive effects.[18] When the action of one drug is facilitated or increased by the other, the interaction is said to be 'Synergistic'.[19] Synergy is most likely to occur when drugs of different classes, or even those with slightly different mechanisms, are used to produce the same effects.[20]

Additive interactions are most likely to occur when drugs with identical mechanisms are combined. In additive effects, the effect of the two drugs are in the same direction and simply add up.

Potentiation also refers to the enhancement of the effects of one drug by another, but this term is usually used when the two drugs have dissimilar actions.

The drugs used in our study – Midazolam, Ketamine and Propofol belong to three different classes. Midazolam and Propofol have similar actions but Ketamine and Propofol have dissimilar actions. So, the combination of midazolam and propofol in the present study can be termed as "Synergism". Short T G et al, Uma Srivastava et al, McClune et al and several other authors have also termed this combination of Midazolam and Propofol as "synergism" The combined effect of Ketamine and Propofol in our study can be termed as "Additive". Similarly, Huiet al.[21] have termed the Ketamine-Propofol combination as 'Additive' interaction in their study. Uma Srivastava and others in their study have also said that the decreased dose requirement of Propofol following Ketamine cannot be explained by the mechanism of synergism as these drugs act via distinctly different receptors. The Propofol–Propofol combination in our study can be termed as "Priming"\Predosing\ Pretreatment\auto-co-induction. The term priming for propofol auto-co-induction has been also used by Maroof et al, Pallavi S et al and Anil K et al

The mechanisms involved in co-induction are poorly understood. It has been suggested that co-induction results from a combination of both pharmacodynamic interactions at a receptor level and pharmacokinetic effects related to the distribution of induction agent. Anderson and Robb (1999) proposed a pharmacokinetic theory that a part of the mechanism of action of co-induction drugs is to reduce the anxiety and associated sympathetic response. Midazolam and propofol act on a common receptor site, GABA receptors, thus potentiating each other's effect. Reduced dose requirement of propofol following ketamine cannot be explained by this mechanism as these agents act via distinctly

different receptors, ketamine acts by antagonism of NMDA receptors, while propofol acts on GABA receptors. Hui T W et al.[21] attributed this to a simple additive interaction of sedative effects of the two drugs.

In addition to the safety and comfort of the patient, it is also important to find a cost effective combination in view of the rather stringent economy of times. Cost containment in anesthesia has become a major concern in recent years. Given the expanding costs of health care, economic considerations have drawn more and more interests over the last decade. Considering this point we also studied whether the concept of co-induction can be used to reduce the cost of induction.

Minaxi et al.[22] in 2008 found that midazolam co-induction is more economical compared to Propofol predosing. We found a similar reduction in the cost of induction dose of Propofol i.e. 33.18%, 29.2%, 18.8% in groups MP,KP and PP respectively compared to control($P<0.001$). However, when the total cost of induction was considered, there was a 22.2% and 14% reduction in groups MP and KP respectively compared to control. Propofol-Propofol appears to be the most expensive combination (1.65% increase in induction cost compared to control) and Midazolam-Propofol to be the most economic combination in our study. Edomwonyi N P et al.[23] in 2000 have also observed the same and concluded that midazolam co-induction is more economical than using propofol alone.

It is accepted that induction of anesthesia with propofol is associated with significant decrease in arterial blood pressure. Analysing data from almost 2500 cases, Hug et al.[24] reported a reduction in SBP to less than 90 mmHg in 16% patients who were given propofol with the majority of the episodes occurring during the first 10min of induction. Thus, propofol when used as the sole induction agent produces adverse effects like hypotension Several studies have measured the changes in hemodynamic parameters following inj. propofol 2.5-3 mg/kg and found that MAP decreased by 22-33% from the base line. Reductions in arterial pressure and heart rate occur usually during the induction of anaesthesia with propofol and are influenced by the dose and rate of administration.

In the present study the mean HR during the first 5 min post induction was increased by 1%,17.3% 6.14% in groups SP, KP, PP respectively and decreased by 0.69% in group MP. The average MAP during the first 5 min post induction was increased by 0.97%, 0.31%, 9.1% in groups SP, MP, KP respectively & decreased by 3.62% in Group PP in the first 5 min after induction. Thus only in group KP, the HR and MAP were increased significantly ($p<0.05$ for HR and $p<0.01$ for MAP) compared with baseline values. In the other groups (SP, MP and PP), the changes in HR and MAP during the first 5 min post induction were not statistically significant. This means that in our study, Midazolam, Ketamine and Propofol combination did not show demonstrable benefits in terms of haemodynamic stability as compared to control group. Our findings regarding haemodynamic stability thus confirm with the findings of Cressy et al and Jones et al who have shown that there were no demonstrable benefits in terms of haemodynamic stability with Midazolam co-induction or Propofol predosing. Nevertheless, our findings do not confirm with the findings of Uma Srivastava et al, Hui et al, Furuya et al.[24] and Shiba Goel et al.[25] regarding the haemodynamic stability during Ketamine co-induction. These authors mention that Ketamine co-induction to Propofol preserves better haemodynamic stability and produces stable haemodynamics. The rise in HR and MAP seen in the KP group in the present study may be be attributed to the sympathetic stimulation produced by Ketamine and could be beneficial in patients with preexisting hypotension.

Nevertheless, the possibility of laryngoscopy and tracheal intubation counteracting cardiovascular depression caused by Propofol and other co-inducing agents like Midazolam and Propofol exists in our study.

In the present study in the other groups (groups SP,MP and PP) the changes in HR and MAP during the first 5 min post induction were not statistically significant($p>0.05$).

We also studied the incidence of Apnoea during induction. Propofol produces dose dependent depression of ventilation, with apnea occurring in 25% to 35% of patients after induction of anesthesia with propofol.[26] In the present study the Saline-Propofol combination showed highest (16%) incidence of Apnoea compared to study groups (8%, 12% and 12% in groups MP, KP and PP respectively). This may be attributed to the high induction dose requirement of Propofol in the control group. However the difference was not statistically significant ($P<0.05$) by Chi-square test. This finding also matches with the results of Anil K et al and Hui et al who respectively found that Propofol predosing and Ketamine co-induction resulted in lesser incidence of Apnea during induction with Propofol.

CONCLUSIONS: The present study concludes that:

1. The average Induction dose of Propofol was 104.4 mg (1.96mg\kg), 73.64 mg (1.31mg\kg), 77.2mg (1.39mg\kg) and 83.04 mg (1.59mg\kg) with Saline, Midazolam, and Ketamine & Propofol as co-induction respectively.
2. There was a highly significant reduction in induction dose of Propofol viz 33.18%, 29.2% and 18.8% reduction in groups MP, KP and PP respectively compared to control group. Thus Midazolam was most effective in reducing the induction dose of Propofol.
3. The total cost of induction was reduced by 22.2% & 14% with Midazolam & Ketamine respectively. An increase of 1.65% in induction cost was observed with Propofol auto-co-induction. Thus, Propofol – Propofol combination was the most expensive. Midazolam-Propofol combination appeared to be the most economical combination.

When compared to control group–none of the three groups-viz Midazolam-Propofol, Ketamine-Propofol and Propofol-Propofol provided more haemodynamic stability during induction.

Midazolam co-induction was associated with least incidence of Apnoea during induction with Propofol when compared to other groups.

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