ORIGINAL RESEARCH PAPER

Anaesthesiology

KEY WORDS: Propofol-ketamine, propofol-fentanyl, haemodynamic attenuation, laryngoscopy and intubation.

A COMPARATIVE STUDY OF INDUCTION WITH LOW DOSE KETAMINE-PROPOFOL VERSUS FENTANYL-PROPOFOL IN ATTENUATING THE HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION IN PATIENTS UNDERGOING GENERAL ANAESTHESIA

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ABSTRACT

Background and Aims: The use of drugs to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation is the standard of care during elective surgery. This study was conducted to compare the effect of two drug combinations using ketamine-propofol and fentanyl-propofol in attenuating haemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing general anaesthesia, duration of analgesia and side effects if any.
Methods: After taking ethical committee clearance a randomized single blind prospective study involving 100 patients(18-60 years)of ASA-I and II undergoing GA for elective surgeries, were divided into 2 groups: Group K received Inj.Ketamine 0.5 mg/kg+inj.Propofol 2 mg/kg, Group F received Inj.Fentanyl 1.0 μg/kg+inj.Propofol 2 mg/kg. Haemodynamic parameters HR, SBP and DBP were recorded at baseline, after study drug, at 1min, 3min, 5 min, 10 min, 20 min after intubation and so on till completion of surgery. Pain score was assessed by Visual Analogue Scale (VAS) score. Student's unpaired t-test and chi-square test tests were used for statistical analysis.
Results: Upon induction with study drugs there was fall in SBP and DBP in both the groups but more in group F (p-value<0.0204 for SBP, p-value<0.0002 for DBP). On induction HR reduced in group F but it was slightly raised in group K (p-value<0.0001). After endotracheal intubation, at 1 minute, BP and HR increased significantly and reached above the baseline in group K but it remained below the baseline in group F(p-value<0.0001for HR and DBP,p-value<0.0158 for SBP). During maintenance phase group K showed more stable haemodynamics as compared to group F. The mean duration analgesia is significantly shorter 83.1 ± 10.814 mins for Group F and for Group K it is 91.64 ± 8.998 mins (P value< 0.0001).
Conclusion: Fentanyl is superior to Ketamine in attenuating haemodynamic response to laryngoscopy and intubation. The duration of analgesia was shorter and rescue analgesia requirement was earlier in fentanyl group as compared to ketamine group and few untoward side effects were seen in both the groups.

INTRODUCTION

Laryngoscopy and Endotracheal intubation is a vital part of general anaesthesia, and are very essential tools in the hands of anaesthesiologists in maintaining airway.

Endotracheal intubation has become an integral part of the anaesthetic management and critical care of the patient and has been practiced following its description by Rowbotham and Magill in 1921.[1]

The circulatory changes arising from airway instrumentation are due to sympathoadrenal discharge trigger by epipharyngeal and parapharyngeal stimulation.[2]

The circulatory responses to laryngeal and tracheal stimulation are known since 1940 (Reid & Brace). The nervous system activity in the cervical sympathetic efferent fibres Increased by the mechanical stimulation of the respiratory tract is shown in the study by Tomori & Widdicombe (1969). King et al., (1951) have described the circulatory responses to laryngeal and tracheal stimulation following laryngoscopy and tracheal intubation as reflex sympathoadrenal stimulation.[3,4,5].

Although increase in heart rate and blood pressure due to sympathoadrenal response are short lived they may have detrimental effects in high risk patients especially those with cardiovascular diseases, increased intracranial pressure or anomalies of cerebral vessels.[6]

Some authors consider the intubation period one of the greatest risk in surgical patients with coronary artery diseases. Although the response may be transient, it is invariable, significant, often persistent, and of great concern. Therefore it is important to find an effective means of attenuating sympathetic response to laryngoscopy and intubation. Several pharmacological and non-pharmacological methods have been used to attenuate the haemodynamic response to laryngoscopy & endotracheal intubation.[7]

Many strategies have been advocated to minimize the haemodynamic adverse responses to laryngoscopy and endotracheal intubation.

The non-pharmacological techniques like smooth & gentle intubation with quick laryngoscopy and insertion of LMA instead of endotracheal tube[7] have been used to attenuate the haemodynamic response to laryngoscopy and endotracheal intubation.

The Pharmacological agents like use of volatile anaesthetics [5,8], intratracheal and intravenous lidocaine,[9,10,11], opioids,[12,13,14] -blockers,[15,16,17] calcium channel blockers,[18,19,20] and vasodilators [21,22] have been tried to attenuate the cardiovascular response.

The choice of premedication as well as adjuvant to propofol is always a matter of differing opinion, some advice opioid premedication, some offers benzodiazepines. Similarly various adjuvants like ketamine, fentanyl, alfentanil or other opioid analgesic have been used as adjuvant.[23]

Among the different means available for attenuation of haemodynamic response to laryngoscopy and intubation, opioids also seem to have a reliable and constant effect. Opioids block afferent nerve impulses resulting from stimulation of the pharynx and larynx during intubation along with an advantage of its perioperative role in analgesia & anaesthesia.[24]

Opioids acts by binding to the opioid receptors (μ, κ and δ) both inside and outside the central nervous system, and depending on the interaction with these receptors, opioids are classified as pure agonist, partial agonist or mixed agonist – antagonist.

Ketamine which is water soluble intravenous anaesthetic belongs to phencyclidine group of drugs. It is the only intravenous anaesthetic which has hypnotic, analgesic and amnesic properties.[25]

Ketamine is a potent analgesic, its anaesthetic and analgesic effects have been suggested to be mediated by different mechanisms. Ketamine in subanaesthetic doses with propofol has gained attention in total intravenous anaesthesia [26] because of its powerful analgesic action in a small dose without causing myocardial and respiratory depression.

Ketamine also causes some degree of sympathetic stimulation, which tends to counter balance the cardiovascular effects of propofol. It has very high margin of safety, no irritation of the veins and no negative influence on ventilation or circulation except the disadvantage of producing hypertension and psycho mimetic emergence phenomena.[27]

The present study is undertaken to compare the efficacy of ketamine 0.5/kg IV and Fentanyl 1.0 μg/kg with propofol 2mg/kg in attenuating the haemodynamic response to laryngoscopy and intubation and in maintaining intraoperative haemodynamics.

Methods:
After taking ethical committee clearance a randomized single blind prospective study involving 100 patients(18-60 years)of ASA-I and II undergoing GA for elective surgeries, were divided into 2 groups: Group K received Inj.Ketamine 0.5 mg/kg+inj.Propofol 2 mg/kg, Group F received Inj.Fentanyl 1.0 μg/kg+inj.Propofol 2 mg/kg. Haemodynamic parameters HR, SBP and DBP were recorded at baseline, after study drug, at 1min, 3min, 5 min, 10 min, 20 min after intubation and so on till completion of surgery and After extubation patients were shifted to the post-operative ward, and the HR, SBP, DBP, Visual analogue score were recorded (post op base line) and thereafter at every 20mins interval till requirement of analgesia. Student's unpaired t-test and chi-square test tests were used for statistical analysis.

Inclusion criteria: 100 patients of either sex, aged between 18 to 60 years, belonging to ASA grade I & II, Patients scheduled for elective surgical procedure under general anaesthesia.

Exclusion Criteria: Refusal to informed consent, Patient with anticipated difficult airway, Patients with ASA grade III and IV, history of allergy to the study drugs, any severe systemic disorders, Pregnant and lactating women.

All patients were explained about the anaesthesia technique & written informed consent was taken. Patients were kept nil per oral (NPO) for 8 hrs prior to surgery. All the patients were given Tablet Alprazolam 0.5 mg orally at bed time on the previous night of the surgery.

Technique of Anaesthesia:
100 patients, aged between 18 to 60 years, belonging to ASA grade I & II were randomly divided into 2 groups and each group consisted to 50 patients.

1) Group K received Inj. Ketamine 0.5 mg/kg with Propofol 2 mg/kg IV
2) Group F received Inj. Fentanyl 1.0 μg/kg with Propofol 2 mg/kg IV

Anaesthesia machine and circuits were checked for proper functioning, and resuscitation drugs and equipments were kept ready.

Patients were pre-medicated with following drugs 20 minutes prior to induction.
Inj. Ondansetron 4 mg i.v stat.
Inj. Ranitidine 50 mg i.v stat.
Inj. Glycopyrrolate 0.2 mg i.v stat.

Induction:
Patients were pre-oxygenated with 100% oxygen for 3 minutes with facemask of appropriate size using Mapleson A circuit. Induction of anaesthesia was done with study drug and propofol.

In Group K induction of anaesthesia was done with Inj. Ketamine 0.5 mg/kg followed by Inj. Propofol 2 mg/kg.

In Group F induction of anaesthesia was done with Inj. Fentanyl 1.0 μg/kg followed by Inj. Propofol 2 mg/kg.

After induction of anaesthesia, muscle relaxation was achieved with Inj. Vecuronium bromide (0.1 mg/kg). After adequate muscle relaxation laryngoscopy was carried out with a standard Macintosh blade and intubation was performed with appropriate sized cuffed endotracheal tube and after confirming bilateral equal air entry by chest auscultation, endotracheal tube was secured and the EtCO2 probe was attached for monitoring end-tidal carbon dioxide. Oral intubation was done in all patients and intubation was accomplished within 15 to 20 seconds.

Maintenance:
Anaesthesia was maintained with mixture of N2O (66%) and O2 (33%) with isoflurane (0.6 to 0.8%) and muscle relaxation was maintained with intermittent dosage of Inj. Vecuronium bromide. Intra-venous fluid was maintained with Ringer's lactate and Normal Saline 0.9% at the rate of 4-6ml/kg/hr. After the initiation of the surgical procedure, infusion Paracetamol 15 mg/kg body wt. was infused to all patients.

At the end of surgery, when patients had respiratory efforts, residual neuromuscular blockade was reversed with Inj Neostigmine 0.05 mg/kg i.v. & Inj. Glycopyrrolate 0.01 mg/kg i.v. Recovery assessment & extubation were done after thorough oropharyngeal suction.

RESULTS AND OBSERVATIONS
Demographic Profile:
The patients in both the groups were statistically comparable with respect to the distribution of Age, Height, Weight and American Society of Anesthesiologists physical status.

Intra Operative Vital Parameters:
Changes In Heart Rate: The mean heart rate of both groups using two tailed unpaired student t- test shows extreme significance during the period (T) just after injecting the study drug ($p < 0.0001$), T1, T3, T5 and significant at T10 and the rest of the study period does not show any statistically significant difference.

Table1:-Comparison of mean heart rate between two groups.

Study period	Mean Heart Rate (beats/min)						P-value
	Group K			Group F			
	Mean	% Change from baseline	SD	Mean	% Change from baseline	SD	
T0	82.26		4.313	82.82		4.702	0.5368
T	82.48	+ 0.26	4.432	77.76	-6.10	4.689	< 0.0001
T1	85.68	+ 4.15	4.438	81.12	-2.05	4.864	< 0.0001
T3	84.82	+ 3.11	4.521	80.44	-2.87	4.717	< 0.0001

T5	84.4	+ 2.60	5.194	80.06	-3.33	5.453	< 0.0001
T10	84.26	+ 2.43	4.539	82.46	-0.43	4.248	0.0446
T20	83.02	+0.92	4.34	84.14	+1.59	4.449	0.2056
T40	82.58	+ 0.38	4.2	83.74	+1.11	3.864	0.1538
T60	82.52	+ 0.31	4.395	83.88	1.27	4.396	0.1239

Change In Systolic Blood Presure: The mean systolic blood pressure (SBP) of both groups using two tailed unpaired t - test shows significant difference during the study period at (T) just after injecting the study drug (p value 0.0204), at T1 (p value 0.0158), at T3 (p value 0.002), at T5 (p value 0.0002) and at T10 (p value 0.0389) and the rest of the study periods does not show any statistical significance during the entire study (p value >0.05).

Table2:-Comparison of mean systolic blood pressure in between two groups.

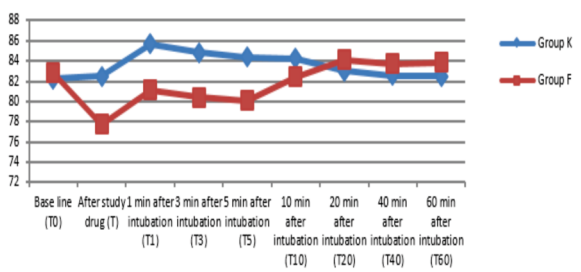
Study period	Systolic Blood Pressure (mmHg)						P-value
	Group K			Group F			
	Mean	% Change from baseline	SD	Mean	% Change from baseline	SD	
T0	125.8		7.866	125.52		6.783	0.8492
T	123.4	-1.90	7.412	120.04	-4.36	6.827	0.0204
T1	128.86	+2.43	6.095	125.88	+0.286	6.043	0.0158
T3	127.88	+1.65	5.133	124.46	-0.84	5.629	0.002
T5	127.62	+1.44	5.127	123.58	-1.54	5.218	0.0002
T10	127.14	+1.06	5.421	124.78	-0.58	5.846	0.0389
T20	126.66	+0.68	5.181	125.88	+0.286	5.517	0.4679
T40	125.44	-0.286	4.621	126.82	+1.03	4.672	0.1407
T60	125.86	+0.047	4.669	127.22	+1.35	4.896	0.1583

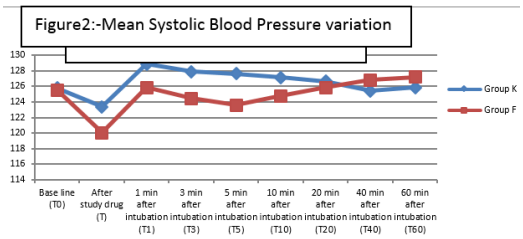
Change In Diastolic Blood Pressure: The mean diastolic blood pressure (DBP) of both groups using two tailed unpaired t - test shows extremely significant difference during the study period at (T) just after injecting the study drug (p value 0.0002), at T1 (p value <0.0001), at T3 (p value <0.0001), significant difference at T5 (p value 0.0013) and the rest of the study periods does not show any statistical significance during the entire study (p >0.05).

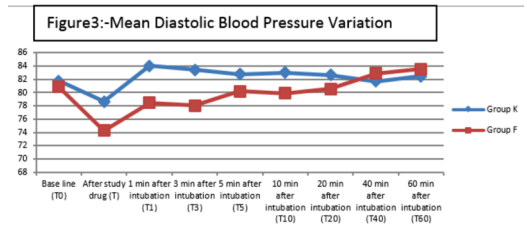
Table3:-Comparison of mean diastolic blood pressure between the two groups.

Study period	Diastolic Blood Pressure (mmHg)						P-value
	Group K			Group F			
	Mean	% Change from baseline	SD	Mean	% Change from baseline	SD	
T0	81.78		5.148	80.88		5.173	0.3853
T	78.66	-3.81	5.524	74.32	-8.11	5.705	0.0002
T1	84.04	+2.7	5.022	78.46	-2.99	5.898	<0.0001
T3	83.46	+2.05	4.892	78.04	-3.51	5.466	<0.0001
T5	82.78	+1.01	4.765	80.22	-0.81	5.448	0.014
T10	83.02	+1.51	4.317	79.92	-1.18	5.034	0.0013
T20	82.68	+1.10	4.211	80.54	-0.42	5.104	0.0244
T40	81.7	-0.09	4.205	82.88	+2.47	4.65	0.1863
T60	82.46	+0.83	4.195	83.58	+3.33	4.824	0.2184

Figure1:-Mean Heart rate variation







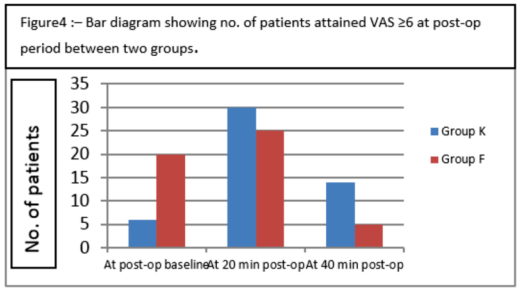
Post-operative period:-

As per study protocol, patients were excluded from the study once they required rescue analgesia. Thus after 20 and 40 min only 30 and 5 patients remained in group F compared to 44 and 14 patients in group K respectively.

Post-operative haemodynamic variables such as HR, SBP, DBP and MAP of both groups using two tailed unpaired t test shows no statistical significance during entire study period (p value>0.05).

Visual Analogue Score: Out of 50 patients in each group, 20 patients attained VAS ≥ 6 in Group F as compare to 6 in Group K just after the shifting of the patients to the post-operative ward (post-op base line).

The VAS of Group K at post op baseline was 3.6 ± 1.212 and for Group F it was 4.84 ± 1.149, which was considered statistically extremely significant.



Time for 1st rescue analgesia was significantly earlier 17.5 ± 11.567 mins for Group F and for Group K it is 24.84 ± 10.813 (P value- 0.0014).

Mean duration analgesia was significantly shorter 83.1 ± 10.814 mins for Group F and for Group K it is 91.64 ± 8.998 mins (P value< 0.0001).

Side Effects: During post-operative period 3 patients in group F had PONV compared to 1 in group K. In group K, one patient had oral secretion during recovery. No other side effects were seen in both study groups.

DISCUSSION

In our study, premedication and anaesthetic techniques were kept constant to exclude any variation in cardiovascular responses due to a variety of drugs and technique. Hypoxia and hypercarbia were avoided. EtCO2 was maintained between 35 – 45 mmHg and saturation maintained at 95 – 100 %.

Demographic characteristics:

The mean age, weight, height and duration of surgery of both the groups were comparable. There was no significant difference amongst the groups with regard to demographic

variables (P value > 0.05).

HaemodynamicVariables:
In our study immediately after study drug administration (T), the mean heart rate increased to 82.70 ± 4.432 bpm (increased by 0.26% of baseline) in Group K and decrease to 77.76 ± 4.689 bpm (decreased by 6.10% of baseline) in Group F, which was statistically extremely significant (p value < 0.0001). These results were similar to study done by Mayer et al,[28] where they found heart rate drops by 9% in fentanyl group, but did not change in ketamine group. Mi et al,[29] also got similar finding when they compared induction with propofol vs propofol and 2μg/kg Fentanyl IV. They observed that heart rate decreased between 5 and 35% in patients who received fentanyl prior to induction of anaesthesia and was comparable with our findings where we observed 6.10% decreases from the baseline.

Following intubation at 1 minute (T1), the heart rate increased to 85.68 ± 4.432 (increased by 4.15% of baseline) in Group K and in Group F it was 81.12 ± 4.864 (decreased by 2.05% of baseline), which was statistically extremely significant (p value < 0.0001) and remained statistically significant till 10 minutes after intubation (T10), after that it remained statistically insignificant (p value > 0.05). GUIT et al,26 in their study observed that patients who received ketamine showed temporary rise in HR directly after tracheal intubation and were comparable with our study findings. Saha and coworkers[30] showed a significant decrease in heart rate after induction and maintenance of anaesthesia with propofol and fentanyl which was comparable with our study. Sukhminder Jit Singh Bajwa et al,[31] observed an increase HR in patients who received ketamine and decrease HR in patients who received fentanyl, which returned gradually toward baseline during the maintenance phase of anesthesia in both the groups, but the difference in both the groups was statistically significant (P < 0.05) and their findings were comparable with our finding.

Immediately after study drug administration (T) the mean systolic blood pressure reduced to 120.04 ± 6.827 mmHg in group F (decreased by 4.36% of baseline) and reduced to 123.4 ± 7.412 mmHg (decreased by 1.90% of baseline) in group K and found statistically significant (p value= 0.0204). At 1 minute following intubation (T1), the mean systolic blood pressure increased to 128.86 ± 6.095 mmHg (increased by 2.43% of baseline) in Group k and in Group F it was 125.88 ± 6.043 mmHg (increased by 0.28% of base line) and found statistically significant (p value= 0.0158) and remained so up to 10 minute after intubation (T10). After that the variation remained statistically insignificant till post-operative period (p value > 0.05). Guit et al,[27] observed decrease in systolic blood pressure after induction and return to baseline after intubation in patients who received propofol/fentanyl. They also found stable systolic blood pressure in patients who receive propofol/ketamine, except for a temporary increase after tracheal intubation. These were comparable with our observation in both the groups. Sukhminder Jit Singh Bajwa et al,[31] observed fall in systolic blood pressure during induction in patients who received propofol-fentanyl and slight increase in systolic blood pressure after induction and intubation in patient who received propofol-ketamine. In our study we observed slight decrease in systolic blood pressure in ketamine group after induction. This finding indicates that the dose of Ketamine administered during the induction of anesthesia may not have been high enough to neutralize the cardio-depressant effect of propofol.

Immediately after study drug administration (T) the mean diastolic blood pressure dropped in both the groups and it was 74.32 ± 5.705 mmHg (decreased by 8.11% of baseline) in group F and 78.66 ± 5.524 mmHg in group K (decreased by 3.81% of baseline) and found statistically extremely significant(p value= 0.0002). Following intubation at 1minute (T1), the mean diastolic blood pressure increased to 84.04 ± 5.022 mmHg (increased by 2.7% of baseline) in Group K and in Group F it was 78.46 ± 5.898 mmHg (decreased by 0.28% of base line) and found statistically extremely significant (p value <0.0001). From 40 minute after intubation (T40) the mean diastolic pressure variation remained statistically insignificant between the two groups till post-operative period (p value > 0.05). This findings were comparable with the study of Guit et al,[27] and Sukhminder Jit Singh Bajwa et al,[31]. In our study post-operative visual analogue scale at post op baseline was lower in group K (3.6 ± 1.212) compared to Group F (4.84 ± 1.149) (p value < 0.0001). Mayer et al,[28] also found that Patients who received ketamine showed better vigilance as well as better pain relief postoperatively than patients who received fentanyl.

In our study the mean time for first rescue analgesia is significantly earlier 17.5 ± 11.567 mins for Group F and for Group K it is 24.84 ± 10.813 (P value- 0.0014). Mayer et al,[28] observed that postoperatively, fewer patients in ketamine group required rescue doses of analgesics (1 of 10) than those in fentanyl group (7 of 10).

Duration of Analgesia: The duration of analgesia was calculated from just after the time of study drug administration to the time of first rescue analgesia. The mean duration of analgesia was 91.64 ± 8.998 min in Group K and 83.10 ± 10.814 in Group F which was extremely significant (p value < 0.0001).

Side Effects: During post-operative period 3 patients in group F had PONV compared to 1 in group K. In group K, one patient had oral secretion during recovery. Sukhminder Jit Singh Bajwa et al,[31] in their study observed post-operative oral secretion in 4 patients in Ketamine group and one in Fentanyl group. The incidences of oral secretions were more in their study probably because they used iv infusion of ketamine during maintenance period.

CONCLUSION:

To conclude, we have observed in our study that fentanyl is superior to ketamine in attenuating haemodynamic response to laryngoscopy and intubation by virtue of its reduction in heart rate, systolic blood pressure and diastolic blood pressure

On the other hand, we observed more stable haemodynamics during maintenance phase and better post-operative pain relief with ketamine than fentanyl. Also the duration of analgesia was shorter and rescue analgesia requirement was earlier in fentanyl group as compared to ketamine group. From the above findings it can be safely concluded that:

Fentanyl was more effective in blocking sympathetic response to laryngoscopy and endotracheal intubation.

Ketamine was more effective in maintaining stable haemodynamic during maintenance period and provided better post-operative pain relief.

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