Original Research Article

Study the impact of ketamine, clonidine and combination of ketamine-clonidine on cardiovascular system during pre and postoperatively: A double blind, placebo controlled study

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Abstract

Background: The use of ketamine as a sole anesthetic induces marked central sympathetic stimulation, causing increased heart rate, blood pressure (BP), and oxygen consumption (VO2). Both alpha 2-agonists and benzodiazepines have been used to attenuate these potentially harmful ketamine-induced responses. **Materials and Methods:** After approval from institutional ethical committee and written informed consent, 120 adult patients, ASA physical status I and II, undergoing elective surgeries e.g. Open abdominal surgery, laparoscopic surgery, open urological surgery were included in this controlled, prospective, randomized, double-blind study. Patients were randomly (envelop randomization) allocated in 4 groups (n=30): Group K received IV ketamine (0.5mg/kg), Group C received IV clonidine (1.5µg/kg), Group KC received combination of IV ketamine (0.25mg/kg) and IV clonidine (0.75µg/kg) and Group P received IV normal saline (placebo). One envelop at a time was chosen by an anaesthesiologist, who was blinded to the preparation of study agents and administered the study drugs in the envelope one after the other, intravenously approximately 20 minutes before extubation. **Results:** Pre operative haemodynamic parameters like mean arterial pressure (MAP) and heart rate are comparable across the groups. There was statistically significant (two tailed p value < 0.001) rise in intra operative heart rate following intubation in groups K, KC and P. There was statistically significant increase in systolic blood pressure (SBP) in groups K and P (two tailed p value < 0.001). In group C and KC, there were significant fall in SBP, from the baseline values, following induction. **Conclusion:** The unwanted effects of the individual drugs like, haemodynamic alteration, hallucination or lower incidences of nausea and vomiting could be achieved by using half of the dose of each of the drugs in combination.

Keywords: Ketamine, Clonidine, General anaesthesia, Cardiovascular functions, SBP, DBP, HR.

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Introduction

Ketamine,2-(o-chlorophenyl)-2-(methylamine) cyclohexanone, a phencyclidine (PCP) and cyclohexamine derivative, was developed and introduced into clinical anaesthesia by Corssen and Domino in 1966[1]. Ketamine is widely used as an anesthetic in surgery and emergency medicine. It is an intravenous induction agent producing a unique dissociative anaesthetic state characterized by a dissociation between the thalamocortical and limbic systems[2]. It produces profound analgesia, normal pharyngeallaryngeal reflexes, normal or slightly enhanced skeletal tone, and respiratory stimulation and occasionally transient and minimal respiratory depression[2]. The increasing use of ketamine as a potential rapid-onset antidepressant necessitates a better understanding of its effects on blood pressure and heart rate, well-known side effects at higher doses. The physiological mechanisms that mediate the adverse cardiovascular effects of ketamine are thus far unclear. In general, transient changes in blood pressure are induced by the baro-reflex, which directly influences cardiac output and vascular resistance, to maintain blood pressure at nearly constant levels [3]. The most important transmitter of this blood pressure regulation system is norepinephrine (NE). The NE transporter (NET) is responsible for the reuptake of NE into the presynaptic nerve cell [4].

Ketamine increased the arterial blood pressure over a duration of 60 minutes and by a mean maximum degree of 13 mmHg both systolic and diastolic in our participants. The increase was visible only within 2 hours after ketamine administration, reflecting the time period within which ketamine-related side effects must be expected[5]. Clonidine is a centrally acting alpha-2 adrenergic agonist that was first investigated for the treatment of hot flashes in the 1970s. The hypotensive effect of clonidine is mediated primarily by agonism of central nervous system α2-receptors, which leads to increased parasympathetic tone and decreased circulating catecholamines. This global reduction in sympathetic output has made the drug a useful adjunct in the treatment of opiate withdrawal.[6] Clonidine produces hemodynamic effects that are mediated through both the heart and the peripheral vascular system. The cardiac effects (decrease in heart rate and stroke volume) appear to predominate early in treatment, but peripheral vascular resistance is usually reduced[7].The aim of present study was to compare the impact of single dose intravenous ketamine (0.5mg/kg) and intravenous clonidine (1.5µg/kg) and combination of intravenous ketamine (0.25mg/kg) plus clonidine (0.75µg/kg) on cardiovascular system during pre and postoperatively.

Materials and Methods

After approval of the study protocol from the National Board of Examination and Ethical Review Committee of Apollo Gleneagles Hospital, Kolkata, the thesis work was carried out in the Departments of Anaesthesiology, Perioperative Medicine and Pain at Apollo Gleneagles Hospital, Kolkata during the period of November 2008- June-2009.

Selection of Patients

120 patients were enrolled for this placebo controlled, prospective, randomized, double-blind study. Informed consent was obtained from each patient after full explanation of the purpose of the study.

Inclusion Criteria

- ASA physical status I and II,
- Aged between 18- 55 yrs,
- Height between 150 cm -170 cm,
- Patients undergoing elective surgeries e.g. open abdominal surgery, laparoscopic surgery, open urological surgery.

Exclusion Criteria

- Patient with known hypersensitivity to study drugs
- Patient with co-morbidities like cardiopulmonary disease, neuromuscular disease, severe renal insufficiency, hypo- or hyperthyroidism
- History of alcohol abuse
- History of psychological disorders
- Pre-operative body temperature >38◦C or <36◦C
- Patient receiving vasodilators, inotropes, clonidine, alpha-methyl-dopa, beta-blockers or
- tricyclic anti-depressants
- Surgical procedures, for example TURP and LUCS
- Body mass index (BMI) more than 30 kg m^2

Plan of Study

Sample size was taken to be 120. Number of patients needed for this study were based on the anticipation that incidence of shivering of the order of 40-65%, an incidence of 45% in the control group and a difference of 40% in the incidence of shivering between control and treated groups as being clinically meaningful, with α =0.05 and β=0.2 and power of the study 90%. Based on these assumptions, 30 patients per group were sufficient. Patients were randomly (envelop randomization) allocated in 4 groups (n=30):

Group K - received IV ketamine (0.5mg/kg)

Group C - received IV clonidine (1.5µg/kg)

Group KC - received combination of IV ketamine (0.25mg/kg) and IV clonidine (0.75µg/kg)
Group P - received IV normal saline (placebo)
The study agents were diluted in identical 2 ml syringes by an anaesthesiologist who were not involved in institution of the anaesthesia and were presented in four coded envelops. Each of the coded envelops contained two syringes. One envelope contained ketamine and normal saline, one had clonidine and normal saline, one had two syringes of normal saline and another had one syringe each of ketamine and clonidine. One envelop at a time was chosen by an anaesthesiologist, who was blinded to the preparation of study agents and administered the study drugs in the envelope one after the other, intravenously approximately 20 minutes before extubation. The investigator collecting the data in postoperative recovery room was also blinded to the preparation of the study drugs as well as the anaesthetic procedure.

Preparation of Patient

A thorough pre-anaesthetic evaluation was performed by taking history and clinical examination. In all the patients, height, weight, basal heart rate, respiratory rate and blood pressure were measured and recorded. Surface temperature (axillary) was measured using digital clinical thermometer and recorded in the pre-operative room. All patients were fasted at least 6 hours before the surgery.

Procedure

Ambient temperature of the operation theater and post-operative recovery room would be maintained at 24^0C during the study. Routine monitoring like pulse-oxymetry (SpO2), noninvasive blood pressure monitoring (NIBP), ECG, capnometry (EtCO2) were monitored continuously throughout the procedures. Intravenous accesses were done with 20G IV cannula. All IV fluids and the IV Infusions used during operations were pre-warmed with hot water tub to a temperature of approximately 37ºC. A standard double-layered blanket was used to cover the chest and upper limbs of all patients. Premedication with glycopyrrolate (0.2 mg) and midazolam (0.05 mg/kg) intravenously followed by induction with intravenous fentanyl (2 mcg/kg) and propofol (1.5-2 mg/kg) were done. Muscle relaxation used was inj atracurium besylate (0.5 mg/kg) followed by tracheal intubation. Maintenance was done with sevoflurane (1-3% MAC) in oxygen with air in controlled ventilation with Datex-Ohmeda Aestiva 5 anesthesia work stations. After completion of the surgery, residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and glycopyrrolate (7-10mcg/kg). Patients were extubated after respiratory efforts were adequate.
Side-effects of the study drugs e.g. hallucination, post-operative nausea and vomiting, hypo or hypertensions were observed also and treatments were instituted accordingly. Hypotension was defined as a decrease in mean arterial pressure (MAP) of more than 20% from baseline (baseline MAP was calculated from their measurements taken in the ward before surgery).[8] Developed hypotension was treated with aliquots of mephentermine 3 mg and a further infusion of lactated Ringer's solution as required. The amount of mephentermine given was recorded in each group.
The data collected were tabulated and analysed by SPSS 16.0 programme (SPSS Inc, Chicago, IL). A post-hoc power analysis was performed using NCSS 2000 (NCSS Statistical and Power Analysis Software). Continuous variables, such as demographic data (age, height and weight), were analysed with one-way analysis (ANOVA). Between group variations in heart rate, MAP, SPO2, core and axillary body temperature were compared by one-way ANOVA test. Within each group, we compared MAP, HR core and axillary body temperature values by paired t test. The results were reported as mean ± standard deviation.

Results

Table 1: Demographic Character of Patients (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Age (Yrs)	39.8±10.37	42.7±10.46	40.07±9.41	43.27±10.09	0.427
Height (cm)	161.47±7.74	163.07±8.06	163.37±9.11	161.7±8.25	0.755
Weight (Kg)	64.7±9.47	61.47±12.62	64.1±12.64	64.7±11.34	0.662
Sex (M/F)	10/20	11/19	13/17	16/14	0.410
ASA I/II	19/11	18/12	20/10	20/10	0.941

*** P value<0.05= statistically significant**

Demographic parameters for age, height, body weight, sex and ASA physical status were statistically comparable across the groups. Two- tailed p values of 0.427, 0.755. 0.662, 0.410 and 0.941for age, height, weight, sex and ASA physical status respectively, being greater than 0.05, become statistically comparable [Table 1].

Table 2: Pre-operative hemodynamic parameters of patients (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Mean Arterial Pressure (mmHg)	94.53±3.51	98.03±7.3	94.87±7.24	93.93±8.99	0.113
Heart Rate (Beats/min)	76.2±7.95	75.73±8.82	80.27±8.42	78.8±8.86	0.131

Pre operative haemodynamic parameters like mean arterial pressure (MAP) and heart rate are comparable across the groups. Two tailed p values of 0.113 and 0.131 respectively for MAP and heart rate indicate that there are no significant differences in haemodynamic parameters among the four groups [Table 2].

Table 3: Intra-operative heart rate (Mean±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Prior Induction	76.2±7.95	75.73±8.82	80.27±8.42	78.8±8.86	0.131
Immediately after intubation	87.4±9.19	72.03±9.02	79.17±5.95	85.63±6.27	<0.001
After 5 Mins	81.17±6.58	67.3±9.49	78.47±7.59	79.97±8.91	<0.001
After 10 Mins	134.43±5.91	120.33±6.48	132.47±6.62	129.17±9.65	<0.001
After 15 Mins	134.97±6.2	123.7±7.48	132.63±7.69	131±8.28	<0.001
After 30 Mins	136.33±6.69	123.67±7.37	132.47±7.74	131.03±8.64	<0.001
After 40 Mins	135.1±5.41	121.07±7.14	132.63±7.72	134.47±8.43	<0.001
After 50 Mins	140.03±6.39	120.93±7.15	133.17±6.63	130.63±8.82	<0.001
After 60 Mins	134.53±5.08	120.9±7.56	132.5±7.45	133.8±7.17	<0.001
End of Surgery	150.07±6.64	132±5.86	136.27±12.59	145.3±8.35	<0.001

Heart rates across the groups were comparable prior to induction with two tailed p value 0.131. There was statistically significant (two tailed p value < 0.001) rise in intra operative heart rate following intubation in groups K, KC and P. This rise was more for group K than P. In group C, there was significant fall in heart rate following intubation (two tailed p value<0.001). In group KC heart rate was maintained at a more or less constant level (vide Fig.1/Table 3).

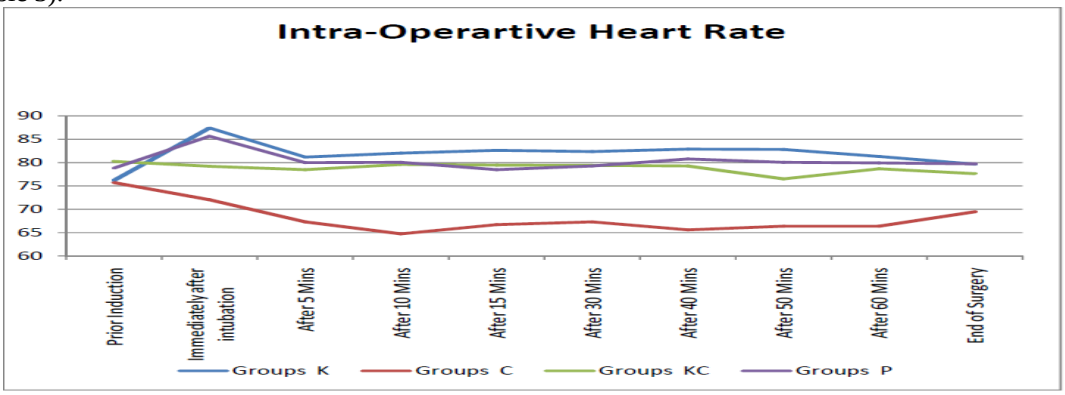

Figure 1: Intra-operative Heart Rate (Mean±SD) [statistically significant increase in systolic blood pressure (SBP) in groups K and P (two tailed p value < 0.001)]

Table 4: Intra-operative systolic blood pressure (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Prior Induction	131.53±10.47	137.33±9.19	132.87±7.54	132.47±13.35	0.139
Immediately after intubation	145.93±10.48	134.13±6.04	130.03±6.63	138.57±7	<0.001
After 5 Mins	133.93±5.67	121.43±7.5	131.9±7.45	131.23±8.19	<0.001
After 10 Mins	134.43±5.91	120.33±6.48	132.47±6.62	129.17±9.65	<0.001
After 15 Mins	134.97±6.2	123.7±7.48	132.63±7.69	131±8.28	<0.001
After 30 Mins	136.33±6.69	123.67±7.37	132.47±7.74	131.03±8.64	<0.001
After 40 Mins	135.1±5.41	121.07±7.14	132.63±7.72	134.47±8.43	<0.001
After 50 Mins	140.03±6.39	120.93±7.15	133.17±6.63	130.63±8.82	<0.001
After 60 Mins	134.53±5.08	120.9±7.56	132.5±7.45	133.8±7.17	<0.001
End of Surgery	150.07±6.64	132±5.86	136.27±12.59	145.3±8.35	<0.001

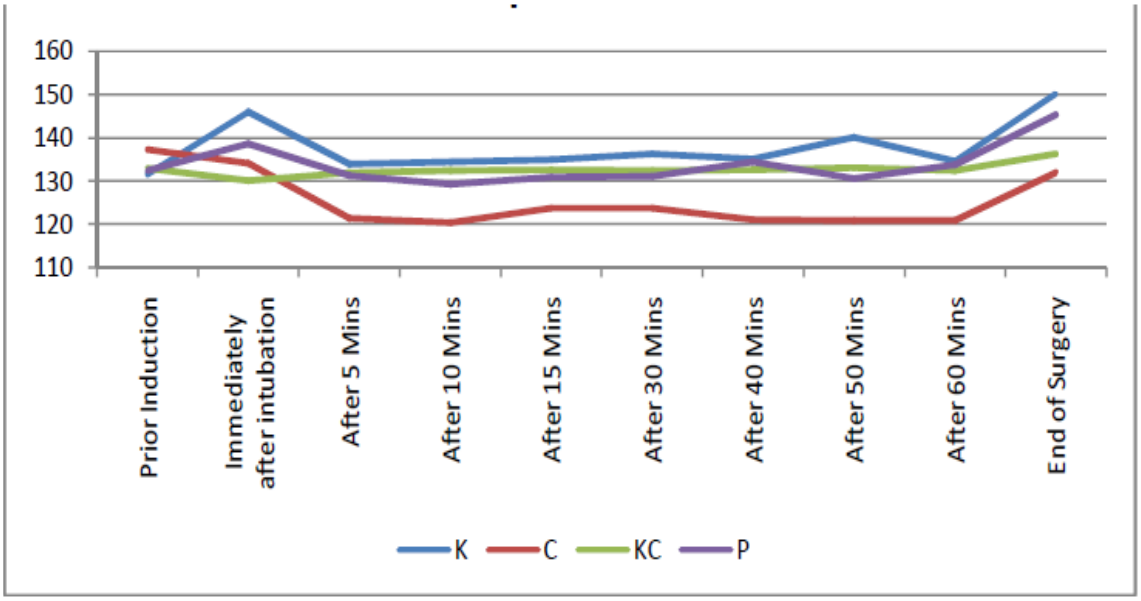

Figure 2: Intra-operative Systolic Blood Pressure [there is statistically significant increase in systolic blood pressure (SBP) in groups K and P (two tailed p value < 0.001)].

Table 4 showing there is statistically significant increase in systolic blood pressure (SBP) in groups K and P (two tailed p value < 0.001). In group C and KC, there were significant fall in SBP, from the baseline values, following induction. After 60 minutes till the end of surgery there were significant rise in SBP across the group, more so in group K and P (Fig. 2).

Table 5: Intra-operative diastolic blood pressure (Mean ±SD)

	Groups	

	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Prior Induction	76.13±4.64	78.33±9.43	75.83±7.97	74.73±7.26	0.311
Immediately after intubation	78.57±8.56	71.87±7.71	76.33±7.26	77.83±5.52	0.003
After 5 Mins	81.2±8.21	69.9±6.56	75.03±6.68	77.67±7.5	<0.001
After 10 Mins	82.17±7.92	72.83±6.63	74.07±5.3	76.17±6.98	<0.001
After 15 Mins	79.2±8.91	71.67±6.75	74.6±5.39	79.8±6.73	<0.001
After 30 Mins	79.7±8	70.9±5.9	72.1±6.8	76±7.62	<0.001
After 40 Mins	80.63±8.22	68.9±6.45	75.8±6.48	76.87±7.49	<0.001
After 50 Mins	82.83±8.87	70.93±5.71	74.33±6.04	77.73±6.36	<0.001
After 60 Mins	80.2±7.37	71±6.03	73.43±6.68	78.67±5.78	<0.001
End of Surgery	82.9±6.74	72.33±4.88	77.87±5.54	80.5±6.46	<0.001

In groups K and P, there is statistically significant rise in diastolic blood pressure following induction, whereas in group C there was significant fall. In group KC, DBP was maintained more or less at a constant level [Table 5/Fig.3].

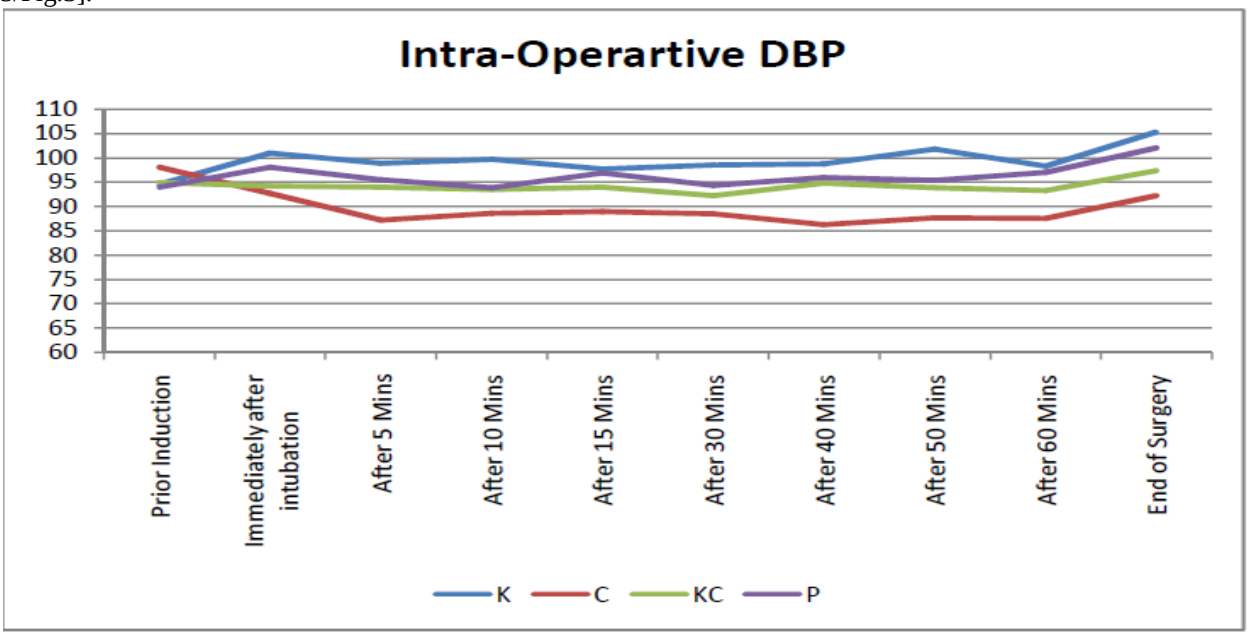

Figure 3: Intra-operative Diastolic Blood Pressure

Table 6: Intra-operative mean arterial pressure (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
Prior Induction	94.53±3.51	98.03±7.3	94.87±7.24	93.93±8.99	0.113
Immediately after intubation	101.03±6.87	92.7±5.43	94.2±5.7	98.07±4.68	<0.001
After 5 Mins	98.87±5.8	87.17±5.22	94±4.65	95.5±5.8	<0.001
After 10 Mins	99.67±5.23	88.63±4.93	93.53±4.38	93.87±6.33	<0.001
After 15 Mins	97.73±5.71	89±4.79	93.97±4.6	96.9±5.61	<0.001

After 30 Mins	98.5±6.4	88.5±4.2	92.2±5.56	94.3±5.93	<0.001
After 40 Mins	98.83±5.87	86.3±4.22	94.8±5.34	96.03±5.7	<0.001
After 50 Mins	101.83±7.15	87.63±5.01	93.9±4.52	95.37±5.46	<0.001
After 60 Mins	98.33±5.09	87.6±4.86	93.23±4.43	97.03±4.22	<0.001
End of Surgery	105.33±5.37	92.23±4.17	97.37±5.79	102.07±4.97	<0.001

In table 6, we see that, in groups K and P, there were statistically significant rise in mean arterial pressure (MAP) following intubation and then again from 60 minutes till end of the surgery. In group C, there was a significant fall in MAP after intubation and a rise at the end of the surgery. In group KC, MAP was maintained at a stable level throughout the surgery. In groups K and P, there were statistically significant rise in mean arterial pressure (MAP) following intubation and then again from 60 minutes till end of the surgery. In group C, there was a significant fall in MAP after intubation and a rise at the end of the surgery [Fig. 4].

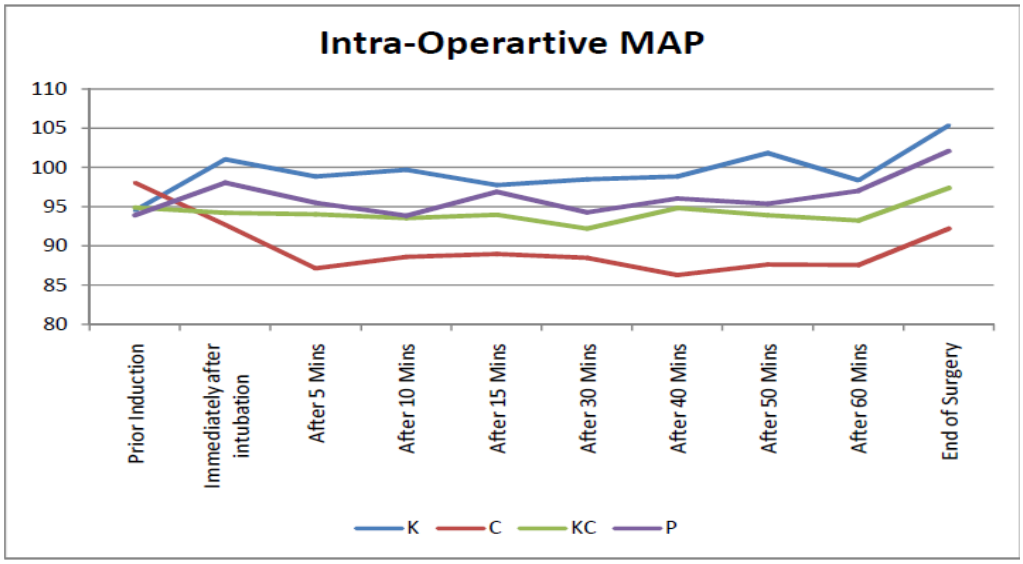

Figure 4: Intra-operative Mean Arterial Pressure

Table 7: Post-operative heart rate (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
After 5 Mins	77.67±6.13	67.2±5.71	75.83±5.09	77.8±5.57	<0.001
After 10 Mins	76.1±6.19	65.7±5.73	74.1±5.18	76.27±5.71	<0.001
After 15 Mins	74.53±6.34	64.1±5.71	72.73±5.12	74.83±5.77	<0.001
After 20 Mins	73±6.4	62.6±5.75	71.17±5.01	73.43±5.92	<0.001
After 25 Mins	71.47±6.45	61.2±5.85	69.8±4.99	71.93±6.03	<0.001
After 30 Mins	69.8±6.41	59.6±5.78	68.2±5.09	70.53±5.93	<0.001

Post operative heart rate was measured at 5 minutes interval till 30th minutes. There was significant fall in heart rate in post operative period across the four groups. From the table 7 it is seen that this fall was more for group C.

Table 8: Post-operative systolic blood pressure (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
After 5 Mins	148.37±6.54	127.17±6.06	140.83±12.1	143.9±8.34	<0.001
After 10 Mins	146.83±6.69	125.6±6.07	139.27±12.18	142.4±8.46	<0.001
After 15 Mins	145.33±6.78	124.17±5.97	137.73±12.34	141±8.57	<0.001
After 20 Mins	143.73±6.77	122.67±6.04	136.13±12.49	139.57±8.39	<0.001
After 25 Mins	142.33±6.75	121.17±6.06	134.6±12.45	137.93±8.52	<0.001
After 30 Mins	140.9±6.7	119.63±6.34	133.07±12.41	136.47±8.54	<0.001

Table 8 shows, there is fall in post-operative SBP across the group, when measured in 5 minutes intervals until 30 minutes and this fall is statistically extremely significant (two-tailed p value <0.001). From table 8, it is seen that this fall was more in group C.

Table 9: Post-operative diastolic blood pressure (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
After 5 Mins	80.33±5.74	69.03±5.18	75.73±4.52	79±6.51	<0.001
After 10 Mins	78.7±5.75	67.57±5.24	74.33±4.57	77.47±6.47	<0.001
After 15 Mins	77.13±5.82	65.9±5.2	72.93±4.59	76.03±6.58	<0.001
After 20 Mins	75.7±5.78	64.4±5.09	71.4±4.53	74.53±6.59	<0.001
After 25 Mins	74.23±5.61	62.73±5.13	69.9±4.51	73±6.62	<0.001
After 30 Mins	72.77±5.6	61.13±5.03	68.5±4.4	71.47±6.68	<0.001

From table 9, mean DBP values at 5 hourly intervals shows a decreasing trend till 30th minute and this fall is statistically significant. From figure it is seen, here also the fall was more for group C.

Table 10: Post-operative mean arterial pressure (Mean ±SD)

	Groups				
	K (n=30)	C (n=30)	KC (n=30)	P (n=30)	Two-tailed p value*
After 5 Mins	103.01±4.63	88.41±4.14	97.43±4.59	100.63±4.94	<0.001
After 10 Mins	101.41±4.7	86.91±4.17	95.98±4.65	99.11±5.01	<0.001
After 15 Mins	99.87±4.72	85.32±4.09	94.53±4.67	97.69±5.12	<0.001
After 20 Mins	98.38±4.73	83.82±4.03	92.98±4.76	96.21±5.17	<0.001
After 25 Mins	96.93±4.63	82.21±4.12	91.47±4.78	94.64±5.25	<0.001
After 30 Mins	95.48±4.68	80.63±4.07	90.02±4.64	93.13±5.27	<0.001

There is statistically significant fall in MAP, across the groups and it was more pronounced for group C [Table 10].

Discussion

In this study, none of our patients showed severe bradycardia (heart rate <50 bpm), hypotension (MAP

<65 mmHg or less than 30% than preoperative baseline value whichever is more), respiratory depression (respiratory rate <8 /min, early or late), hypoxia (SPO2 < 90%) and hypercarbia (ETCO2 >45 mm Hg). These findings corroborate with the findings by D. Dal et al, Talakoub et al., A. M. H. Chan et al[9-11]. On the contrary, O Sagir et al reported incidence of hypotension is 5-23% in different groups but they defined hypotension as 20% fall of MAP from baseline value. They used inj. ephedrine for the patients with hypotension. None of our patients needed rescue drugs for hypotension, bradycardia, etc[12].

Ketamine increased the arterial blood pressure over duration of 60 minutes and by a mean maximum degree of 13 mmHg both systolic and diastolic in our participants. The increase was visible only within 2 hours after ketamine administration, reflecting the time period within which ketamine-related side effects must be expected[5]. This observation is consistent with previous findings[13-16]. There was statistically significant (two tailed p value < 0.001) rise in intra operative heart rate following intubation in groups K, KC and P. This rise was more for group K than P. In group C, there was significant fall in heart rate following intubation (two tailed p value<0.001). In group KC heart rate was maintained at a more or less constant level. In group KC, MAP was maintained at a stable level throughout the surgery. In groups K and P, there were statistically significant rise in mean arterial pressure (MAP) following intubation and then again from 60 minutes till end of the surgery. In group C, there was a significant fall in MAP after intubation and a rise at the end of the surgery.

The increase in heart-rate and MAP following administration of ketamine may be due to its intrinsic sympathomimetic activity while opposite effects were seen after administration of clonidine due to increase in parasympathetic outflow and decrease in sympathetic outflow due to activation of α2 receptors in brainstem[17]. In addition, some of the antihypertensive effects of clonidine may be mediated by activation of presynaptic α 2 receptors that suppress the release of NE, ATP, and NPY from postganglionic sympathetic nerves[18]. In group KC as these opposing factors in mechanism of actions of both the individual drugs played together, so more or less stable haemodynamic parameters were maintained.

Oral clonidine premedication may be useful to attenuate the cardiostimulatory effects of ketamine in healthy patients but cannot be relied upon to protect against unwanted increases in heart rate and blood pressure in predisposed patients. It is possible that the partial attenuation of the hypertension and tachycardia by clonidine is a result of a functional antagonism of ketamine's centrally mediated sympathetic discharge by a presynaptic alpha2 adrenergically mediated inhibition of catecholamine release or by a postsynaptic alpha2 adrenergically mediated depression of the vasomotor centres in the brain[19,20].

Conclusion

There was statistically significant (two tailed p value < 0.001) rise in intra operative heart rate following intubation in groups K, KC and P. In group C and KC, there were significant fall in SBP, from the baseline values, following induction. In groups K and P, there is statistically significant rise in diastolic blood pressure following induction, whereas in group C there was significant fall. In group KC, DBP was maintained more or less at a constant level. There was significant fall in heart rate in post operative period across the four groups. There is fall in post-operative SBP across the group, when measured in 5 minutes intervals until 30 minutes and this fall is statistically extremely significant (two-tailed p value <0.001). There is statistically significant fall in MAP, across the groups and it was more pronounced for group C. The unwanted effects of the individual drugs like, haemodynamic alteration, hallucination or lower incidences of nausea and vomiting could be achieved by using half of the dose of each of the drugs in combination.

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