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Attenuation of Cardiovascular Response of Ketamine Comparison and Evaluation between Intravenous Lignocaine and Oral Clonidine

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Abstract
Aim: *The objective of this study were to compare the reduction of cardiovascular response of ketamine between oral clonidine and intravenous lignocaine*
Methods: *In a randomized, prospective, parallel group, double blinded study, 150 patients were recruited and allocated into three groups. Group I(n=50) received ketamine 2mg/kg with normal saline 10 ml, Group II (n=50) received ketamine 2mg/kg with lignocaine 1.5mg/kg made upto 10ml and Group III (n=50) received ketamine 2mg/kg with oral clonidine 3mg/kg with normal saline 10ml. The patients were observed for pulse rate, systolic blood pressure, diastolic blood pressure, before induction and for 10 minutes after induction.*
Results: *The difference in pulse rate was much less in Group III 84.26 +/- 9.99) in comparision to Group I (99.14 +/- 15.11) bpm and Group II (93.48 +/- 14.86) bpm which is statistically significant (P= 0.0428). The mean arterial pressure of group III 100.2mm hg in comparision to group II 109.4 mm hg and group I :112.2 mm Hg was statistically significant (P= 0.0006).*
Conclusion: *Oral clonidine attenuate the increase in heart rate and blood pressure of intravenous keatmine effectively than intravenous lignocaine in puerperal sterilization.*
Keywords: *pulse rate, mean arterial pressure, mean rate pressure product, ketamine, clonidine, lignocaine.*

Introduction

The ideal intravenous induction agent should have rapid onset and short duration of action with adequate anaesthesia. It should provide good haemodynamic stability with less side effects. The induction agents like thiopentone and midazolam provide hypotension followed by hypertension during laryngoscopy(1). They need high dose narcotics to provide haemodynamic stability which may cause bradycardia, chest wall rigidity and post operative respiratory depression(2). Ketamine is a non Barbiturate induction agent, produces "dissociative anesthesia "characterized by a functional and electrophysiological dissociation between limbic and thalamo cortical systems(3). It also provide analgesic effect at sub anaestheic doses(4). When used as induction agent it does not produce respiratory depression. Even

though it causes myocardial deopression in high doses, it produce haemodynamic stability in hypovolumic patients by its sympathetic action[4].
Ketamine is a highly lipid soluble with rapid onset and short duration of action. In part this may be related to its cardio stimulatory effects in normovolumic patients[5,6] which may be unacceptable in some circumstances.
Clonidine is an oral antihypertensive agent by its α2 adrenergic stimulatory action [7]. It reduces the anaesthetic requirements of halothane[8,9] and isoflurane[10]. It reduce the narcotic requirements in coronary artery bypass surgery[11,12]. It attenuate the tachycardia and hypertension associated with tracheal intubation. [10,13,14].
Lignocaine is a local anaesthetic agent. A tertiary amide, very stable, not decompesed by boiling, acids or alkalis. It is metabolized by oxidase and amidase from microsomes in liver.It is excreted renally. Duration of effect of 1% solution, 1 hour; with adrenaline 1.5 -2 hours.
The objective of this study was to compare the effectiveness for the reduction of cardiovascular response to intravenous ketamine between oral clonidine and intravenous lignocaine and also determine the other effects of oral clonidine and intravenous lignocaine.

Subjects and Methods

After obtaining approval from ethical committee a written informed consent was obtained from all the patients who participated in this study.
Inclusion criteria – the study was conducted in 150 patients of ASA physical status I and II, aged between 15 – 35 yrs.

Exclusion Criteria

Patients suffering from HT, ↑ IOT, ↑ ICP, psychiatric patients and endocrinal disturbances were excluded.

Allocation: The patients were randomly allocated into three groups

Group I (n=50) received a placebo of 10 ml of saline intravenously prior to intravenous ketamine 2mg/kg.

Group II(n=50) received intravenous lignocaine 1.5 mg/kg (made upto 10ml) 90 secs prior to intravenous ketamine 2mg/kg.

Group III (n=50) received oral clonidine 3mg/kg 90 mins before surgery and 10ml of saline intravenously prior to intravenous ketamine 2mg/kg.

All patients received diazepam 10 mg orally as premedication 90 minutes before surgery.

In the operating room patients baseline heart rate and blood pressure were recorded and MAP and rate pressure product calculated. After giving intravenous ketamine the pulse rate and BP were recorded at 1 minute interval for the next 10 minutes. During this period patient was mask ventilated with N2O and O2. If ketamine is to be repeated, it is repeated in a dose of 1ml/kg. side effects such as bradycardia, hypotension, increased salivary secretion and delirium were observed.

Statistical Analysis

All the observations were recorded and all the results were analysed. Statistically data were presented as a mean t standard deviation. A value of P <0.05 was considered as a statistically significant difference with unpaired student t-test.

Results

Parameters observed are pulse rate (beats/mi), systolic B.P (mm Hg), Diastolic BP (mm Hg) and parameters derived are MAP and rate pressure product.

Mean arterial pressure = Diastolic B.P + 1/3 of pulse pressure

Pulse pressure = systolic B.P – Diastolic BP

Rate pressure product = pulse rate x systolic B.P

There was no difference in demographic profile of age distribution and body weight distribution among the three groups.

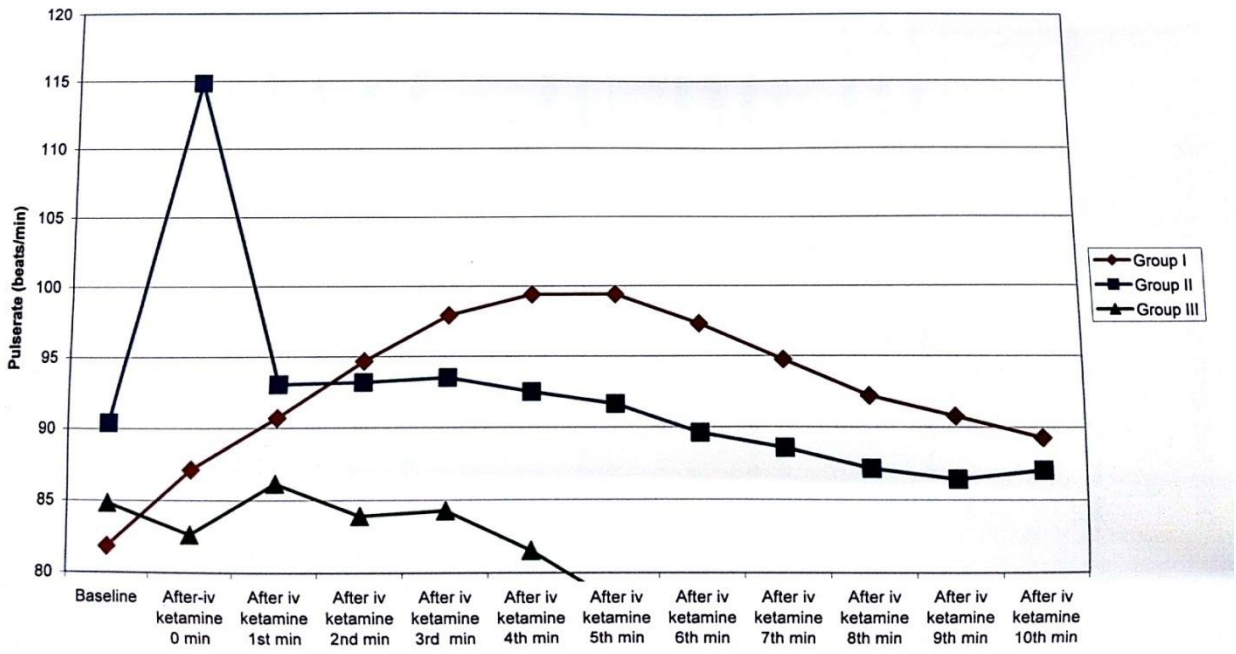
Table 1 :

Table - 1. Mean values of Pulse Rate (beats/minute)

GROUP	Baseline	0 minute	After Intravenous ketamine				
			1st min	2nd min	3rd min	4th min	5th min
GROUP 1	81.86±11.53	87.14±10.6	90.7±9.09	94.66±10.35	97.92±11.88	99.4±13.8	99.4±15.11
GROUP 2	90.4±13.93	114.84±169.46	93.04±12.87	93.16±13.38	93.48±14.86	92.48±13.09	91.62±12.6
GROUP 3	84.84±12.86	82.64±18.76	86.14±16.11	83.92±10.51	84.26±9.99	81.52±10.27	77.96±10.98

6th min	7th min	8th min	9th min	10th min
97.3±11.69	94.74±9.40	92.18±8.66	90.76±7.53	89.28±6.54
89.6±11.04	88.54±10.11	87.14±9.54	86.4±8.49	87.04±8.00
72.84±10.49	70.96±6.64	69.66±5.65	68.22±4.7	68.32±4.3

GRAPH - 1 MEAN PULSERATE CHANGES



The mean Pulse rate in group Iat baseline of 81.86 (+/- 11.537) bpm increased to 99.114 (+/-15.11) bpm after IV ketamine. In group II the base line Pulse rate of 90.4 bpm get increased to 93.48 (=/- 14.86) bpm. In group III the base line PR of 84.84 (=/- 16.11) bpm get changed to 84.26 (+/- 9.99) bpm. There was rise in PR in group II when compare to Group III after IV ketamine. The difference was sound to be statistically significant (P= 0.0428).

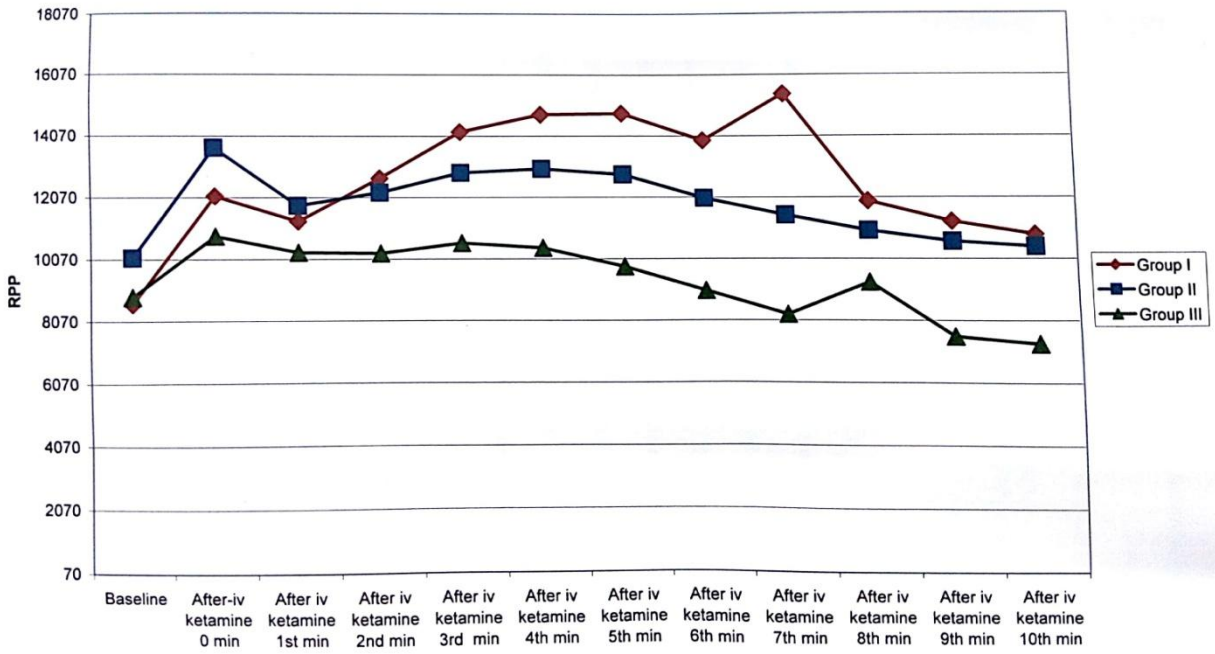
Table 02

Table - 2. Mean values of Mean Arterial Pressure (mm of Hg)

GROUP	Baseline	0 minute	After Intravenous ketamine				
			1st min	2nd min	3rd min	4th min	5th min
GROUP 1	83.42±9.36	91.68±10.69	101±12.84	106.2±11.39	110.8±9.48	112.2±9.41	111.9±7.87
GROUP 2	88.22±8.14	94.22±13.63	99.97±12.09	104.9±10.17	108.5±9.26	109.4±9.68	108.9±10.54
GROUP 3	81.67±7.22	89.57±11.18	93.72±11.21	95.88±11.58	99.15±8.4	100.2±8.74	98.25±8.7

6th min	7th min	8th min	9th min	10th min
108.03±7.05	103.26±7.03	99.47±6.63	96.07±6.34	94.82±7.79
103.9±12.57	101.35±7.87	98.14±6.68	95.5±5.85	93.4±5.26
94.50±8.25	90.41±7.47	88.73±7.33	86.61±6.04	84.91±5.91

GRAPH - 3 MEAN RATE PRESSURE PRODUCT CHANGES



In group I the baseline MAP of 83.42 ± 9.36 mm Hg get increased to 112.2 ± 9.41 mm Hg after IV ketamine.

In group II the baseline MAP of 88.22 ± mm hg get increased to 109.4 ± 9.68 mm Hg

In group III from the baseline value of 81.67 ± 7.22 mm Hg there was an increase upto 100.2 ±8.74 mm Hg. Comparing group II and III the difference was statistically significant (P <0.05 i.e P = 0.0006).

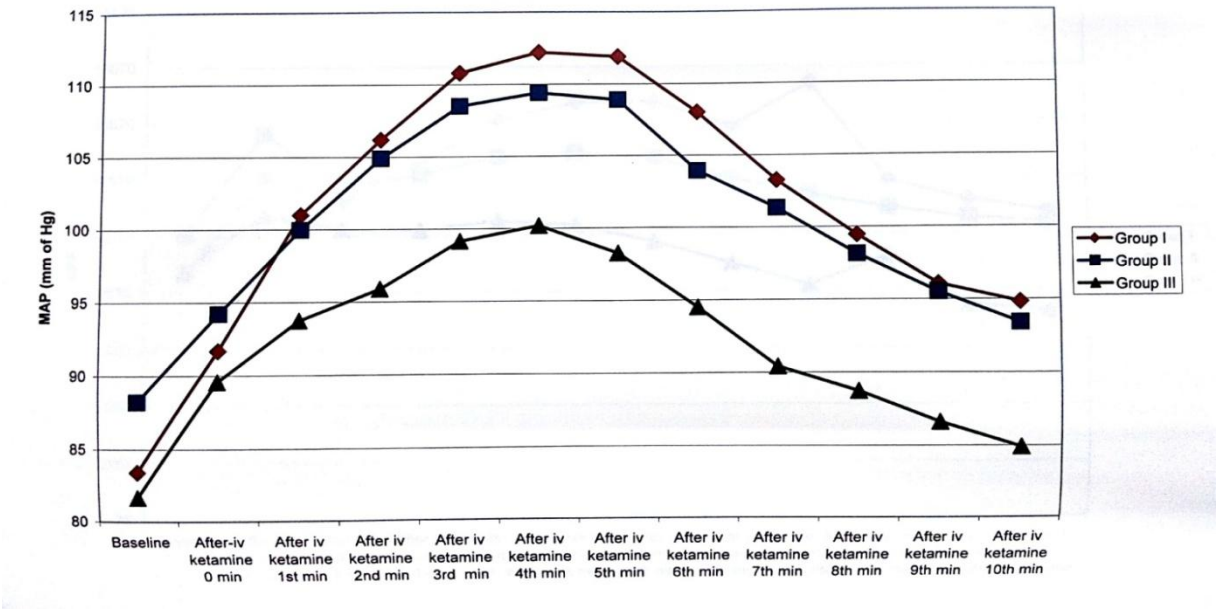
Table -3 :

Table - 3. Mean values of Rate Pressure Product

GROUP	Baseline	0 minute	After Intravenous ketamine				
			1st min	2nd min	3rd min	4th min	5th min
GROUP 1	8632.8±1863.29	12120.08±14383.84	11299±2329	12693±2282	14202±2171	14765±2428	14808±2603
GROUP 2	10120±1946.22	13692.12±20787	11812±2386	12232±2040	12873±2035	12991±1683	12807±1973
GROUP 3	8858±1487	10815±9918	10288±2820	10258±1951	10588±1594	10425±1483	9813±1722

6th min	7th min	8th min	9th min	10th min
13927±1986	15439±18634	11948±1535	11279±1426	10856±1163.8
12043±1065	11491±1473	10985±1293	10629±1232	10460±1174
8991±1628	8260.5±1134	9306±10029	7560±939.7	7331.2±1259.8

GRAPH - 2 MEAN ARTERIAL PRESSURE CHANGES

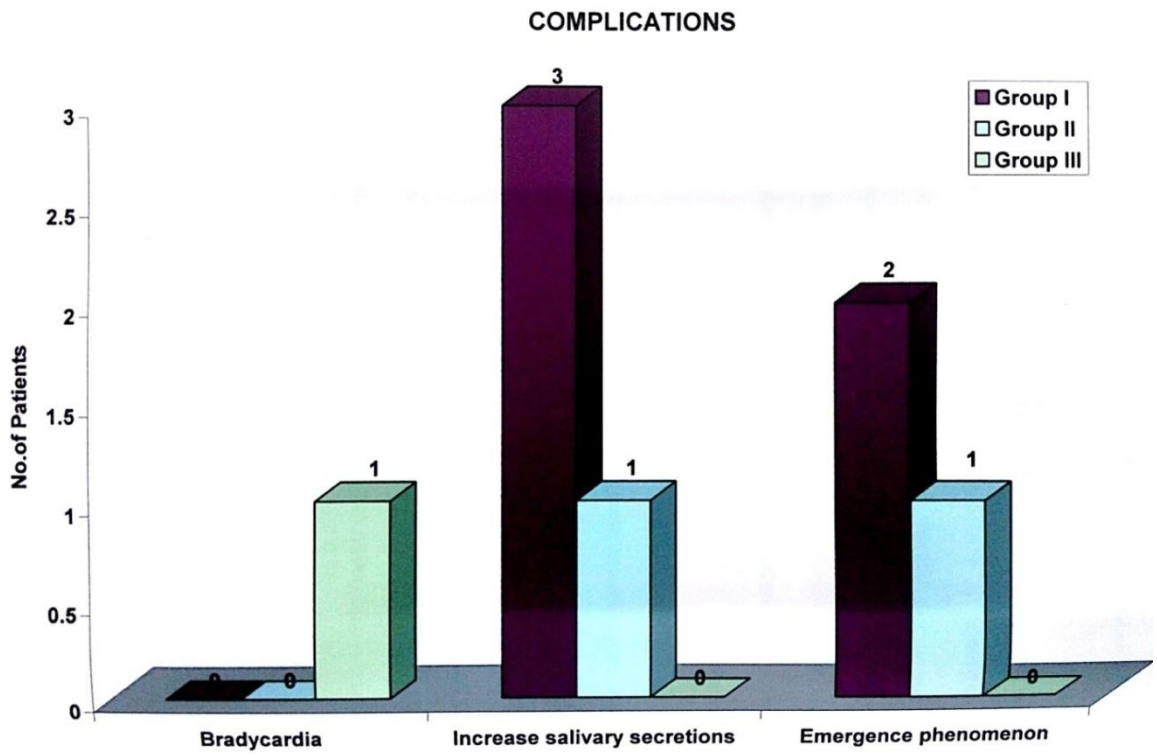


The mean rate pressure product values in group I showed an increase after IV ketamine from baseline of 8632.8±1863.29 to 14808 ±2603. In group II from baseline of 10120.08 ±1946.22 to 12991± 1683. And in group III from a baseline of 8858.22 ±1487.63 to mximum of 10588 ± 1594. When comparing group II and group III the difference was statistically significant (P<0.05 that is P=0.00049).

Complications: In group III one patient had bradycardia. (P.R< 50/min).

Three patients in group I and one patient in group II had increased salivary secretion.

Two patients in group I had emergence phenomenon.



Discussion

Ketamine is frequently described as an unique drug because it has hypnotic, analgeis and amnesic effects (3,$). It was used clinically in 1970 and because of these combined effects it was thought that it might be the perfect anaesthetic agent. But it is not quite the case because of its various side effects [(5,6)]. But still it is used for certain situations (eg) as in state of shock, cardiac tamponade, and in asthmatic patients[(4)].

Ketamine causes increase in P.R, systemic and pulmonary arterial blood pressure, C.O and myocardial O2 consumption. These effects were obtunded by prior administration of benzodiazepines. [(19,20)]

Clonidine is a central α2 adrenergic receptor agonist[(7)] induces sedation, decrease the sympathetic and cardio vascular responses to tracheal intubation, potentiation of opioids and volatile anaesthetic agents [(8,9,10)], reduction of IOP and post operative pain.

The cardiovascular effects of Ketamine due to direct stimulation of CNS, lead to increased sympathetic outflow. Clonidine α2 receptor agonist which inhibit the medullary vasomotor centres. As a result there is a decrease in sympathetic nervous system outflow. But in some patients its mechanism would be incomplete as the peripheral action of ketamine to inhibit catecholamine reuptake would still be operative. This may explain why clonidine is unable to eliminate completely, the cardiovascular stimulatory effects of ketamine.

Munro et al used premedication with oral diazepam and clonidine and demonstrated attenuation of the increase in BP. HR, rate pressure product associated with induction of anaesthesia with IV ketamine (2mg/kg) [15]

Abou- Madi. H.N, studied the efficacy of IV lignocaine to protect against cardiovascular reaction associated with laryngoscopy and tracheal intubation. The possible mechanism are direct myocardial depressant effect and peripheral vasodilator effect [16].

Doak and duke also reported that oral premedication with clonidine 5mg/kg 90 minutes before induction of anaesthesia attenuates both pressure and heart rate response compared with diazepam or placebo [17].

Harbhejsingh et al observed in their study that clonidine treated patients had 50 % incidence of bradycardia.

The haemodynamic effects also correlated well with the study of Dobrydnjov et al. In their study they demonstrated that oral clonidine treated patients had more incidence of hypotension (19%) and bradycardia (9%).

Conclusion

It was observed that all patients who received clonidine premedication had reduced HR, MAP, RPP and thus clonidine significantly attenuates the cardiovascular response of iv ketamine. Patients who received the iv lignocaine provides a little protection against tachycardia response to ketamine and this attenuation is clinically not significant. It attenuate the BP rise induced by iv ketamine to some extent. The complication associated with clonidine is bradycardia and with IV ketamine is increased salivary secretion and emergence delirium.

From this study it is concluded that the oral clonidine an α2 agonistin a dose of 3mg/kg 90 min before iv ketamine attenuates increase in HR, BP effectively. Thus oral clonidine may be an useful premedicant with ketamine in attenuating the cardiovascular response of ketamine.

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