



## A Comparative Study Of Intravenous Clonidine And Intravenous Dexmedetomidine Premedication On Cardiovascular Response To Ketamine Anesthesia In Patients Undergoing Dilatation & Curettage.

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### ABSTRACT:

*Background- Ketamine induced hemodynamic pressor response should be attenuated by appropriate premedication. The present study was designed to evaluate and compare the efficacy of dexmedetomidine and clonidine premedication to counter the effects of ketamine. Method-A total of 68 normotensive adult female patients of ASA grade I and II, aged 20-50 years, weighing between 40-65 kgs and undergoing dilatation and curettage under ketamine anaesthesia were randomized for this double blind, interventional, hospital based study. These patients were divided into two treatment groups of 34 patients each.*

*Group A (n=34) received Clonidine 1mcg/kg as continuous i.v. infusion over 30 minutes before induction.*

*Group B (n=34) received Dexmedetomidine 1mcg/kg as continuous i.v. infusion over 10 minutes before induction. Observations regarding the demographic profile, preoperative and intraoperative heart rate, mean arterial pressure were recorded. Analysis of data was done using unpaired student "t" test and chi-square tests. A "p" value <0.05 was considered significant. Result: No statistically significant difference was found in age, weight & ASA grade of both groups (p>0.05). Mean heart rate in Group A was 81.91± 6.84 and in Group B 80.94±7.09 (P value = 0.56 no statistical significance); after induction with ketamine, HR in Group A was 102.35± 12.55 and in Group B 78.02± 9.91 (P value = 0.000 high statistical significance). Mean arterial pressure in Group A was 90.85± 5.86 and in Group B 93.43± 8.14 (P value = 0.13 no statistical significance); after induction with ketamine, MAP in Group A was 103.76±7.74 and in Group B 99.05± 11 (P value = 0.04 statistical significance). Conclusion: Dexmedetomidine attenuates ketamine induced hemodynamic pressor response more effectively than clonidine. It maintains stable hemodynamic parameters during dilatation & curettage under ketamine anaesthesia.*

**Key Words:** Clonidine, dexmedetomidine, hemodynamic response, ketamine.

### INTRODUCTION

An ideal intravenous anaesthetic regime used in day care surgery should provide rapid recovery

and early discharge with minimal side effects and should be cost effective. Intravenous anaesthetics have evolved from being used primarily for

induction of anaesthesia to provide unconsciousness and amnesia for surgical procedures. Several anaesthetic drugs like alfentanil, methohexitone and propofol have been used for short gynaecological procedures.

Ketamine has become a useful drug in the armamentarium of anaesthesiologists. Despite several unpleasant intraoperative and postoperative side effects, its value has been established because of its lack of cardiovascular and respiratory depressant effects.

Ketamine, a phencyclidine analogue and a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, was introduced in clinical anaesthesia by Corssen and Domino in 1966<sup>[1]</sup> as an induction agent for repetitive procedures as it induces analgesia, amnesia and unconsciousness which lasts for about 15 to 25 minutes.<sup>[2]</sup> It is a potent intravenous anaesthetic produces dissociative anaesthesia and is characterized by rapid onset of action, preservation of airway reflexes and immediate recovery.

However, in spite of several advantages, the clinical usefulness of ketamine has been limited because of its intraoperative cardiostimulatory response and post operative recovery with psychomimetic effects.<sup>[2]</sup>

Cardiovascular stimulation by ketamine was first reported by Domino and associates<sup>[3]</sup> in 1965. In 1968, Dowdy and Kaya<sup>[4]</sup> proposed that this stimulatory action of ketamine resulted from depression or inhibition of peripheral baroreceptors. Ketamine raises the cardiac output, the pulse rate, the arterial and central venous pressures and has little effect on total peripheral resistance.<sup>[5]</sup> The stimulation is maximal after the first dose and persists for about 20 minutes. The effect has been variously ascribed to activation of the central sympathetic nervous system,<sup>[6]</sup> blockade of the cardiac vagus nerves,<sup>[7]</sup> increased levels of circulating

catecholamines,<sup>[8]</sup> activation of adrenocortical system,<sup>[9]</sup> and constriction of alpha adrenoceptor blood vessels with increased venous return to the heart.<sup>[10]</sup> Propranolol has little influence on the cardiac effects of ketamine which indicates that adrenergic overactivity is not the main cause of cardiac reaction to ketamine.<sup>[11]</sup>

The possibility that ketamine may act directly on the myocardial cells was considered by Hamilton and Bryson.<sup>[12]</sup> They showed that the drug has a dual action on the transmembrane potentials of the Purkinje fibres of the isolated perfused pig heart. The primary effect seems to be a veratrine-like facilitation of ionic movements across the cell membranes. The drug also increases the response to the preparation of small doses of adrenaline. Drugs with a veratrine-like action increase the permeability of cell membranes and make the cells more excitable and responsive to physiological stimuli.<sup>[13]</sup>

Numerous drugs have been tried to attenuate these undesirable responses.<sup>[14]</sup> Lilburn JK, Moore J, Dundee JW<sup>[14]</sup> used labetalol in doses of 0.5 mg/kg and 1 mg/kg. It proved to be a promising drug. Doak GJ, Duke PC<sup>[15]</sup> studied the effect of oral clonidine premedication in attenuating the haemodynamic effects associated with ketamine induction. Munro HM, Sleight JW, Paxton LD<sup>[16]</sup> studied the effectiveness of clonidine or lignocaine in reducing the cardiostimulatory effects of ketamine. Handa F, Tanaka M, Nishikawa T, Toyooka H<sup>[17]</sup> conducted a study to determine the effects of oral clonidine premedication on haemodynamic changes during the entire course of ketamine anaesthesia and concluded that oral clonidine 2.5 microgram/kg and 5 microgram/kg attenuate cardiostimulatory effects associated with ketamine induction. Levanen J, Makela ML, Scheinin H<sup>[18]</sup> studied the effects of dexmedetomidine premedication on ketamine induced cardiostimulatory effects and

postanaesthetic delirium. Their results suggested that premedication with 2.5 microgram/kg dexmedetomidine is effective in attenuating the cardiostimulatory and postanaesthetic delirium effects of ketamine. Gupta K, Gupta A, Gupta PK<sup>[19]</sup> studied dexmedetomidine premedication in relevance to ketamine anaesthesia. They concluded that the dexmedetomidine premedication effectively attenuated the ketamine induced haemodynamic pressor response and postanaesthetic delirium effects.

However, no study has been conducted so far to compare the effects of i.v. clonidine and i.v. dexmedetomidine on ketamine induced cardiovascular stimulatory response. These are  $\alpha_2$  adrenergic agonists that induce preoperative sedation, reduce anaesthetic requirements and improve hemodynamic stability with postoperative analgesia, which suggests that they might be suitable adjuncts to ketamine anaesthesia.<sup>[20]</sup> Clonidine has  $\alpha_2:\alpha_1$  specificity ratio of 220:1 while dexmedetomidine has 1620:1. The improved specificity causes it to be much more effective sedative and analgesic than clonidine.

In the present study, intravenous clonidine and dexmedetomidine have been used as premedication and haemodynamic effects of ketamine anaesthesia have been compared.

## MATERIALS & METHOD

**Study design-** A Randomized, Double Blind, Interventional Hospital based study. Due permission from the institutional ethical committee, review board and written informed consent of the patient was obtained.

**Sample Size:** - A power analysis determined a sample size of 34 subjects per group, when a power of 0.80 and  $\alpha$  error of .05 were used.

## ELIGIBILITY CRITERIA

### INCLUSION CRITERIA:-

- Age group between 20-50 years.
- Weight of the patient between 40-65 Kgs.
- Patients belonging to ASA class-I and II.
- Patients undergoing dilatation and curettage.

### EXCLUSION CRITERIA:-

- Patients not willing to participate in the study.
- Uncooperative patients.
- History of convulsions, allergy to the drug used, bleeding disorder, severe neurological deficit.
- Patient with history of hypertension, respiratory, cardiac, hepatic or renal diseases (necessitating classification in ASA Class III or above).

### PROCEDURE:-

**Pre anesthetic check up** was done a day before the surgery that included

- 1) Complete history of patient including any known drug allergy.
- 2) Pulse rate, blood pressure, respiratory rate and weight of the patient.

### Investigations:

- Hematological – Hb%, TLC, DLC, BT,CT.
- Fasting / Random blood sugar.
- Blood Urea, Serum Creatinine.
- Urine- Albumin, sugar
- Chest X ray, ECG.

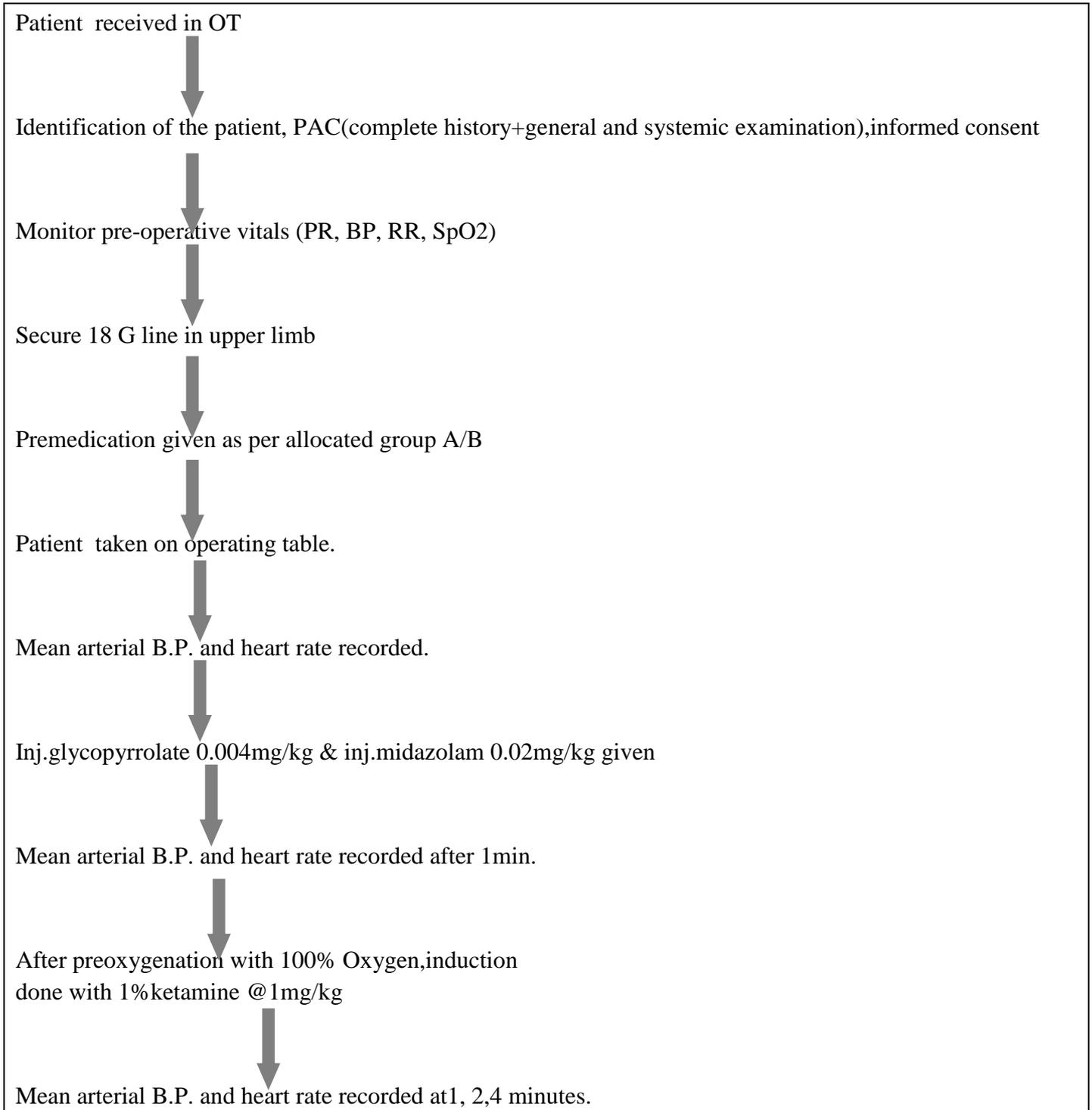
Informed consent was obtained after complete explanation about the study protocol and the procedure. The patients were randomly allocated into one of the two predefined groups by chit in box method. This randomization and preparation of medications was done by another person so that the person who was injecting the drug and the

person doing the study did not know which group a particular patient was allotted.

**Group A** (n=34) received Clonidine 1mcg/kg as continuous i.v. infusion over 30 minutes before induction.

**Group B** (n=34) received Dexmedetomidine 1mcg/kg as continuous i.v. infusion over 10 minutes before induction.

### Methodology



Anaesthesia maintained with 60% N<sub>2</sub>O+40% O<sub>2</sub>

### Analysis of data

Data was analyzed using unpaired student “t” test and chi-square tests. A “p” value of less than 0.05 was considered significant.

### DRUGS AND EQUIPMENTS

- Boyle’s Anesthesia Workstation.
- Multipara monitor having pulse oxymeter, NIBP, ECG
- IV infusion set, blood transfusion set
- IV Cannula: 18G; 20G, IV extension line
- IV Fluids: crystalloids; colloids including normal saline
- Disposable syringes: 5 ml; 10 ml; 50ml
- Infusion pump
- Suction machine
- Laryngoscope
- ET tubes of different sizes
- Emergency drugs- Atropine, Adrenaline, Dopamine, Isoprenaline, Hydrocortisone, Xylocard, Deriphylline
- Drugs used in study- Inj. Ketamine, Inj. Clonidine, Inj. Dexmedetomidine, Inj. Glycopyrrolate

### RESULTS

This study was conducted to assess and compare the effect of intravenous clonidine and intravenous dexmedetomidine premedication on cardiovascular response to ketamine anaesthesia in patients undergoing dilatation & curettage. A total of 68 patients, 34 in each group, were evaluated. The study was conducted in following two groups of patients:-

**Group A** (n=34) received Clonidine 1mcg/kg as continuous i.v. infusion over 30 minutes before induction.

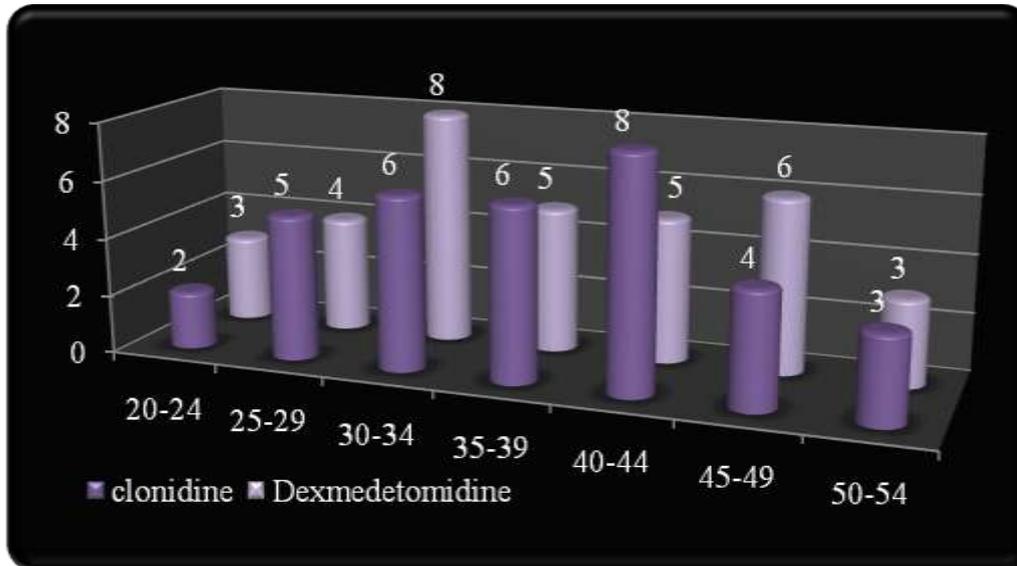
**Group B** (n=34) received Dexmedetomidine 1mcg/kg as continuous i.v. infusion over 10 minutes before induction.

The effect of intravenous clonidine & intravenous dexmedetomidine on heart rate & mean arterial pressure were compared in both the groups.

Unpaired t-test was applied to know the statistical significance of difference between the groups.

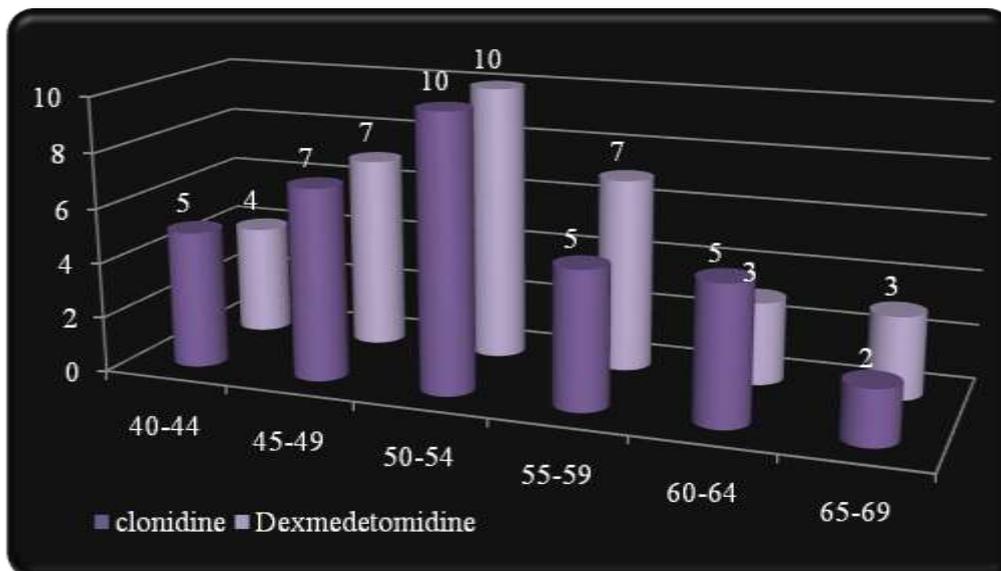
Both groups were comparable with respect to the demographic profile and operational factors. ( Table 1,2; Bar graphs 1,2)

### \*[1] AGE DISTRIBUTION



\*original

\*[2] WEIGHT- DISTRIBUTION



\*Table No. 1

Patient demographic profile (Mean±SD)

Demographic profile	Group A	Group B	P Value
Age( in years )	36.5±7.96	36.17±8.94	0.873
Weight( in kg )	51.97±7.31	51.76±7.00	0.904

ASA/II	15/19	21/13	0.224
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**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A- Clonidine; Group B- Dexmedetomidine

\*original

**\*Table No. 2**

**Patient preoperative operational factors (Mean±SD)**

Demographic profile	Group A	Group B	P Value
Sedation	Awake	Awake	-
Heart Rate ( beats/min)	81.91±6.84	80.94±7.09	0.568
MAP ( mm of Hg )	90.85±5.86	93.43±8.14	0.138

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A- Clonidine; Group B- Dexmedetomidine

\*original

There was negative inotropic effect after peak effect of both study drugs. In Group A, there was significant fall in heart rate after peak effect of clonidine. After induction with ketamine heart rate increased significantly.( tables 3,4,6; Bar graph 3)

In Group B, significant fall in heart rate was observed after peak effect of dexmedetomidine. Heart rate continued to fall after induction with ketamine, though insignificant rise was observed at 4 minutes. (Tables 3,5,6; Bar graphs 3)

**\*Table No. 3**

**Heart rate at different points during ketamine anesthesia (Mean±SD)**

Heart Rate	Group A	Group B	P Value
Preoperative	81.91±6.84	80.94±7.09	0.568
After peak effect of drug	80.09±5.51	72.64±7.39	0.000
After IV Premedication	80.15±6.01	74.23±10.28	0.000
After ketamine induction	89.97±5.64	78.02±9.91	0.000
At 2 minutes	96.44±5.98	80.47±9.86	0.000

At 4 minutes	102.21±11.06	82.05±10.12	0.000
At 6 minutes	105.68±12.52	83±10.9	0.000

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A-Clonidine; Group B-Dexmedetomidine

\*original

**\*Table No. 4**

**Change in Heart Rate from baseline at different time periods (Mean±SD) in Group A**

Time period	Mean	S.D.	P value
After peak effect of study drug	1.82	4.85	0.036
After premedication	1.76	5.77	0.084
After ketamine induction	-8.05	6.78	0.000
After 2 minutes	-14.52	8.69	0.000
After 4 minutes	-20.29	13.02	0.000
After 6 minutes	-23.76	13.63	0.000

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A-Clonidine

\*original

**\* Table No. 5**

**Change in Heart Rate from baseline at different time periods (Mean±SD) in Group B**

Time period	Mean	S.D.	P value
After peak effect of study drug	8.29	7.56	0.000
After premedication	6.67	9.79	0.000
After ketamine induction	2.91	10.46	0.000
After 2 minutes	0.47	10.01	0.000
After 4 minutes	-0.35	10.25	0.067
After 6 minutes	-0.30	10.28	0.061

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group B-Dexmedetomidine

\*original

\* Table No. 6

Change in Heart Rate from baseline at different time periods (Mean±SD)

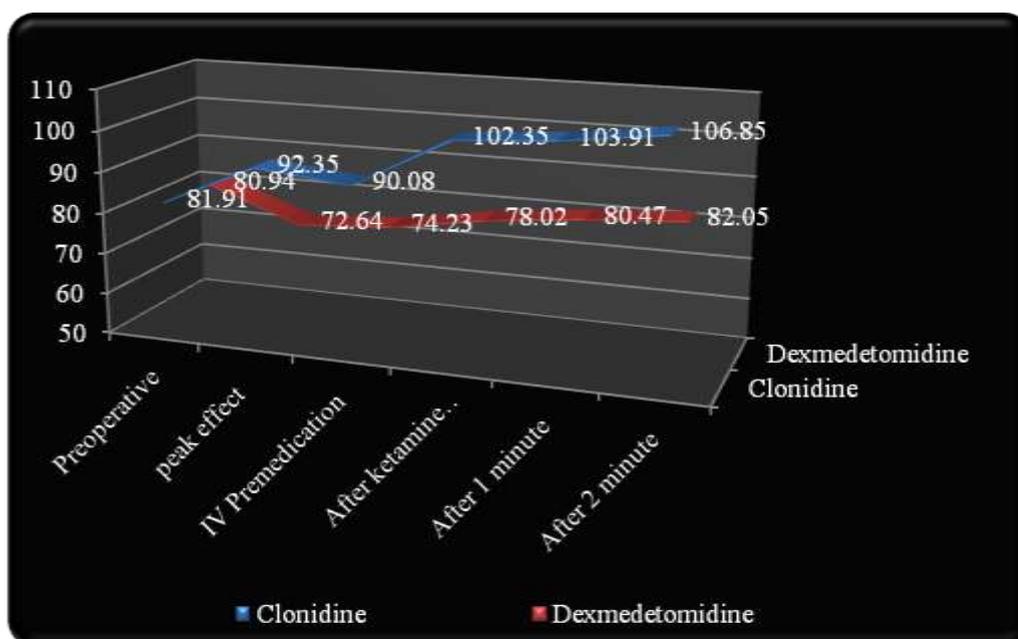
Heart Rate	Group A	Group B	P value
After peak effect of drug	1.82±4.85	8.29±7.56	0.000
After i.v. premedication	1.76±5.77	6.67±9.79	0.000
After ketamine induction	-8.05±6.78	2.91±10.46	0.000
At 2 minutes	-14.52±8.69	0.47±10.01	0.000
At 4 minutes	-20.29±13.02	-0.35±10.25	0.000
At 6 minutes	-23.76±13.63	-0.30±10.28	0.000

P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant

Group A-Clonidine; Group B-Dexmedetomidine

\*original

\*[3] Heart rate at different points during ketamine anesthesia (Mean±SD)



There was decrease in mean arterial pressure after peak effect of clonidine and dexmedetomidine. In Group A, significant reduction in MAP was noticed after peak effect of clonidine. After induction with ketamine, highly significant rise in MAP was observed at all points.(Tables7,8,10; Bar graphs 4,5) In Group B, highly significant ( $p < 0.001$ ) fall in MAP was observed at all points of study.(Tables7,9,10; Bar graphs4,5)

**\*Table No. 7**

**Mean arterial pressure at different points during ketamine anesthesia (Mean±SD)**

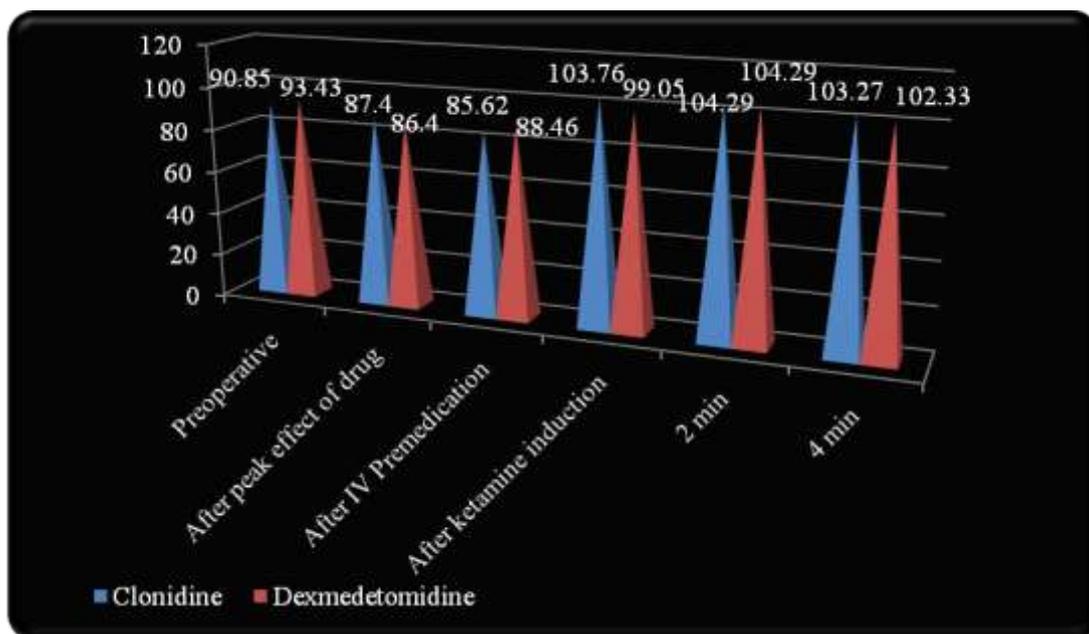
Mean Arterial Pressure	Group A	Group B	P Value
Preoperative	90.85±5.86	93.43±8.14	0.138
After peak effect of drug	87.40±6.77	86.40±9.8	0.625
After IV Premedication	85.62±8.13	88.46±11.79	0.252
After ketamine induction	103.76±7.74	99.05±11.00	0.045
At 2 minutes	104.29±5.87	104.29±5.87	0.270
At 4 minutes	103.27±6.24	102.33±9.22	0.624
At 6 minutes	102.11±5.63	101.56±6.78	0.521

**P > 0.05 – Non significant; P < 0.05 or 0.01 – Significant; P < 0.001 – Highly significant**

Group A-Clonidine; Group B-Dexmedetomidine

\*original

**\*[4] Mean arterial pressure at different points during ketamine anesthesia (Mean±SD)**



\*original

**\*Table No. 8**

**Change in MAP from baseline at different time periods (Mean±SD) in Group A**

Time period	Mean	S.D.	P value
After peak effect of study drug	3.45	9.21	0.038
After premedication	5.52	9.75	0.005
After ketamine induction	-12.70	7.54	0.000
After 2 minutes	-13.22	7.10	0.000
After 4 minutes	-13.33	7.01	0.000
After 6 minutes	-13.10	6.98	0.000

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A-Clonidine

**\*original**

**\*Table No. 9**

**Change in MAP from baseline at different time periods (Mean±SD) in Group B**

Time period	Mean	S.D.	P value
After peak effect of study drug	7.13	8.87	0.000
After premedication	4.51	12.09	0.000
After ketamine induction	-5.16	11.51	0.007
After 2 minutes	-8.48	10.10	0.000
After 4 minutes	-8.89	8.44	0.000
After 6 minutes	-8.76	8.99	0.000

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant** Group B- Dexmedetomidine

**\*original**

**\*Table No.10**

**Change in MAP from baseline at different time periods (Mean±SD)**

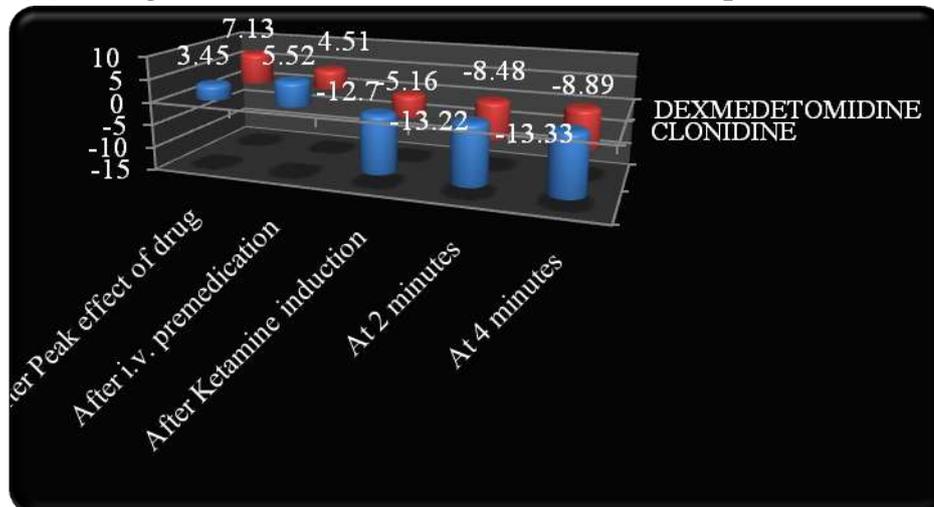
Mean Arterial Pressure	Group A	Group B	P value
After Peak effect of drug	3.45±9.21	7.13±8.87	0.000
After i.v. premedication	5.52±9.75	4.51±12.09	0.000
After Ketamine induction	-12.70±7.54	-5.16±11.51	0.000
At 2 minutes	-13.22±7.10	-8.48±10.10	0.000
At 4 minutes	-13.33±7.01	-8.89±8.44	0.000
At 6 minutes	-13.10±6.98	-8.76±8.99	0.000

**P >0.05 – Non significant; P <0.05 or 0.01 – Significant; P <0.001 – Highly significant**

Group A-Clonidine; Group B-Dexmedetomidine

\*original

**\*[5] Change in MAP from baseline at different time periods (Mean±SD)**



\*original

### Recovery and postoperative follow up

The patients were transferred to the PACU and monitored for 3 hours. There was no difference among the groups with respect to recovery and awakening time.

### DISCUSSION

Ketamine, a phencyclidine analogue and a non-competitive antagonist of NMDA receptors, functionally “dissociates” the thalamus from the limbic cortex which is involved with the awareness of sensation. It is the only anaesthetic available with analgesic, hypnotic and amnestic effects. In spite of several advantages, its anaesthetic use has been limited due to its cardiostimulant response even in therapeutic doses. After an intravenous dose, the heart rate increases progressively upto 33% for 10-15 minutes and then subsides.

Numerous drugs have been evaluated for attenuation of cardiovascular effects of ketamine. The present study was designed to compare and assess the efficacy of intravenous premedication with clonidine and dexmedetomidine on ketamine-induced haemodynamic pressor response and psychomimetic effects. A total of 68 patients, 34 in each group A&B were evaluated. Both the study drugs are alpha<sub>2</sub> adrenoceptor agonist and induce central sympatholysis by activating presynaptic autoreceptors, but, dexmedetomidine is about 10 times more selective towards the alpha<sub>2</sub> adrenoceptor and act as a full agonists in some pharmacological tests. Therefore, dexmedetomidine stabilizes the hemodynamics rate during ketamine anaesthesia better than clonidine.

### DEMOGRAPHIC PROFILE

No statistically significant difference was found in age, weight & ASA grade of both groups (  $p > 0.05$  )

### HEART RATE

In the present study, mean heart rate in Group A was  $81.91 \pm 6.84$  and in Group B  $80.94 \pm 7.09$  (  $P$  value = 0.56 implies no statistical significance); In Group A, there was significant increase in heart rate after peak effect of clonidine. After induction with ketamine heart rate increased significantly and remained high even thereafter. ( tables 3,4,6; Bar graph 3)

In Group B, significant fall in heart rate was observed after peak effect of dexmedetomidine. Heart rate continued to fall after induction with ketamine, though insignificant rise was observed at 4minutes. (Tables 3,5,6; Bar graph 3)

**Gupta K et al** in their study on comparison of intravenous premedication of midazolam and dexmedetomidine in ketamine anaesthesia concluded that dexmedetomidine has effectively attenuated the ketamine-induced haemodynamic pressor response and psychomimetic effects. Due to its tendency to cause bradycardia, routine use of an anticholinergic drug was advised. In the present study Inj. Glycopyrrolate was given before ketamine induction. Incidence and intensity of bradycardia were less in the present study as compared to the previous study.

**Aho M et al** studied the effect of intravenously administered dexmedetomidine on perioperative haemodynamics in patients undergoing abdominal hysterectomy. The increase in heart rate was significantly less in dexmedetomidine group than in the saline group (  $P < 0.01$  ). Also, the postintubation increase in heart rate was significantly less (  $P < 0.05$  ) in the dexmedetomidine group (increase of  $18 \pm 3$  beats per min).

In a study by **Munro et al** oral clonidine was found to be more effective than intravenous lidocaine in preventing the cardiostimulatory effects of ketamine.

**B. Scheininet al** observed that dexmedetomidine attenuated the

cardiovascular responses to laryngoscopy and tracheal intubation.

In the present study, clonidine and dexmedetomidine have stabilized heart rate perioperatively which is in accordance with previous studies. Comparison of the two study drugs suggests that dexmedetomidine has better controlled heart rate after ketamine than did clonidine.

### MEAN ARTERIAL PRESSURE

In this study, mean arterial pressure in Group A was  $90.85 \pm 5.86$  and in Group B  $93.43 \pm 8.14$  (P value = 0.13 implies no statistical significance). In Group A, significant reduction in MAP was noticed after peak effect of clonidine. After induction with ketamine, highly significant rise in MAP was observed at all points. (Tables 7,8,10; Bar graphs 4,5) In Group B, highly significant ( $p < 0.001$ ) fall in MAP was observed at all points of study. (Tables 7,9,10; Bar graphs 4,5)

**Doak et al** reported that oral clonidine attenuates mean arterial pressure after anaesthetic induction with ketamine when compared to diazepam.

**Gupta PK et al** compared the effects of clonidine and lidocaine on hemodynamics after ketamine anaesthesia and concluded that clonidine was better in attenuating hemodynamic pressor response of ketamine.

**Levanen et al** reported that premedication with dexmedetomidine is effective in attenuating the cardiostimulatory and post anaesthetic delirium effects of ketamine and reported its superiority over midazolam.

**Taittoven et al** [21] compared clonidine and midazolam as premedication in ketamine anaesthesia and observed no difference in oxygen consumption, anxiolysis, energy expenditure and carbondioxide production. They also observed that clonidine improved hemodynamic stability as compared to midazolam. The results of present study coincide with previous studies.

The observations of this study suggest that dexmedetomidine premedication is superior to clonidine premedication in attenuating cardiostimulatory response and post anaesthetic delirium effects of ketamine.

### CONCLUSION

A total of 68 patients, 34 in each group A&B were evaluated. Both the study drugs are alpha2 adrenoceptor agonist and induce central sympatholysis by activating presynaptic autoreceptors, but, dexmedetomidine is about 10 times more selective towards the alpha2 adrenoceptor and act as a full agonists in some pharmacological tests. Therefore, dexmedetomidine stabilizes the hemodynamics during ketamine anaesthesia better than clonidine. Following conclusions were drawn:

1. Patients in both the groups were comparable in terms of demographic profile.
2. reoperatively, all patients were awake. Mean heart rate in Group A was  $81.91 \pm 6.84$  and in Group B  $80.94 \pm 7.09$  ( $p = 0.56$ ): mean arterial pressure in Group A was  $90.85 \pm 5.86$  and in Group B  $93.43 \pm 8.14$  ( $p = 0.13$ )
3. heart rate in both the groups decreased significantly after peak effect of respective study drugs.
4. Group A showed significant increase in heart rate after induction with ketamine and it continued to remain high significantly.
5. In Group B, significant decrease in heart rate was observed immediately after induction with ketamine and after 2

minutes. Then there was an insignificant increase in heart rate.

6. After peak effect of respective study drugs, mean arterial pressure dropped in both groups.
7. After induction with ketamine, highly significant increase in MAP was noticed in Group A and it continued to remain high.
8. Group B was found to have significant increase in MAP after induction with ketamine but on comparing with Group A, the increase was significantly less. This indicates more stability with dexmedetomidine than clonidine.

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